Lifestyle Medicine

SECOND EDITION

Edited by

James M. Rippe, MD

CRC Press
Taylor & Francis Group

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CRC Press
Taylor & Francis Group
Boca Raton London New York

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CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

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Version Date: 20120621

International Standard Book Number-13: 978-1-4398-4544-8 (eBook - PDF)

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Dedication

To my dear wife, Stephanie, and our children, Hart, Jaelin, Devon, and Jamie, the wind beneath my wings.

Contents

Preface xix
Acknowledgments xxiii
Editor xxv
Contributors xxvii

PART I Lifestyle Management and Prevention of Cardiovascular Disease

James M. Rippe, MD

Chapter 1 Rationale for Intervention to Reduce the Risk of Coronary Artery Disease 3
James M. Rippe, MD and Theodore J. Angelopoulos, PhD, MPH

Chapter 2 Lifestyle Strategies for Risk Factor Reduction, Prevention, and Treatment of Coronary Artery Disease 19
James M. Rippe, MD and Theodore J. Angelopoulos, PhD, MPH

Chapter 3 Nutrition Interventions for Cardiovascular Disease: Behavioral and Educational Considerations 35
Carol E. O'Neil, PhD, MPH, RD and Theresa A. Nicklas, DrPH

Chapter 4 Physical Activity and Fitness in the Prevention of Cardiovascular Disease 49
Robert F. Zoeller, PhD

Chapter 5 Clinical Strategies for Managing Dyslipidemias 65
Ulf G. Bronas, PhD, ATC, ATR, FSVM and Arthur S. Leon, MD, MS

Chapter 6 Lifestyle Management and Prevention of Hypertension 75
Ulf G. Bronas, PhD, ATC, ATR, FSVM and Arthur S. Leon, MD, MS

Chapter 7 Community Approaches to Reduce the Risks of Cardiovascular Disease 83
Cherise B. Harrington, PhD, MPH, Meridith Eastman, BA, and Laura Linnan, ScD, CHES

PART II Nutritional Aspects of Lifestyle Medicine

Johanna Dwyer, DSc, RD

Chapter 8 Nutrition 101: The Concept of Nutritional Status and Guides for Nutrient Intakes, Eating Patterns, and Nutrition 103
Johanna Dwyer, DSc, RD

Chapter 9 Healthy People 2020: Highlights in the Nutrition and Weight Status Focus Area 119
Pamela Starke-Reed, PhD, Crystal McDade-Ngutter, PhD, and Van S. Hubbard, MD, PhD

Chapter 10 Dietary Guidelines for Americans, 2010: National Nutrition Policy 131
Rachel Hayes Polon, MPH, RD and Eve Essery Stoody, PhD

Chapter 11 Nutritional Considerations for the Active Adolescent 149
Rebecca J. Boulos, MPH and Christina D. Economos, PhD

Chapter 12 Nutrition for the Elite Athlete 163
Ladd Harris, MS, RD and Katherine Beals, PhD, RD, FACSM, CSSD

Chapter 13 Optimal Nutrition Guidance for Older Adults 177
Alice H. Lichtenstein, DSc

Chapter 14 Role of Communication in Changing Nutrition Behaviors to Promote Healthy Lifestyles 185
Jeanne Goldberg, PhD, RD and Lindsay Peterson, MS, MEd

PART III Physical Activity and Fitness
Theodore J. Angelopoulos, PhD, MPH

Chapter 15 Physical Fitness Evaluation 199
Peter F. Kokkinos, PhD and Jonathan Myers, PhD

Chapter 16 Exercise Prescription for Apparently Healthy Individuals and for Special Populations 209
Paul G. Davis, PhD, RCEP

PART IV Behavioral Psychology
Bess Marcus, PhD

Chapter 17 Applying Psychological Theories to Promote Healthy Lifestyles 223
Sarah E. Linke, PhD, MPH and Dori Pekmezi, PhD

Chapter 18 Cognitive and Behavioral Approaches to Enhancing Exercise Participation 233
Barbara A. Stetson, PhD, John M. Cooper, BA, and Patricia M. Dubbert, PhD

Chapter 19 Behavioral Approaches to Enhancing Smoking Cessation 245
Joseph T. Ciccolo, PhD, Ernestine G. Jennings, PhD, and Andrew M. Busch, PhD

Chapter 20 Behavioral Approaches to Enhancing Weight Loss and Maintenance 255
Teresa K. King, PhD, Elizabeth E. Lloyd-Richardson, PhD, and Matthew M. Clark, PhD

PART V Women's Health

Pamela M. Peeke, MD, MPH, FACP

Chapter 21 Women's Health: Challenges and Opportunities 269
Pamela M. Peeke, MD, MPH, FACP

Chapter 22 Menopause 271
Margery Gass, MD, NCMP

Chapter 23 Breast Health: Lifestyle Modification 287
Beth Baughman DuPree, MD, FACS

Chapter 24 Osteoporosis 299
Sobia Khan, MD, NCMP, CCD and Holly Thacker, MD, FACP, NCMP, CCD

Chapter 25 Physical Activity and Health in Women 313
Shari S. Bassuk, ScD and JoAnn E. Manson, MD, DrPH

Chapter 26 Women's Body Composition and Lifestyle 331
Pamela M. Peeke MD, MPH, FACP

Chapter 27 Health and Wellness Coaching Skills for Lasting Change 343
Elizabeth Pegg Frates, MD and Margaret Moore, MBA

PART VI Men's Health

Craig Garfield, MD, MAPP

Chapter 28 Perspectives on Men's Health 363
Craig Garfield, MD, MAPP

Chapter 29 Addressing Men's Mental Health through a Strength-Based Approach 369
Anthony Isacco, PhD, Edvina Talovic, MS, Lindsay C. Chromik, MS, and Nicole K. Yallum, MS

Chapter 30 Promoting Nutrition in Men's Health 383
Brendan Gough, PhD

Chapter 31 Management and Prevention of Urological Diseases in Men 391
Geoffrey R. Nuss, MD and Christopher M. Gonzalez, MD

Chapter 32 Health Promotion and Risk Reduction in Men 405
Lisa Terre, PhD

PART VII Endocrinology and Metabolism

Samuel Crockett, MD

Chapter 33 Lifestyle and Insulin Resistance 421
Samuel Crockett, MD

Chapter 34 Lifestyle Approaches to the Prevention and Treatment of Diabetes 431
Marion J. Franz, MS, RD, CDE

Chapter 35 Lifestyle Medicine and the Treatment of Glucose Intolerance 441
Mary Beth Weber, MPH, PhD, Lisa R. Staimez, MPH, Jennifer Gilligan, MD, PhD, K.M. Venkat Narayan, MD, and Lawrence S. Phillips, MD

Chapter 36 Lifestyle Approaches to the Metabolic Syndrome 455
April J. Stull, PhD, RD, Catherine M. Champagne, PhD, RD, and William T. Cefalu, MD

PART VIII Lifestyle Issues in the Prevention and Treatment of Cancer

Clarence H. Brown, III, MD and Naren Ramakrishna, MD, PhD

Chapter 37 Lifestyle Interventions in the Prevention and Treatment of Cancer 471
Clarence H. Brown, III, MD, Said M. Baidas, MD, Julio J. Hajdenberg, MD, FACP, Omar R. Kayaleh, MD, Gregory K. Pennock, MD, Nikita Shah, MD, and Jennifer E. Tseng, MD

Chapter 38 Obesity and Cancer 483
Clarence H. Brown, III, MD

Chapter 39 The Role of Physical Activity across the Cancer Survivorship Continuum 491
Catherine M. Sabiston, PhD, Jeff K. Vallance, PhD, and Jennifer Brunet, PhD

Chapter 40 Nutrition and Cancer 505
Clarence H. Brown III, MD, Naren Ramakrishna, MD, PhD, Lenore S. Hodges, PhD, RD, CSO, LD/N, and Dawn Napoli, RD, LD/N

PART IX Obesity and Weight Management

John P. Foreyt, PhD

Chapter 41 Epidemiology of Adult Obesity 515
R. Sue Day, PhD, Nattinee Jitnarin, PhD, Austin L. Brown, MPH, and Walker S. Carlos Poston, PhD

Chapter 42 Exercise Management for the Obese Patient 529
John M. Jakicic, PhD, David O. Garcia, MS, and Renee J. Rogers, MS

Chapter 43 Dietary Management of the Overweight and Obese Patient 537
Eileen Stellefson Myers, MPH, RD, LDN, FADA, Raymond A. Plodkowski, MD, Maureen Molini-Blandford, MPH, RD, CSSD, and Sachiko T. St. Jeor, PhD, RD

Chapter 44 Pharmacological Management of the Obese Patient 547
Donald Schumacher, MD and Nikhil Dhurandhar, PhD

Chapter 45 Surgery for Severe Obesity 571
Robert F. Kushner, MD, MS and Lisa M. Neff, MD, MS

Chapter 46 Future Directions in Obesity Research and Treatment 583
Risa J. Stein, PhD, Katie Birkenfeld, and Rachel MacPhee

PART X Immunology and Infectious Disease
David Nieman, DrPH, FACSM

Chapter 47 Exercise, Inflammation, and Respiratory Infection 597
David C. Nieman, DrPH, FACSM

Chapter 48 Chronic Exercise and Immunity: Practical Applications 605
Paul M. Coen, PhD and Michael G. Flynn, PhD

Chapter 49 HIV Infection: Exercise and Immune Function 615
Jason R. Jaggers, MS, PhD and Gregory A. Hand, PhD, MPH

Chapter 50 Exercise, Aging, and Immunity 625
Jeffrey A. Woods, PhD, Brandt D. Pence, PhD, Stephen A. Martin, BS and Marc D. Cook, MS

PART XI Pulmonary Medicine
Nicholas A. Smyrnios, MD

Chapter 51 Respiratory Symptoms 635
Jeremy B. Richards, MD, MA and Richard M. Schwartzstein, MD

Chapter 52 Chronic Obstructive Pulmonary Disease 651
Crescens M. Pellecchia, DO, MS and J. Mark Madison, MD

Chapter 53 Asthma 659
David Ciccolella, MD and Gilbert E. D'Alonzo, DO

Chapter 54 Pulmonary Rehabilitation 677
Emil Lambert G. Tigas, MD

Chapter 55 Food Allergy and Anaphylaxis 689
Michelle E. Conroy, MD

Chapter 56 Influenza 699
Gail Scully, MD, MPH

Chapter 57 Indoor Air Quality 709
Ramesh Donepudi, MD, MRCP and Anthony C. Campagna, MD, FCCP

PART XII Sports Medicine and Orthopedics
Eric McCarty, MD and Sourav K. Poddar, MD

Chapter 58 Sports Supplements 721
Morteza Khodaee, MD, MPH, John Spittler, MD, and Stacy R. Livingwell, MD

Chapter 59 Prevention of Injury 729
Bradley J. Sandella, DO and Eugene Hong, MD, CAQSM, FAAFP

Chapter 60 Female Athlete Triad 739
Stephanie M Chu, DO and Matthew Leiszler, MD

Chapter 61 The Role of Rehabilitation in Injury Management 745
Joy Anderson, PT, ATC, CSCS and Andrea Fetzer, MS, ATC

Chapter 62 Physiology of the Athlete: Bioenergetics, Performance, Physiological Testing, and Monitoring 757
Iñigo San Millán, PhD

Chapter 63 Evaluation of Acute Sports Injuries in the Adult Athlete 773
Rebecca Sjostrom, MD, Eric McCarty, MD, Jennifer FitzPatrick, MD, Amy K. MacDougall, MD, and Lucas Rylander, MD

Chapter 64 Concussion in Sport 789
Kelsey Logan, MD, MPH, FAAPL, FACP and Paul Gubanich, MD, MPH

Chapter 65 Scientific Basis for the Use of Modalities in Sports Medicine 799
Tara Jo Manal, PT, DPT, OCS, SCS, Anna Shovestul, PT, DPT, OCS, Laura A. Schmitt, PT, DPT, OCS, SCS, ATC, DCE, and Lynn Snyder-Mackler, PT, ScD, FAPTA

PART XIII Obstetrics and Gynecology

Hope A. Ricciotti, MD

Chapter 66 Preconception Care 821
Katharyn Meredith Atkins, MD

Chapter 67 Nutrition and Lifestyle for a Healthy Pregnancy 831
Hope A. Ricciotti, MD

Chapter 68 Exercise in Pregnancy 841
Kristin Bixel, MD

Chapter 69 Breast-Feeding 853
Julia Head, MD, Stephanie-Marie L. Jones, MD, and Marcie K. Richardson, MD

Chapter 70 Contraception 867
Sadia Haider, MD, MPH

Chapter 71 Prevention, Screening, and Treatment of Sexually Transmitted Infections 885
Maria Wachendorf Fradinho, MD

Chapter 72 Maintaining a Healthy Pelvic Floor through Childbirth and Menopause 899
Sybil Dessie, MD and Eman Elkadry, MD

Chapter 73 Risk Reduction and Screening for Women's Cancers 911
Jo Marie Tran Janco, MD

Chapter 74 Preventing Medical Errors in Obstetrics and Gynecology 927
Toni Golen, MD

PART XIV Dermatology

Zoe Diana Draelos, MD

Chapter 75 Nutritional Deficiencies, Diseases, and the Skin 939
Christopher Mazur, BS and David H. McDaniel, MD

Chapter 76 Aging and the Skin 953
Omer A. Ibrahim, MD, Diana Bolotin, MD, PhD, and Murad Alam, MD, MSCI

Chapter 77 Sun and the Skin 965
Amy Y.-Y. Chen, MD and Henry W. Lim, MD

Chapter 78 Exercise and the Skin 977
Brian B. Adams, MD, MPH

Chapter 79 Skin Care 991
Zoe Diana Draelos, MD

PART XV Cardiovascular Rehabilitation and Secondary Prevention

Kathy Berra, MSN, NP-C, FAACVPR, FAAN and Barry A. Franklin, PhD, FAHA, FACSM, MAACVPR

Chapter 80 Stress Testing for the Coronary Patient: Beyond ST Segment Depression 1005
Eileen M. Hsich, MD, FACC, Benico Barzilai, MD, and Gordon Blackburn, PhD

Chapter 81 Exercise Prescription for the Coronary Artery Disease Patient 1017
Peter H. Brubaker, PhD and James H. Ross, MS

Chapter 82 Contemporary Guidelines for Cardiac Rehabilitation 1027
Randal J. Thomas, MD, MS

Chapter 83 Benefits and Risks of Exercise for the Coronary Patient 1037
Barry A. Franklin, PhD, FAHA, FACSM, MAACVPR and Kashish Goel, MD

Chapter 84 Psychosocial Considerations in Coronary Heart Disease: Implication for Cardiac Rehabilitation 1053
James A. Blumenthal, PhD and Elizabeth C.D. Gullette, PhD

Chapter 85 Evaluation and Treatment of the Patient with Peripheral Arterial Disease 1067
Kerry J. Stewart, EdD, FAHA, MAACVPR, FACSM

Chapter 86 Impact of Medical Therapy on Cardiovascular Secondary Prevention 1075
Reynaria Nieva, MD, Ahsan Achtchi, DO, Danny J. Eapen, MD, Allen L. Dollar, MD, FACC, FACP, Jefferson Baer, MD, MPH, Kreton Mavromatis, MD, and Laurence S. Sperling, MD, FACC, FACP, FAHA

Chapter 87 Exercise-Based Cardiac Rehabilitation: Outcomes and Expectations 1101
Carl J. Lavie, MD, FACC, FACP, FCCP, Richard V. Milani, MD, FACC, FAHA, and Ross A. Arena, PT, PhD, FAHA

Chapter 88 Future of Cardiovascular Disease Prevention and Rehabilitation 1109
Kathy Berra, MSN, NP-C, FAACVPR, FAAN, Nancy Houston Miller, BSN, FAACVPR, and Shannon Hamilton, BA

Chapter 89 Secondary Prevention: It's a Family Affair 1113
Laura L. Hayman, PhD, MSN, Semira Semino-Asaro, MSN, RN, and Eileen M. Stuart-Shor, PhD, ANP

PART XVI Lifestyle Components of Pediatric Medicine

Thomas W. Rowland, MD

Chapter 90 Pediatric Preventive Medicine: An Introduction 1123
Thomas W. Rowland, MD

Chapter 91 Childhood Obesity and Metabolic Syndrome 1131
Scott Owens, PhD

Chapter 92 Arterial Function in Children: Effect of Exercise and Lifestyle 1141
Bo Fernhall, PhD

Chapter 93 Prevention of Osteoporosis and Bone Fragility: A Pediatric Concern 1155
Saija Kontulainen, BSc, MSc, PhD and Donald Bailey, MA, MSc, PED

Chapter 94 Identification and Management of Children with Elevated Cholesterol Levels 1163
Frank R. Greer, MD and Stephen R. Daniels, MD, PhD

Chapter 95 Cardiovascular Risk Factors and Physical Activity in Children 1171
Lars Bo Andersen, PhD, Dr Med Sci and Robert G. McMurray, PhD, FACSM

Chapter 96 Prenatal Influences on Future Health 1181
Debbie A. Lawlor, MB, ChB, MPH, MSc, PhD, Marie-Jo A. Brion, BA, MSc, PhD, Laura D. Howe, MSc, PhD, and Abigail Fraser, PhD, MPH

PART XVII Family Practice

Charles B. Eaton, MD, MS

Chapter 97 Introduction to Family Medicine Section 1199
Charles B. Eaton, MD, MS

Chapter 98 Office-Based Physical Activity Counseling in Healthy Adults 1201
Charles B. Eaton, MD, MS, Arnold Goldberg, MD, and Emma Simmons, MD, MPH

Chapter 99 Exercise Prescription for Patients with Chronic Health Problems 1209
Carol Ewing Garber, PhD, RCEP, FACSM, FAHA

Chapter 100 Nutrition Counseling in a Busy Office Practice 1215
Kim M. Gans, PhD, MPH, LDN, Kelli Drenner, PhD, and Gemma Gorham, MPH

Chapter 101 e-Health Resources to Support Lifestyle Medicine and Management 1227
David K. Ahern, PhD and Judith M. Phalen, MPH

Chapter 102 Pharmacogenomic Tailored Therapy for Smoking Cessation: The Promise of Personalized Medicine 1235
Aditi Mallick, AB and Sean P. David, MD, SM, DPhil

PART XVIII Lifestyle Medicine in Geriatrics

Charlotte A. Tate, PhD

Chapter 103 Lifestyle Medicine and the Older Population: Introductory Framework 1243
Charlotte A. Tate, PhD

Chapter 104 Aging Successfully: Predictors and Pathways 1247
Debra J. Rose, PhD

Chapter 105 Role of Physical Activity in Successful Aging 1257
Wojtek J. Chodzko-Zajko, PhD and Andiara Schwingel, PhD

PART XIX Epidemiology of Lifestyle-Related Diseases

Alan C. Utter, PhD, MPH, FACSM

Chapter 106 Epidemiology of Child and Adolescent Obesity 1271
Jennifer Utter, PhD, MPH

Chapter 107 Epidemiology and Prevention of Type 2 Diabetes 1281
Edward W. Gregg, PhD

Chapter 108 Physical Activity and Aging 1289
Caroline A. Macera, PhD

Chapter 109 Sex Differences in the Prevention and Treatment of Hypertension: The Physiological Responses to Exercise 1297
Scott R. Collier, PhD, FACSM

PART XX Health Promotion

Kenneth R. Pelletier, PhD, MD

Chapter 110 Health Promotion in the Workplace 1303
Catherine M. Baase, MD and John White, PhD

Chapter 111 Health Promotion in Health Systems 1311
Nicolaas P. Pronk, PhD and Thomas E. Kottke, MD, MSPH

Chapter 112 Financial Impact of Worksite Health Management Programs and Quality of the Evidence 1325
Seth Serxner, PhD, MPH, Daniel Gold, PhD, and Kristin Parker, PhD, MPH

Chapter 113 Future of Health Promotion in the Twenty-First Century 1337
Dee W. Edington, PhD and Alyssa Schultz, PhD

PART XXI Exercise Psychology

Steven J. Petruzzello, PhD

Chapter 114 Taking Stock of Where We Are in Understanding Mind/Body Interactions in the Exercise Domain 1353
Steven J. Petruzzello, PhD, Tina A. Greenlee, MS, Paula Y.S. Poh, MA, and Megan Nickrent, MS

Chapter 115 Genetic Influences on Regular Exercise Behavior 1367
Marleen H.M. de Moor, PhD and Eco J.C. De Geus, PhD

Chapter 116 Influence of Physical Activity on Brain Aging and Cognition: The Role of Cognitive Reserve, Thresholds for Decline, Genetic Influence, and the Investment Hypothesis 1379
Maureen K. Kayes, MS and Bradley D. Hatfield, PhD, FACSM, FNAK

Chapter 117 Physical Activity and Anxiety 1397
Katharina Gaudlitz, MSc, Brigitt-Leila von Lindenberger, MSc, and Andreas Ströhle, MD

Chapter 118 Physical Activity and Depression 1409
Chad D. Rethorst, PhD and Madhukar H. Trivedi, MD

Chapter 119 Redrawing the Model of the Exercising Human in Exercise Prescriptions: From Headless Manikin to a Creature with Feelings 1421
Panteleimon Ekkekakis, PhD, FACSM

Chapter 120 Determinants of Physical Activity: Research to Application 1435
Claudio R. Nigg, PhD, Ryan E. Rhodes, PhD, and Katie R. Amato, BS

PART XXII Injury Prevention

David A. Sleet, PhD, FAAHB

Chapter 121 Injuries and Lifestyle Medicine 1447
David A. Sleet, PhD, FAAHB, Michael F. Ballesteros, PhD, and Grant T. Baldwin, PhD, MPH

Chapter 122 Patient Counseling for Unintentional Injury Prevention 1457
Michael F. Ballesteros, PhD and Andrea Gielen, ScD

Chapter 123 Preventing Traffic Injuries: Strategies That Work 1463
Ann M. Dellinger, MPH, PhD and David A. Sleet, PhD, FAAHB

Chapter 124 Child Injury: The Role of Supervision in Prevention 1473
Barbara A. Morrongiello, PhD and Michael R. Corbett, MA

Chapter 125 Preventing Injuries at Home 1485
Karin A. Mack, PhD and Karen DeSafey Liller, PhD

Chapter 126 Falls and Fall Injuries among Older Adults....1495

Judy A. Stevens, MS, MPH, PhD, Grant T. Baldwin, PhD, MPH, Michael F. Ballesteros, PhD, Rita K. Noonan, PhD, and David A. Sleet, PhD, FAAHB

Chapter 127 Preventing Repeat Intimate Partner Violence 1507

Samantha Illangasekare, PhD, MPH and Andrea Gielen, ScD

Chapter 128 Sports and Recreation-Related Traumatic Brain Injury....1519

Victor G. Coronado, MD, MPH, Lisa C. McGuire, PhD, Michael R. Lionbarger, MPH, Marlena M. Wald, MPH, MLS, Kelly Sarmiento, MPH, and Julie Gilchrist, MD

PART XXIII Public Policy and Environmental Supports for Lifestyle Medicine

Gregory W. Heath, DHSc, MPH, FACSM, FAHA

Chapter 129 Lifestyle Medicine in an Era of Healthcare Reform—2011 1533

Gary B. Wilkerson, EdD, ATC and Gregory W. Heath, DHSc, MPH, FACSM, FAHA

Chapter 130 Policy and Environmental Supports in Promoting Physical Activity and Active Living....1539

Gregory W. Heath, DHSc, MPH, FACSM, FAHA and Paul M. Gordon, PhD, MPH, FACSM, FAHA

Chapter 131 Public Policy and Environmental Supports for Healthy Eating 1545

Zaida Cordero-MacIntyre, PhD, PharmD, MPH, REHS, MS, RD and Alyssa Mompoint, MPH

Chapter 132 Building Strategic Alliances to Promote Healthy Eating and Active Living....1551

Risa Wilkerson, MA, Elizabeth A. Baker, PhD, MPH, and Matt M. Longjohn, MD, MPH

Chapter 133 Obesity and Health 1557

James M. Rippe, MD and Theodore J. Angelopoulos, PhD, MPH

Preface

An overwhelming body of scientific and medical literature supports the concept that daily habits and actions exert an enormous influence on short- and long-term health and quality of life. This influence may be either positive or negative. Hundreds, if not thousands, of studies provide evidence that regular physical activity, maintenance of a healthy weight, not smoking cigarettes, and following sound nutritional and other health-promoting practices all profoundly impact health.

Since the publication of the first edition of *Lifestyle Medicine* (Blackwell Science, 1999), this literature has grown even stronger and more robust. Clearly, the time has come to update and summarize this information in one place and bring it to the attention of physicians and other health care workers with the hope and belief that it will impact on the way they practice medicine. This has been the goal and challenge of the second edition of *Lifestyle Medicine*.

The strength of the literature supporting the health impact of daily habits and actions is underscored by their incorporation into virtually every evidence-based clinical guideline addressing the prevention and treatment of metabolic diseases. For example, the following guidelines and consensus statements from various prestigious medical organizations all provide significant emphasis on lifestyle medicine principles and practices as key components of the prevention and treatment of disease:

- *JNC VII Guidelines for Hypertension, Prevention and Treatment*
- *NCEP (ATP III) Guidelines for Cholesterol Management*
- *Institute of Medicine Guidelines for Obesity Management*
- *Guidelines from the American Heart Association for the Prevention and Management of Coronary Artery Disease*
- *Guidelines from the American Diabetes Association for the Management of Diabetes*
- *Dietary Guidelines for Americans 2010*
- *American Heart Association Nutrition Implementation Guidelines*
- *Guidelines from the American Academy of Pediatrics for the Prevention and Treatment of Childhood Obesity*
- *Guidelines from the American Academy of Pediatrics for Heart Disease Risk Factor Reduction in Children*
- *Guidelines from the American Heart Association and the American Academy of Pediatrics for the Prevention and Treatment of the Metabolic Syndrome*
- *American Heart Association Strategic Plan for 2020*
- *Joint Statement from the American Heart Association and American Cancer Society for the Prevention of Heart Disease and Cancer*

Despite the widespread recognition in evidence-based guidelines of the important role lifestyle measures and practices play in the prevention and treatment of metabolic diseases, little progress has been made in improving the habits and actions of the American population. In some instances, risk factors for chronic diseases have actually gone in the opposite direction and increased over the last decade. Consider the following:

- More than 70% of the adult population in the United States does not get enough physical activity to result in health benefits.
- Over two-thirds of the adult population in the United States are either overweight or obese (a staggering 40% increase over the past 20 years).
- Less than one-third of the adult population gets adequate servings of fruits and vegetables and follows other simple, evidence-based nutritional principles related to good health.
- Of the adult population in the United States, 20.6% still smoke cigarettes.
- The prevalence of diabetes in the United States has doubled in the past 20 years.
- The metabolic syndrome is now thought to be present in 25% to 35% of the adult population in the United States.
- Over one-third of the adult population in the United States has high blood pressure.
- Cardiovascular disease, which remains the leading killer of both men and women in the United States resulting in 37% of all mortality each year, has multiple lifestyle factors as underlying risk factors.
- The choice of an inactive lifestyle increases an individual's risk of developing heart disease as much as smoking a pack of cigarettes per day.
- Obesity is the leading cause of osteoarthritis in women and the second leading cause in men.
- Obesity is the second leading cause of cancer in the United States and is projected to surpass cigarette smoking in the next decade.

Despite these grim statistics, an impressive body of evidence has also emerged regarding how powerful daily practices, when incorporated into a positive lifestyle, can be in

lowering risk factors and promoting good health. For example, the Nurses' Health Study demonstrated that 80% of all heart disease and over 91% of all diabetes in women could be eliminated if they would adopt a cluster of positive lifestyle practices, including maintenance of a healthy body weight (BMI of 19–25 kg/m^2), regular physical activity (30 min or more on most days), not smoking cigarettes, and following a few simple nutritional practices such as increasing whole grain and consuming more fruits and vegetables. The U.S. Health Professionals Study showed similar dramatic reductions in men from these same positive behaviors. In fact, if individuals adopted only one of these positive behaviors, their risk of developing coronary artery disease would be cut in half.

Furthermore, proper nutrition has been demonstrated to significantly decrease the likelihood of developing diseases—most prominently, obesity, diabetes, and cancer. Physical activity has been repeatedly shown to lower the risk of heart disease and many cancers. Smoking cessation has been clearly associated with increased risk of cancer and chronic obstructive pulmonary disease. The benefits of smoking cessation are profound and occur rapidly.

Even small amounts of weight loss substantially lower the risk of developing chronic disease. For example, in the Diabetes Prevention Program individuals with baseline glucose intolerance, who increased physical activity and lost 5%–7% of their body weight, reduced their risk of developing diabetes by 58%.

In addition to the adverse health consequences of poor lifestyle decisions, these choices also carry a significant economic burden. Each year, the United States spends more than $6700 for every man, woman, and child on what is essentially "sickness" care. In contrast, virtually every other industrial economy spends considerably less. For example, Greece, which ranks as the 16th largest economy in the world, spends less than $600 annually for every man, woman, and child on health care. Yet, Greece achieves superior outcomes on virtually every recognized international standard of health outcomes than does the United States. Every other industrialized economy also spends less money per capita than the United States and often achieves superior health outcomes.

Poor lifestyle choices such as lack of physical activity, poor nutritional choices, smoking cigarettes, and failure to maintain a healthy body weight all represent significant risk factors for such costly diseases as diabetes, coronary artery disease, and cancer. Clearly, until we can make a positive impact on lifestyle measures and practices in modern medical care, we will not solve this enormous financial drain on the American economy as well as the toll of human lives. These facts have been recognized in the recent health care reform debate in the United States and are incorporated into the Accountable Care Organization guidelines.

As the literature relating lifestyle practices and habits has grown deeper and more complex, the challenge for physicians and other health care professionals has become even more daunting to keep abreast of this ever-expanding field and incorporate the findings into the modern medical practice. This challenge is all the more complex since the literature relating to lifestyle and health is spread over a wide variety of disciplines, journals, and textbooks. The need to summarize the evidence behind lifestyle and health into one comprehensive textbook that spans the field of lifestyle medicine has become clearer as the evidence has become deeper and more persuasive. This is what we have attempted to accomplish with the second edition of *Lifestyle Medicine*.

I was proud to serve as the editor of the first edition of *Lifestyle Medicine* that was published in 1999. With this initial comprehensive volume, we coined the term "lifestyle medicine," summarized key findings across multiple disciplines as they existed in the late 1990s, and launched a new emphasis in medicine related to the links between daily behaviors and outcomes. Subsequently, the field of lifestyle medicine has grown dramatically and has matured significantly. There is now an academic, peer-reviewed journal in lifestyle medicine (the *American Journal of Lifestyle Medicine*, SAGE Publications). Physician competencies have been published based on the recommendations from major medical groups, including the American Medical Association, the American College of Physicians, the American Academy of Pediatrics, the American College of Sports Medicine, the American College of Preventive Medicine, and others.

In addition, an academic medical society has been established for physicians and other health care workers (the American College of Lifestyle Medicine) and an educational track in lifestyle medicine is now offered at the American College of Preventive Medicine's annual meeting.

While the field of lifestyle medicine is still in its infancy, there is clearly momentum. It is also clear that the academic discipline relating to short- and long-term health consequences of daily habits and actions will be called lifestyle medicine.

A key consideration for incorporating information and counseling concerning lifestyle and health will be broad acceptance of this imperative in the physician community. While most physicians and other health care professionals support the general concept that physical activity, proper nutrition, weight management, not smoking, and other behaviors profoundly impact on health, incorporation of counseling and information in these areas into the daily practice of medicine has lagged. This is extremely unfortunate since multiple surveys have demonstrated that physician recommendation is the leading reason why individuals change actions and habits. Moreover, 75% of the adult population in the United States sees a primary care physician at least once a year. The opportunity to underscore the links between lifestyle habits and practices and health outcomes is, therefore, extremely large.

So what is "lifestyle medicine"? We defined lifestyle medicine in the first edition of this reference book as "the integration of lifestyle practices into the modern practice of medicine both to lower the risk factors for chronic disease and/or, if disease is already present, serve as an adjunct in its therapy. Lifestyle medicine brings together sound, scientific evidence in diverse health related fields to assist the clinician

in the process of not only treating disease, but also promoting good health." While this definition was put forth over a decade ago, the connections between daily habits and health outlined in this initial formulation remain the fundamental premise behind the field of lifestyle medicine and the organizing principle behind the second edition of our textbook.

With this definition providing the intellectual framework for the textbook, the second edition of *Lifestyle Medicine* is divided into 23 parts based on key disciplines related to lifestyle medicine. The second edition is approximately 20% longer than the first edition. All chapters have been fundamentally rewritten or substantially revised and brought up to date with current understandings and references. Many new chapters and several new parts have been added to reflect the modern understandings and enormous changes that have occurred in lifestyle medicine since the publication of the first edition.

The second edition of *Lifestyle Medicine* opens with Part I on "Lifestyle Management and Prevention of Cardiovascular Disease." We chose to open the second edition with an in-depth exploration concerning lifestyle and cardiovascular disease for several reasons. First, I am a cardiologist, and as such, my initial interest in lifestyle practices and health related specifically to measures designed to lower the risk of cardiovascular disease. Second, the area of cardiovascular medicine has been a leader in identifying linkages between lifestyle-related risk factors and risk of heart disease. Third, despite very significant progress in multiple areas of cardiovascular disease, it remains the leading killer of both men and women in the United States. Finally, it seemed appropriate to open the second edition of *Lifestyle Medicine* with issues in cardiovascular disease, since the American Heart Association has clearly articulated the central role of lifestyle practices and cardiovascular health as a key component in its strategic plan for the year 2020.

Part II on "Nutritional Aspects of Lifestyle Medicine," underscores the key role that nutrition plays in multiple aspects of health and disease. This part contains in-depth analyses of the clinical implications of the Dietary Guidelines for Americans 2010 as well as an extensive discussion of how to evaluate nutritional status and nutrient intakes. Special populations are the focus of several chapters, including nutrition for the active adolescent, nutrition for elite athletes, and nutrition for older adults. An important new chapter relates to how nutrition principles and behaviors can be communicated to patients to help them achieve healthy lifestyles. Part III on "Physical Activity and Fitness" provides clinically important information on how to evaluate physical fitness and prescribe exercise. In addition, since physical activity and exercise are so key to positive lifestyle measures and health, there are individual chapters on these behaviors scattered throughout the book in disease- or condition-specific sections.

Part IV on "Behavioral Psychology" starts from the premise that most of the issues related to lifestyle medicine involve approaches to changing behavior. This part provides an outstanding, clinically relevant framework for how to apply psychological theories to the promotion of healthy lifestyles. These theories have been applied in subsequent chapters within this part to approaches for enhancing adherence to exercise prescription, smoking cessation, and weight loss and maintenance.

Part V on "Women's Health" has been expanded and updated to cover important emerging data in this key area. Chapters on breast health, osteoporosis, and physical activity are complemented by new chapters on menopause, osteoporosis, and wellness coaching for women's lifestyle choices. Part VI on "Men's Health" is an entirely new part that addresses key considerations for this medically underserved population. Mental health issues, nutrition for men's health, and management and prevention of urological diseases as well as health promotion and risk reduction specifically geared toward men are welcome, new, and timely contributions to this important area of the book.

A new part on "Endocrinology and Metabolism" (Part VII) provides in-depth discussions of diabetes, glucose intolerance, and the metabolic syndrome as well as the use of lifestyle measures in their prevention and treatment. Part VIII on "Lifestyle Issues in the Prevention and Treatment of Cancer" is another new part that will be highly relevant to every practicing clinician. Such topics as obesity, physical activity, and nutrition and their role in cancer prevention and treatment are discussed in depth as well as their role in cancer survivorship.

Part IX on "Obesity and Weight Management" remains a key part in our textbook. In a sense, obesity represents the quintessential lifestyle disease since nutrition, exercise, pharmacologic management, and surgery all play significant roles. The linkage between the immune system and infectious disease is also an important and often underappreciated area of both research and clinical application. The role of exercise both in immune function, infections, and aging is ably discussed with current understandings from the research literature in Part X on "Immunology and Infectious Disease."

Part XI on "Pulmonary Medicine" has been totally reworked with updated chapters on asthma and pulmonary rehabilitation and new chapters on indoor air quality and influenza among others. This expanded part will be of great interest to all clinicians.

"Sports Medicine and Orthopedics" (Part XII) occupy prominent places in lifestyle medicine. The greatly expanded part in these areas focuses not only on injury prevention and treatment, but also on rehabilitation and sports supplements. The new chapter on concussions in sports is particularly timely given the recent emphasis on this underdiagnosed condition both in professional and amateur sports.

Part XIII on "Obstetrics and Gynecology" remains a great strength in this textbook with several new chapters and a complete rewriting and updating of all previous chapters. This part adds further depth and clinical relevance to the expanded commitment to women's health issues found in this edition of *Lifestyle Medicine*. Part XIV on "Dermatology" is greatly expanded based on new understandings from research with an emphasis on clinical applications. Particularly important are completely revised

chapters on sun and the skin, exercise and the skin, and overall approaches to skin care for the active individual.

Part XV on "Cardiovascular Rehabilitation and Secondary Prevention" complements the opening part on "Lifestyle Management and Prevention of Cardiovascular Disease." Important advances have occurred both in cardiovascular rehabilitation and the secondary prevention of cardiovascular disease. These topics are admirably discussed with modern evidence-based understandings emphasized.

The power of a positive lifestyle clearly extends into the pediatric population. The modern epidemic of pediatric obesity in the United States and the accompanying dramatic increases in both diabetes and metabolic syndrome in the pediatric population are discussed in detail in the Part XVI on "Lifestyle Components of Pediatric Medicine" as are specific guidelines and recommendations for prescribing pediatric exercise and prevention of osteoporosis. An important new chapter on prenatal influences on future health summarizes modern understandings of an emerging area about how the earliest influences on risk factors may occur in utero. The chapter on cholesterol management in children provides an evidence-based discussion to what has become a controversial topic.

The greatly expanded Part XVII on "Family Practice" provides a comprehensive approach to how busy family practitioners can integrate lifestyle measures and counseling into their daily practice of medicine. Practical advice and recent evidence concerning exercise and nutritional counseling as well as ehealth resources are all discussed in detail. Part XVIII is a new part on "Lifestyle Medicine and Geriatrics" that corrects a significant omission from the first edition of our textbook. The concept of "successful aging" that has gained considerable momentum in the last decade is discussed in detail as are practical strategies for increasing physical activity in the older population.

The greatly expanded Part XIX on "Epidemiology of Lifestyle-Related Diseases" provides a useful framework for the application of epidemiologic principles to both identify and potentially help ameliorate multiple lifestyle-related problems. Part XX on "Health Promotion" has been greatly expanded to include modern understandings of health promotion in the workplace and managed care. This field has grown exponentially in the last 15 years. This part concludes with a provocative chapter on the future of health promotion, taking the reader from current successes in health promotion to an expanded role for corporate health promotion in the future of medicine.

The greatly expanded Part XXI on "Exercise Psychology" moves beyond the part on "Exercise and Sport Psychology," which was contained in the first edition of *Lifestyle Medicine*. New tools and new approaches to understanding mind–body interactions as well as the genetic influences on behavior are discussed in detail. Physical activity and its relationship to anxiety and depression are also thoroughly discussed. A new and important chapter on the impact of physical activity on brain aging and cognitive function is a highlight of this part. A new chapter on how psychological issues help determine the level of physical activity provides new insights for how research can impact on practical application.

Part XXII is a new part on "Injury Prevention" that represents another highlight of the second edition. Injuries are a very significant component of lifestyle medicine and also often underappreciated by practicing clinicians. This part, with an internationally prominent group of contributors, organized by the Division of Unintentional Injury Prevention at the Centers for Disease Control and Prevention, provides a broad approach to research in injury prevention and how it is impacting on the practice of lifestyle medicine.

The final part on "Public Policy and Environmental Supports for Lifestyle Medicine" (Part XXIII) reminds us that we do not practice medicine in a vacuum. Public policy issues concerning health care reform and public and environmental supports for physical activity, healthy eating, and obesity prevention all play important roles in the modern practice of medicine.

The work of generating this comprehensive volume in *Lifestyle Medicine* involved the talent of 25 outstanding part editors who have devoted great energy and talent to the difficult task of organizing and editing parts to be not only scientifically accurate but clinically useful. What has emerged from their efforts and those of the over 200 distinguished contributors is a textbook that I hope and believe will be clinically useful to the practicing health care professional while providing state-of-the-art summaries and practical applications of modern scientific and medical understandings related to the interaction between lifestyle practices, modern medicine, and good health. This dual emphasis can only help all of our patients lead happier, healthier, and more productive lives while lowering their risk of developing the chronic diseases that are so endemic in our society.

Over the last 14 years since the publication of the first edition of *Lifestyle Medicine*, important new information has emerged to provide the scientific links between daily habits and actions and their impact on short- and long-term health and quality of life. The key consideration now will be for those of us in the health care community to apply these understandings to the modern practice of medicine. This is, in my view, the single greatest opportunity that we have to improve health outcomes and lower costs. This is crucial to bringing additional value to the practice of medicine. It is, in essence, both the challenge and opportunity for the future of lifestyle medicine.

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Acknowledgments

Textbook writing and editing are collaborative efforts. Individuals who have contributed to my thinking about the interaction between lifestyle and health over many years are too numerous to acknowledge all by name. I would, however, like to acknowledge a few individuals who have made particularly important contributions to the second edition of *Lifestyle Medicine*.

First, I would like to thank my long-time editorial director, Elizabeth Grady, who plays a critically important role in all of the major writing and editing projects that emerge from my research organization. The second edition of *Lifestyle Medicine* is one of over 40 books that Beth has managed, which have been generated through our organization. In addition, she provides editorial direction to two academic journals that I edit and coordinates a variety of other academic endeavors. Beth's superb organization skills, hard work, and unfailing good humor make these difficult projects possible.

I would also like to thank the 25 section editors who contributed hard work and outstanding editorial skills to ensure scientific accuracy and clinical relevance for each of the sections of this textbook. I am deeply grateful to all of these individuals. A special thanks also to the more than 200 scientists and clinicians who have contributed chapters to this textbook. These individuals, who are experts in the key fields related to lifestyle medicine, have made invaluable contributions to assemble and explain vast amounts of data in this emerging discipline.

I would also like to express appreciation to my office support staff including my executive assistant, Carol Moreau, who seamlessly coordinates my schedule and travel plans to free up the time necessary for such large writing and publishing projects. Our office assistant, Deb Adamonis, assists all of us in multiple daily tasks required to expedite diverse projects in our office, while our chief financial officer, Connie Martell, makes sure that processes are in place for all our projects to move forward smoothly.

The research team at Rippe Lifestyle Institute (RLI) has contributed numerous insights and helped clarify my thinking on a number of aspects of lifestyle medicine. This team is admirably led by Dr. Ted Angelopoulos, who has been a friend and colleague for many years as well as a coauthor and collaborator on multiple papers, books, and other projects. Josh Lowndes directs the day-to-day processes and work flow of the research team, while Amy Stachnik coordinates the day-to-day interactions with multiple research sponsors and the patient population of Rippe Health Evaluation, our executive health program. Noy Supaswud, our research office manager and my executive assistant in Florida, does a superb job in coordinating this large research team and my work schedule when I am at our research facilities in this location.

I would like to thank the superb editorial team at Taylor & Francis Group/CRC Press: Randy Brehm, senior editor, who was an early and key supporter of this project; Jessica Vakili, who coordinated all aspects of the publication process and provided important day-to-day leadership and invaluable assistance on multiple issues related to manuscripts; and Ira Wolinsky, who was an early and strong supporter of this project. We would also like to thank Richard Tressider, project editor at Taylor & Francis Group/CRC Press. who managed every step of the production process with expertise, patience and knowledge. Arun Kumar Aranganathan of SPi Global managed the editing, design, and typesetting of this book with great skill.

Finally, I am grateful to my family including my loving wife, Stephanie Hart Rippe, and our four beautiful daughters, Hart, Jaelin, Devon, and Jamie, who continue to love and support me through the arduous process of editing major textbooks and journals and the other diverse professional responsibilities I juggle along with family life.

If there are errors or omissions in *Lifestyle Medicine*, the responsibility is mine. If there is credit due for this project, it belongs to the numerous people who have made substantial contributions along the way.

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Over the past 25 years, Dr. Rippe has established and run RLI, the largest research organization in the world that explores how daily habits and actions impact short- and long-term health and quality of life. RLI has published hundreds of papers that form the scientific basis for the fields of lifestyle medicine and high-performance health. It also conducts numerous studies every year on physical activity, risk factor reduction, nutrition, and healthy weight management.

A lifelong and avid athlete, Dr. Rippe maintains his personal fitness with a regular walk, jog, swim, and weight training program. He holds a black belt in karate and is an avid wind surfer, skier, and tennis player. He lives outside of Boston with his wife, television news anchor Stephanie Hart, and their four children, Hart, Jaelin, Devon, and Jamie.

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Part I

Lifestyle Management and Prevention of Cardiovascular Disease

James M. Rippe, MD

1 Rationale for Intervention to Reduce the Risk of Coronary Artery Disease

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CONTENTS

Introduction 4
Pathophysiology of Atherosclerosis 4
Understanding Risk Factors 5
Concept of Risk Factors 5
Relative Risk versus Absolute Risk 5
Primary versus Secondary Prevention 5
Primordial Prevention and "Ideal" Cardiovascular Health 5
Implementing Risk Factor Reduction Guidelines 6
Scientific Basis for Risk Factor Reduction 6
Modifiable Risk Factors 6
Tobacco Use 6
Dyslipidemias 7
Elevated Low-Density Lipoprotein Cholesterol and Hyperlipidemia 7
Low Levels of HDL Cholesterol 7
Hypertriglyceridemia 7
Hypertension 7
Diabetes and Glucose Intolerance 7
Obesity 8
Inactive Lifestyle 9
Poor Nutritional Habits 10
Non-Modifiable Risk Factors 10
Age 10
Gender 10
Family History 11
Metabolic Syndrome and the Concept of Multiple Risk Factors 11
Emerging Risk Factors 11
High-Sensitivity C-Reactive Protein 11
Other Markers of Inflammation 11
Hemostatic Factors 11
Homocysteine 11
LDL Subclasses and Particle Size 12
Lipoprotein (a) 12
Other Risk Factors 12
Levels of Antioxidants 12
Alcohol 12
Stress and Type A Personality 12
Depression 12
Future Trends in Risk Factor Assessment 12
Direct Plaque Imaging 12
Genomic Approaches 13
New Risk Factor Scoring Systems 13
Implementation of Risk Factor Reduction Strategies 13
Conclusions 13
References 13

INTRODUCTION

Cardiovascular disease remains the leading cause of death for both men and women in the United States each year [1]. Over 37% of all mortality in the United States comes from cardiovascular disease [2]. Although knowledge of many factors contributing to coronary heart disease (CHD) is incomplete, it is clear that many risk factors contribute in significant ways to the ongoing epidemic of cardiovascular disease.

Lifestyle habits and practices constitute a significant contributor to this ongoing epidemic. While progress has been made in some of these areas (e.g., hypertension, total cholesterol, smoking cessation, physical activity), unfortunately, regression has occurred in such areas as obesity and diabetes [3]. The increasing prevalence of these latter two conditions has the potential to wipe out progress made on all the other lifestyle-related risk factors for CHD [3].

In addition to its human cost, CHD also represents an enormous financial drain in the United States. It has been estimated that over $150 billion per year is spent on direct medical expenses and other associated costs related to CHD [4,5].

Lifestyle factors play a particularly prominent role in the development and pathogenesis of CHD. Indeed, five of the major risk factors for developing CHD relate to lifestyle practices: (1) the choice of whether or not to use tobacco products, (2) level of physical activity, (3) control of lipids, (4) diabetes, and (5) obesity. In this chapter, we will focus on the rationale for intervening to reduce risk factors for CHD. The next chapter will discuss applications of lifestyle interventions in clinical practice to reduce the risk of CHD.

Deaths from CHD and stroke have been declining in the United States for the past four decades. For example, between 1963 and 1990 the mortality of CHD fell by more than 50% [6]. Nonetheless, CHD and stroke remain the leading causes of morbidity and mortality in the United States and in most other industrialized countries. The decline in CHD and stroke is a result of not only reduced prevalence of risk factors but also advances in treatment and therapies. Nonetheless, the increased prevalence of diabetes and obesity and an aging population work against reductions in CHD and stroke prevalence and require expanded efforts to reduce lifestyle-related risk factors in order to continue reducing the burden of CHD.

Between 1980 and 2000, the decline in the age-related death for CHD led to an estimated decrease of 341,745 deaths [3]. About half of this decline resulted from improvements and advances in treatment while approximately 44% related to risk factor reduction. An estimated 149,635 fewer deaths from CHD came from improved treatment [3] of some of its risk factors while an estimated 59,370 increase in deaths occurred from the higher rates of obesity and diabetes [3]. As depicted in Figure 1.1, the increasing prevalence of obesity and diabetes has the potential to completely wipe out the advances in the reduction of other risk factors if the trends of these two lifestyle risk factors are not reversed.

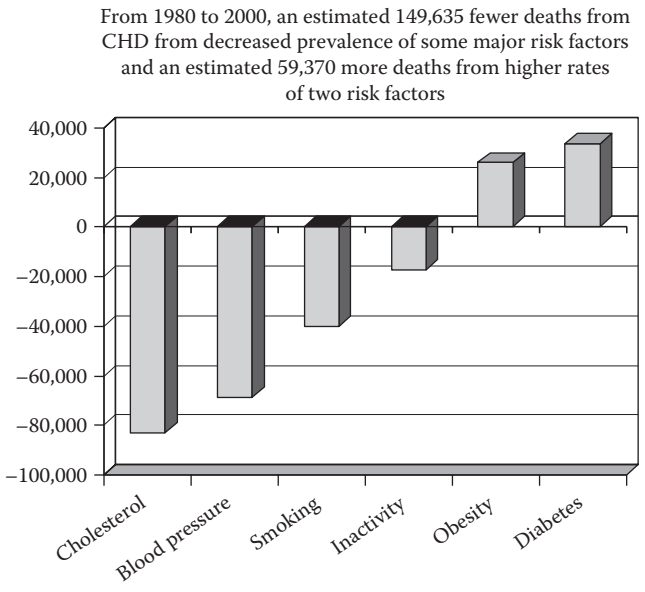


FIGURE 1.1 Impact of lifestyle choices on CVD. (From Ford, E.S. et al., *N. Engl. J. Med*., 256, 2388, 2007.)

Despite advances in reducing certain lifestyle-related risk factors for CHD, these factors remain extremely common. For example, the prevalence of hypertension in the United States has continued to increase with recent data suggesting that more than one-third of American adults have high blood pressure [7]. The Surgeon General's Report on Physical Activity and Health documented that over 70% of the adult population in the United States fail to get enough regular physical activity to lower their risk of CHD [8], despite the fact that the *2008 Physical Activity Guidelines for Americans* demonstrate multiple health benefits for virtually every population group [9]. Overweight and obesity has continued to rise in the United States with over 68% of the population showing one of these two conditions [10].

The epidemic of diabetes in the United States continues to rise with approximately 9% of the adult population currently suffering from this chronic condition—almost double the rate of 20 years ago [11]. After several decades of encouraging declines in cigarette smoking, progress unfortunately appears to have leveled off in this area with about 20% of the overall population in the United States still smoking [12]. Thus, some progress in reducing risk factors has occurred, but enormous challenges and opportunities remain for applying lifestyle measures often, in conjunction with pharmaceutical therapy, to reduce the risk of CHD.

Pathophysiology of Atherosclerosis

As knowledge of the pathophysiology of atherosclerosis has advanced, new understandings have provided crucial linkages to the role of various lifestyle interventions in reduction of risk of CHD. For example, the role of poor

diet (e.g., elevated consumption of saturated fats, etc.) and diminished physical activity have been known for years to contribute to atherogenesis [13,14]. However, only in the past decade has the significant role for inflammation as an initiating event in the process of atherosclerosis begun to be elucidated. Since multiple related entities such as CHD, obesity, diabetes, glucose intolerance, and the metabolic syndrome have significant overlap, it may indeed be a component of systemic inflammation that unites all of these processes.

Fundamental to the understanding of the interplay between lifestyle and atherosclerosis is the evolving concept of the role of various structures and the interaction of components of both normal and diseased arteries (e.g., endothelium, smooth muscle, and intima) as well as how various cells in these structures function both in health and disease [15–17].

The evolving understanding of the biology of atherosclerosis is beyond the scope of the current chapter. The reader is referred to several recent excellent reviews that discuss current understanding of the atherosclerotic process in detail [17,18].

UNDERSTANDING RISK FACTORS

Concept of Risk Factors

The concept of risk factors is relatively new in the history of medicine. In fact, until the initial findings from the Framingham Study were published in the 1960s, the concept of risk factors for CHD did not formally exist [19]. Framingham data showed that factors such as diabetes [20–23], dyslipidemia [24–28], high blood pressure [29–32], and cigarette smoking [33–36] each independently and significantly increased the risk of CHD. Recently, the concept of CHD risk factors has been expanded to include physical inactivity [33,37] and obesity [38]. Other emerging risk factors where lifestyle habits and practices may play a role are under active investigation.

Framingham data also demonstrated that risk factors act synergistically and tend to cluster with each other [39]. Thus, in the presence of two risk factors, an individual quadruples their chance of developing CHD compared to individuals with no risk factors. Individuals with three risk factors increase their risk of developing CHD between 8- and 20-fold compared to individuals with no risk factors [40].

In addition to the lifestyle-related risk factors identified by the Framingham Study and other observational and interventional studies, other risk factors have been determined including age, gender, family history of CHD, elevated C-reactive protein (CRP), hemostatic factors, excessive alcohol consumption, hypertriglyceridemia, elevated homocysteine levels, and perhaps stress and other psychological factors such as depression.

Numerous studies have demonstrated that reducing risk factors for CHD can significantly decrease its likelihood [41–43]. Lifestyle measures are a particularly powerful and effective way of lowering risk factors since these measures are low risk and many of them simultaneously affect multiple risk factors.

Relative Risk versus Absolute Risk

It is important to differentiate between "relative" and "absolute" risk since this distinction underlies treatment strategies for risk factor reduction in CHD. *Relative risk* is a comparison between different risk levels. It compares the likelihood that an individual who possesses a specific risk factor will develop CHD in comparison to an individual without that risk factor. *Absolute risk* represents the likelihood of developing CHD over a specified period of time. Framingham risk scores, for example, typically assess the absolute risk of developing CHD over a 10 year period.

The difference between relative and absolute risk is a critical factor in clinical decision making. For example, a young individual with abnormal lipids would be treated differently than an older individual with a similar lipid profile, all other things being equal; since their increased relative risk may be the same, their absolute risk may be quite different [44–46].

One way of viewing relative risk may be that it provides an indication of how rapidly an individual may move to absolute risk. Thus, a young individual with high relative risk would be at greater risk of ultimately developing high absolute risk and motivates the clinician to devise strategies for lowering risk as a means of slowing the early stages of developing CHD. Such interventions as lifestyle measures which carry multiple benefits and relatively little risk and expense are attractive means for lowering both relative and absolute risk of CHD.

Primary versus Secondary Prevention

It is also important to distinguish between "primary" and "secondary" prevention when approaching risk factor reduction. Primary prevention is based on the goal of preventing or delaying the development of CHD while secondary prevention focuses on interventions designed to reduce the likelihood of repeat cardiovascular events and/or mortality in individuals who already have established CHD. More aggressive measures for risk factor reduction are typically indicated in individuals when they are used in secondary prevention (see Chapters 83 and 88).

Guidelines for risk factor reduction in primary prevention are available from a variety of sources. Perhaps, the most widely used is the Framingham Risk Scoring System [47]. Guidelines for interventions for secondary prevention have also been published by the American Heart Association and are discussed in detail in Chapters 83 and 88.

PRIMORDIAL PREVENTION AND "IDEAL" CARDIOVASCULAR HEALTH

In 2010, the American Heart Association issued a strategic plan through the year 2020 and beyond [48]. New to this plan was a concept of "primordial" prevention. The goal of primordial prevention as articulated by AHA is "that by 2020 to

improve the cardiovascular health of Americans by 20% while reducing deaths from cardiovascular and stroke by 20%." In issuing this statement, the AHA recognized and declared that "Health is a broader, more positive construct than just the absence of clinically evident disease." It defined "primordial" prevention as a process to avoid adverse levels of risk factors in the first place rather than trying to reduce risk factors when they are already present or treating already established disease. This broader risk factor reduction strategy is completely consistent with the goals and vision of lifestyle medicine and will require careful attention to daily lifestyle habits and actions and their impact on risk factors and overall health.

The AHA Strategic Plan [48] also defined a construct of "ideal" cardiovascular health which was defined as the following:

> The simultaneous presence of four favorable health behaviors: absence of smoking within the last year, physical activity at goal, consumption of a "heart healthy" dietary pattern and an ideal body mass index (BMI).
>
> Simultaneous presence of four favorable health factors: absence of smoking for at least one year, untreated cholesterol less than 200 mg/dL, untreated blood pressure less than <120/<80 mm Hg, and the abstinence of diabetes mellitus, absence of clinical cardiovascular disease (including CHD, stroke, heart failure, etc.).

Clearly, this very welcome framework will result in an increased emphasis on physicians treating, and patients following, positive lifestyle behaviors to improve their cardiovascular health.

IMPLEMENTING RISK FACTOR REDUCTION GUIDELINES

Another welcome trend in the area of risk factor reduction comes from the *Dietary Guidelines for Americans 2010* [49], Physical Activity Guidelines for Americans 2008 [9,50], and American Heart Association Scientific Statement on Implementing Pediatric and Adult Nutrition Guidelines [51]. All three of these guidelines have emphasized real world, practical implementation of guidelines. This is an important and new emphasis from these three widely read and influential documents.

SCIENTIFIC BASIS FOR RISK FACTOR REDUCTION

Multiple observational and interventional studies, including the Framingham Study [52], the Nurses Health Trial [53], the U.S. Male Professional Health Trial, and the Women's Health Initiative [54], have all demonstrated the link between risk factors and developing CHD as well as the power of reducing risk factors to reduce the likelihood of developing CHD. Results from these and other studies form the basis for recommendations in the following sections on specific risk factors.

MODIFIABLE RISK FACTORS

This section will focus on risk factor reduction for those risk factors which can be modified, while the next section will focus on those risk factors which cannot be modified. The modifiable risk factors represent a particularly important area for clinical intervention. Numerous studies have demonstrated that lifestyle measures for reducing modifiable risk factors are an effective strategy for reducing the risk of developing CHD.

Tobacco Use

Cigarette smoking is the leading preventable cause of death from all causes in the United States and the single most prevalent modifiable risk factor for the development of CHD [55]. CHD causes 35%–40% of smoking-related deaths and an additional 8% has been attributed to secondhand smoke exposure [56,57].

Unfortunately, following many years of declines in cigarette smoking prevalence in the United States, the percentage of adults who smoke has recently stabilized at about 20% [12]. Rates of tobacco use are actually increasing among adolescents, young adults, and women [12].

The link between cigarette smoking and increased risk of CHD has been established in multiple studies. Individuals who consume 20 or more cigarettes/day have a two- to threefold increase in CHD. Framingham Study data demonstrated that cardiovascular mortality increases 31% in women and 18% in men for each 10 cigarettes smoked per day [58]. Multiple observational studies have also shown that smokeless tobacco and low tar cigarettes do not reduce the risk of CHD.

Numerous studies have demonstrated that smoking cessation improves longevity and reduces the risk of CHD [58]. Thus, stopping cigarette smoking remains the single most important intervention in preventive cardiology and lifestyle medicine. Smoking cessation yields significant benefits in a relatively short period of time [59]. In one study comparing 1282 cigarette smokers to 2068 controls, the risk of developing CHD among those individuals stopping cigarette smoking approached the level of never smokers within 3 years [60]. In addition to contributing greatly to the risk of CHD, cigarette smoking also significantly increases the likelihood of developing lung cancer and chronic obstructive pulmonary disease.

Despite the important and powerful health benefits of cigarette smoking cessation, the medical community has not been active enough in this area. The Centers for Disease Control and Prevention (CDC) estimates that only slightly more than half of smokers who had at least one physician visit in the previous year reported were advised to quit smoking cigarettes [61]. The impact of spouse, friends and families on cigarette smoking cessation is also significant. Recent studies suggest that smoking cessation by a spouse decreases an individual's chance of smoking by 67% while smoking cessation by a coworker, sibling, or friend contributes to a person's decrease in likelihood of smoking by 25%–36% [62].

Dyslipidemias

Numerous trials have demonstrated that a variety of dyslipidemias or combination of dyslipidemias increase the risk of CHD [42,63–73].

Elevated Low-Density Lipoprotein Cholesterol and Hyperlipidemia

Hypercholesterolemia has been clearly associated with increased risk of CHD. In particular, increased plasma levels of low-density lipoprotein (LDL) have been associated with increased incidence of CHD. Based on these data, the Nutrition Cholesterol Education Program Adult Treatment Panel Guidelines (ATP III) established LDL as the primary target for intervention [74]. Numerous observational trials including the Framingham Study, MRFIT, the Nurses Health Study, and the U.S. Male Health Professional follow-up study have all demonstrated an association between elevated blood cholesterol and increased risk of CHD. Numerous interventional studies have also established that elevated blood cholesterol, and in particular elevated LDL, is associated with increased incidence of CHD [63–73]. These studies have become particularly robust since the development of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). These agents lower LDL cholesterol much more efficiently than previously available drugs. Numerous, large clinical trials where statins have been utilized to lower LDH cholesterol by 20%–60% reduced coronary events by up to one-third over a 5 year period without evidence of increased nonvascular mortality [41].

Low Levels of HDL Cholesterol

A number of prospective cohort studies have also demonstrated an inverse relationship between high-density lipoprotein (HDL) cholesterol and risk of CHD. Conversely, low HDL increases the risk of CHD [42]. Each increase in HDL cholesterol by 1 mg/dL is associated with a 2%–3% decrease in risk of total cardiovascular disease [41]. Low HDL cholesterol has been defined as an HDL lower than 40 mg/dL. Levels lower than this are defined as an independent risk factor for CHD in the most recent National Cholesterol Education Program Guidelines. Moreover, the NCEP Adult Treatment Panel (ATP III) Guidelines support an HDL level of >60 mg/dL as a negative risk factor for CHD [74]. It should be noted that several recent trials of novel pharmaceutical agents designed to raise HDL have been somewhat disappointing and have resulted in untoward side effects such as hypertension.

Hypertriglyceridemia

An association between elevated triglyceride levels and cardiovascular disease has been known for many years [75,76]. However, the evidence supporting a direct linkage is less robust than that for elevated LDL or low HDL and CHD. Recent attention has been focused on elevated triglycerides as a risk for heart disease, given its association with obesity, insulin resistance, and diabetes. Recently released statements from the American Heart Association on Childhood and Adolescent Obesity and on Triglycerides and Cardiovascular Health emphasize the importance of lowering triglycerides through lifestyle measures as a means of lowering risk of CHD [77]. Current designations for triglyceride levels are as follows: 150–199 mg/dL borderline high, 200–499 mg/dL high, and >500 mg/dL very high. Overall, 31% of the adult population in the United States has a triglyceride level ≥150 mg/dL [42].

Hypertension

High blood pressure constitutes a significant increased risk of CHD. The prevalence of hypertension has increased steadily in the United States over the past 10 years [78]. According to the report of the most recent Joint National Committee on Prevention, Evaluation and Treatment of High Blood Pressure (JNC VII), one out of every three adults suffers from high blood pressure [78]. This means that more than 50 million individuals have high blood pressure [78]. A subsequent report based on data from the most recent National Health and Nutrition Evaluation Survey (NHANES III) places the number even higher at 38% of the population (65 million individuals) [79]. Even individuals who have normal blood pressure at the age of 55 years have a 90% lifetime risk of developing hypertension during their lifetime according to recent data from the Framingham Heart Study [80].

The relationship between blood pressure and the risk of CHD events is independent of other risk factors for CHD. For every 10 mm Hg rise in diastolic blood pressure or 20 mm Hg rise in systolic blood pressure above 115/75 mm Hg, the increase in risk of CHD doubles [78].

The JNC VII guidelines create a lower than previously established guideline for normal blood pressure (below 120/80 mm Hg) and create a new category of "prehypertension" to replace the old category of "high normal." The JNC VII classification for blood pressure in adults is found in Table 1.1 [78].

High blood pressure is also frequently found coexisting with other risk factors for CHD. For example, individuals with high blood pressure have a greater than 40% chance of having elevated blood cholesterol [81–83]. This is particularly important since over half of heart disease occurs in individuals with two or more risk factors. JNC VII guidelines recommend a 6 month trial of lifestyle-related measures such as weight loss, smoking cessation, regular exercise, and improved nutrition for individuals with stage 1 hypertension before starting pharmacologic therapy [78].

Diabetes and Glucose Intolerance

The incidence of type 2 diabetes, which represents a major risk factor for CHD, has increased dramatically in both men and women in the United States over the past 20 years.

TABLE 1.1
Classification and Management of Blood Pressure for Adults Aged 18 Years or Older

				Management[a]		
					Initial Drug Therapy	
BP Classification	Systolic BP (mm Hg)[a]		Diastolic BP (mm Hg)[a]	Lifestyle Modification	Without Compelling Indication	With Compelling Indication
Normal	<120	and	<80	Encourage		
Prehypertension	120–139	or	80–89	Yes	No antihypertensive drug indicated	Drug(s) for the compelling indications[b]
Stage 1 hypertension	140–159	or	90–99	Yes	Thiazide-type diuretics for most and may consider ACE inhibitor, ARB, β-blocker, CCB, or combination	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed
Stage 2 hypertension	≥160	or	≥100	Yes	2-Drug combination for most and ACE inhibitor or ARB or β-blocker or CCB[c]	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed

Source: Adapted from Chobanian A.V. et al., *JAMA*, 289, 2561, 2003.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker.

[a] Treatment determined by highest BP category.

[b] Treat patients with chronic kidney disease or diabetes to BP goal of less than 130/80 mm Hg.

[c] Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

Diabetes now affects over 8% of adults [11]. Perhaps of even greater importance is that an estimated 35%–40% of adults have impaired glucose tolerance or impaired fasting glucose levels [81]. Diabetes represents a significant risk factor for CHD. Individuals with diabetes have between two and eight times higher rates of cardiovascular events, compared to nondiabetic controls [82]. This risk factor is particularly potent in women with diabetes who increase their risk of developing CHD by three- to sevenfold compared to two- to threefold increased risk in men. The increase in diabetes parallels the increase of obesity in the United States [83]. It has been estimated that individuals born in the United States in the year 2000 will have a 36% chance of developing diabetes in their lifetime [84].

For all of these reasons, prevention, early detection, and treatment of diabetes assume great importance as a modality for reducing risk of CHD. Typical treatment involves multiple components of lifestyle measures such as weight loss for individuals who are overweight or obese and regular physical activity.

Obesity

The prevalence of overweight and obesity has increased significantly in the United States and other developed countries over the past 30 years. It is estimated that over two-thirds of the adult population in the United States are now overweight or obese [10]. Increases have been particularly prominent in the area of stage 1 obesity and severe obesity. Between 1980 and 2004, the prevalence of obesity among adults in the United States doubled. In 2006, it was estimated that 35% women and 33% of men in the United States were obese [85]. Numerous studies have demonstrated that obesity constitutes a strong and independent risk factor for CHD in addition to its association with other risk factors such as dyslipidemia, diabetes, and hypertension. The American Heart Association classifies obesity as a major risk factor for CHD because of these associations.

The most practical and recognized way of assessing obesity in clinical practice is to determine an individual's body mass index (BMI). BMI has also been shown in numerous studies to correlate with health risk. BMI classifications, according to the Institute of Medicine [86], are listed in Table 1.2.

The linkages between obesity and CHD are not completely understood although they are probably mediated not only by direct effects on the cardiovascular system (a hyperdynamic state and increased blood flow) but also through systemic inflammation. Adipocytes used to be considered relatively inactive storage depots; however, recent studies have shown that, in fact, adipocytes are very metabolically active and generate a variety of inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and CRP [87–90]. Excess weight is also associated with a variety of novel risk factors including an atherogenic dyslipidemia (low HDL cholesterol, elevated triglycerides, elevated apoprotein B, and elevated LDL). In addition, obesity is associated with elevations in thrombotic factors such as plasminogen activator inhibitor I (PAI-1) and increased levels of fibrinogen [91,92].

Distribution of body fat is also strongly and independently associated with CHD over and above increased body weight. In particular, increased abdominal obesity

TABLE 1.2
Classification of Overweight and Obesity as Recommended by the National Heart, Lung, and Blood Institute Guidelines

Disease Risk[a] Relative to Normal Weight and Waist Circumference

			Waist Circumference	
	BMI (kg/m²)	Obesity Class	<102 cm (Men) <88 cm (Women)	>102 cm (Men) >88 cm (Women)
Underweight	<18.5		—	—
Normal[b]	18.5–24.9		—	—
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	1	High	Very high
	35.0–39.9	2	Very high	Very high
Extreme obesity	≥40.0	3	Extremely high	Extremely high

Source: National Heart, Lung, and Blood Institute, The practical guide: Identification, evaluation, and treatment of overweight and obesity in adults. NIH 00–4084, NIH, Bethesda, MD, 2000.

BMI, body mass index.

[a] Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.

[b] Increased waist can also be a marker for increased risk in normal weight individuals.

has been demonstrated to increase risk of CHD [93,94]. A practical way of estimating abdominal obesity is to measure waist circumference. A waist circumference of ≥40 in. in men and ≥35 in. in women confers a significantly increased risk of CHD compared to lower levels of abdominal fat.

Adult weight gain also confers additional risk of CHD. According to the Nurses' Health Study [95] and U.S. Men's Health Professional Study [96], individuals who gained 20 lb or more during their adult life significantly increased their risk of type 2 diabetes and CHD.

Inactive Lifestyle

Physical activity carries multiple health benefits [50]. Unfortunately, the population in the United States (both children and adults) has become increasingly inactive. Numerous studies have demonstrated that an inactive lifestyle significantly increases the risk of CHD. In one recent study, fitness level was more strongly associated with heart disease than any other risk factor, including cigarette smoking and hypertension [97]. The recently released Physical Activity Guidelines for Americans 2008 lists multiple significant benefits for increased physical activity as demonstrated in Table 1.3.

There is strong evidence that regular physical activity lowers the risk of high blood pressure, adverse lipid profiles, type 2 diabetes, the metabolic syndrome, and weight gain. In addition, regular physical activity also overall risk for CHD, risk for stroke, and all-cause mortality.

TABLE 1.3
From 2008 Physical Activity Guidelines for Americans

Health Benefits Associated with Regular Physical Activity—Children and Adolescents

Strong evidence

- Improved cardiorespiratory and muscular fitness
- Improved bone health
- Improved cardiovascular and metabolic health biomarkers
- Favorable body composition

Moderate evidence

- Reduced symptoms of depression

Adults and Older Adults

Strong evidence

- Lower risk of early death
- Lower risk of coronary heart disease
- Lower risk of stroke
- Lower risk of high blood pressure
- Lower risk of adverse blood lipid profile
- Lower risk of type 2 diabetes
- Lower risk of metabolic syndrome
- Lower risk of colon cancer
- Lower risk of breast cancer
- Prevention of weight gain
- Weight loss, particularly when combined with reduced calorie intake
- Improved cardiorespiratory and muscular fitness
- Prevention of falls
- Reduced depression
- Better cognitive function (for older adults)

Moderate to strong evidence

- Better functional health (for older adults)
- Reduced abdominal obesity

Moderate evidence

- Lower risk of hip fracture
- Lower risk of lung cancer
- Lower risk of endometrial cancer
- Weight maintenance after weight loss
- Increased bone density
- Improved sleep quality

The Healthy People 2010 Initiative recommends the goal that at least 30% of the population over the age of 6 years should engage in light to moderate physical activity of at least 30 min/day. This goal has been repeated in the Healthy People 2020 guidelines. Clearly, we are falling far short of these goals. The Surgeon General's Report on Physical Activity documented that 24% of individuals report no recent physical activity, 54% are active but fall short of the recommendations from Healthy People 2010 while only 22% of adults achieve this level of activity [8].

Numerous guidelines including those from the American Heart Association, the American College of Sports Medicine [98], the Centers for Disease Control, and most recently the Physical Activity Guidelines for Americans 2008 [50] all consistently recommend that adults accumulate at least 30 min of moderate intensity physical activity on most, if not

TABLE 1.4
From 2008 Physical Activity Guidelines for Americans

Classification of Total Weekly Amounts of Aerobic Physical Activity into Four Category Levels of Physical Activity	Range of Moderate Intensity	Summary of Overall Health Benefits	Comment
Inactive	No activity beyond baseline	None	Being inactive is unhealthy
Low	Activity beyond baseline but fewer than 150 min/week	Some	Low levels of activity are clearly preferable to an inactive lifestyle
Medium	150 to 300 min/week	Substantial	Activity at the high end of this range has additional and more extensive health benefits than activity at the low end
High	More than 300 min/week	Additional	Current science does not allow researchers to identify an upper limit of activity above which there are no additional health benefits

all, days. The Physical Activity Guidelines for Americans 2008 provides an alternative of 75 min/week of vigorous intensity physical activity [50]. Definitions of low, medium, and high physical activity are found in Table 1.4.

Numerous studies have shown that physician recommendation is a powerful motivator to change lifestyle habits including level of physical activity. Moreover, several studies support the finding that if the physicians themselves are physically active they are more likely to recommend physical activity to their patients [99,100]. The most common form of physical activity recommended by physicians (first choice of over 90% of physicians) is walking [101].

Poor Nutritional Habits

A large body of research supports a linkage between nutritional habits and risk of CHD. The American Heart Association Guidelines for Pediatric and Adult Nutrition [102], the *Dietary Guidelines for Americans 2010* [49], and the American Heart Association's Strategic Impact Goal Plan through 2020 and Beyond all recommend nutrition intervention to lower the risk of CHD. These guidelines are consistent in recommending lower fat, higher fiber, increased consumption of fruits and vegetables, and control of calories to maintain a healthy body weight [103].

The AHA Strategic Plan for 2020 [48] establishes the following metric for nutrition goals to lower the risk of CHD and states "in the context of diet that is appropriate in energy balance pursing an overall dietary pattern that is consistent with a DASH (Dietary approaches to Systolic Hypertension] type eating plan including, but not limited to:

- Fruits and vegetables: five of more cups per day
- Fish: two or more 3.5 servings per week" (preferably oily fish)
- Fiber rich whole grains: 1.1 g or more of fiber per 10 g of carbohydrate (three or more 1 oz equivalent servings per day)
- Sodium: <1500 mg/day
- Sugar sweetened beverages: ≤450 kcal (36 oz)/week

While these recommendations do not cover all aspects of a heart healthy diet, they represent a good starting point for physicians counseling patients about improved nutritional practices to lower the risk of CHD.

NON-MODIFIABLE RISK FACTORS

The risk factors described in the previous section can all be reduced through appropriate lifestyle practices and habits in patient's daily lives. There are also a number of non-modifiable risk factors for CHD which will be discussed in this section.

Although this second group of risk factors cannot be altered through lifestyle habits, they play an important role as part of the overall patient risk factor profile. Specifically, individuals who have significant non-modifiable risk factors should be even more strongly counseled to make appropriate lifestyle changes to alter those risk factors which are modifiable.

Age

Strong and consistent evidence associates increased age with increased risk of CHD. Approximately 80% of all fatal myocardial infarctions occur in individuals over the age of 65 [104]. Thus, in the elderly population control of modifiable risk factors assumes increasing importance. Regular physical activity, weight management, control of lipids, and blood pressure are all important areas for physicians to counsel patients over the age of 65.

Gender

More women die each year than men of heart disease, although CHD typically occurs at a younger age in men than in women [105]. Framingham Study data demonstrate that men typically display the onset of symptoms of CHD 10 years younger than women [105]. It is important to note that symptoms of CHD may present differently in women than in men. The American Heart Association "Wear Red" program has provided an important emphasis on reducing risk factors for heart disease in women [106].

Family History

A positive family history CHD before the age of 65 in a first-degree relative constitutes an independent risk factor for CHD [104]. Why CHD tends to aggregate in some families is not completely understood although it may be mediated through genetics or through risk factors that relate to lifestyle components, such as levels of physical activity, nutritional habits, dyslipidemia, or weight.

METABOLIC SYNDROME AND THE CONCEPT OF MULTIPLE RISK FACTORS

Framingham data clearly support that clustering of risk factors is common [39]. One type of clustering of risk factors has been referred to the "metabolic syndrome." While there is ongoing debate about the criteria for the metabolic syndrome [107], and numerous different definitions exist, the one most commonly employed (such as in the National Cholesterol Education Program ATP III Guidelines) [74] includes the following criteria:

- Waist circumference: >40 in.
- Blood pressure: >135/85 mm Hg
- Fasting blood glucose: >110 mg/dL
- HDL cholesterol: <40 mg/dL
- Fasting triglycerides: >150 mg/dL

According to the ATP III Guidelines if an individual has three or more of these five criteria, he or she is considered to have the metabolic syndrome.

Individuals with metabolic syndrome are at significantly higher risk for both CHD and diabetes than the general population. The ATP III Guidelines recommend that an individual with the metabolic syndrome should be treated as though they already have CHD. Data from the Framingham Study demonstrate that 60% of CHD is found in individuals who possess two or more risk factors.

Debate is ongoing about the exact mechanism through which metabolic syndrome increases the risk of CHD. Some investigators maintain that the mechanism is through insulin resistance [108]. Others have emphasized underlying inflammatory processes as part of the metabolic syndrome which link to increased risk of CHD [109]. While the metabolic syndrome and obesity are not synonymous, they are strongly linked to each other. According to Framingham Study data, obese individuals have approximately a 50% chance of having at least two other risk factors for CHD [40].

The increased prevalence of obesity in children has drawn attention to its linkage to the increasing prevalence of both diabetes and the metabolic syndrome in children [110]. While considerable controversy exists about the criteria for the metabolic syndrome in children, the American Heart Association has recommended careful exploration for other risk factors for CHD in children who are obese.

It should also be noted that recent data support that metabolic syndrome also results in a proinflammatory state. This is recognized by the most recent definition of the metabolic syndrome by the National Heart, Lung, and Blood Institute [111]. This observation is important since a proinflammatory state also occurs in diabetes, hypertension, and obesity.

EMERGING RISK FACTORS

Recent research has identified a variety of other risk factors which are associated to a greater or lesser degree with CHD. These risk factors are discussed in this section.

High-Sensitivity C-Reactive Protein

Inflammation has been identified as a key component of atherosclerothrombosis and provides an important link between plaque formation and acute rupture [112]. CRP, which is a marker of inflammation, has been identified as a significant cardiovascular CHD risk marker [113]. Numerous prospective studies have demonstrated that high-sensitivity CRP (hs-CRP) independently predicts the risk of CHD [114–119]. These data also apply not only to individuals with existing CHD but also to healthy individuals including both men and women at all age levels. Elevated hs-CRP is not only associated with obesity and diabetes but also found in increased prevalence in individuals who lead sedentary lifestyles or are cigarette smokers [113]. These findings carry significant practical implications for counseling individuals concerning a variety of lifestyle measures.

Several of the statin medications have been demonstrated to lower CRP in addition to lowering LDL cholesterol, which carries significant implications for combining pharmaceutical therapies along with lifestyle measures [120,121].

Other Markers of Inflammation

The relationship between CHD and inflammation is an area of active research. A variety of other markers of inflammation in addition to CRP have emerged as potential risk factors for CHD. Most prominently, TNF-α and IL-6 have been associated with increased risk of CHD but the data supporting these relationships are not as advanced as with CRP [41].

Hemostatic Factors

Factors that may contribute to thrombogenesis have also been associated with increased risk of CHD. Factors currently under investigation that may contribute to thrombogenesis include PAI-1, fibrinogen [122,123], and coagulation factor VII.

Homocysteine

Elevated levels of homocysteine, an amino acid derived from the degradation of methionine, have been associated with increased risk of CHD. While laboratory tests are available to assess homocysteine, studies attempting to reduce the risk

of CHD by reducing homocystine levels have not yielded promising results [124,125]. Thus, homocystine is not currently included as part of a risk factor profile.

LDL Subclasses and Particle Size

Laboratory tests are available to determine the amount of cholesterol carried by individual lipoprotein particles which are characterized by their particle size. Some studies have suggested that small, dense LDL particles may be more atherogenic than larger LDL particles [126,127]. Of note, small, dense LDL particles have been associated more frequently in obese individuals and individuals with abdominal obesity than normal weight individuals. The data have not established the association between LDL particles size and CHD risk at a level that is useful for risk factor reduction strategies.

Lipoprotein (a)

Lipoprotein (a) (Lp (a)) is an LDL particle linked to a protein by a disulfide bridge. A number of studies have supported the role for LP (a) as a determinant vascular risk [128]. However, it remains uncertain that LP (a) contributes further sensitivity or specificity to standard risk factor reduction strategies [129].

OTHER RISK FACTORS

A variety of other risk factors for CHD have been either identified or postulated to potentially influence the likelihood of its development.

Levels of Antioxidants

Initial observational studies including the Health Professional Follow-up Study [130] and the Nurses Health Trial [131] showed an association between high levels of vitamin E and other antioxidants and reduced risk of CHD. Subsequent interventional trials, however, have not corroborated these findings [132]. The American Heart Association does not currently advocate antioxidant supplementation as a means of reducing CHD risk.

Alcohol

Alcohol consumption exerts a variety of effects on the overall cardiovascular system. A number of studies have demonstrated that moderate alcohol consumption reduces the overall risk of CHD [133]. "Moderate" alcohol consumption is typically defined as no more than one to two beers, one to two glasses of wine, or one to two "shots" of distilled spirits daily. Men are typically able to drink higher amounts of alcohol within the moderate range than women because of higher levels of alcohol dehydrogenase—the enzyme in the liver that breaks down alcohol. The mechanism by which moderate alcohol consumption may reduce the risk of CHD is attributed either to increasing HDL or decreasing platelet aggregation [134]. In contrast, alcohol consumption of three alcoholic drinks per day or more has been associated with increased risk of hypertension, overall risk of heart disease, congestive heart failure, a variety of gastrointestinal cancers, and motor vehicle accidents.

Stress and Type A Personality

Some studies have supported the concept that personality type may contribute to the risk of CHD; however, these data remain controversial and inconclusive [135,136]. In particular, the anger element of Type A personality (a Type A personality is often found in individuals who are highly competitive and ambitious and perceive a constant struggle with their environment) may increase the risk of CHD. The mechanism by which stress may lead to increased risk of vascular disease is not completely understood but is possibly related to platelet and endothelial dysfunction as well as the induction of ventricular arrhythmias.

Depression

Depression has been demonstrated in a number of studies to predict CHD [137,138]. This association appears to be an independent one although depression is also associated with lack of physical activity, hypertension, and smoking [137,138]. The mechanism through which depression may increase the risk of CHD includes elevated levels of hs-CRP, increased platelet activation, and decreased heart rate variability. Depression occurs in one out of three patients with heart failure and one out of five patients with CHD. Whether therapy for depression lowers risk for CHD is uncertain.

FUTURE TRENDS IN RISK FACTOR ASSESSMENT

Some technological enhancements, both in imaging techniques and genomics, have provided opportunities which may yield more precise and individualized characterizations of atherosclerotic plaque and risk of CHD.

Direct Plaque Imaging

High-speed computed tomography (CT scanning) of the coronary arteries has been demonstrated in several studies to detect preclinical atherosclerosis [139]. Advances such as volume CT scanning (VCT) may further enhance precision and predictive value of these technologies. At the current time, these technologies remain investigational. Concern has also been raised about the potential to over interpret predictive values from imaging techniques such as coronary calcium scoring. In one study, 41% of all future vascular events occurred in individuals with a coronary calcium score lower than 100 and 17% occurred with a coronary calcium score of zero [140]. In this study, individuals with high risk scores by Framingham criteria but low coronary calcium scores still remained at high risk of CHD.

Genomic Approaches

Advances continue to be made in genetic determinants of atherothrombosis. Although this field remains in its early stages of development, progress continues to be made [141–143]. Challenges exist because of multiple gene–environment interactions. Although this remains an area of active research, no genetic markers for atherothrombosis have yet achieved clinical utility.

New Risk Factor Scoring Systems

The Framingham Risk Scoring System has contributed in substantial ways to the ability to predict the risk of CHD; however, it is limited but does not incorporate such risk factors as level of physical activity and obesity. One particularly attractive system has emerged from the New Zealand Guidelines Group which provides useful information on 5 and 10 year risk of atherosclerosis. This area remains one of active research.

Implementation of Risk Factor Reduction Strategies

One encouraging trend in risk factor reduction is an increased emphasis on more sophisticated and comprehensive approaches to implementation of currently existing risk factor reduction guidelines [49,51,102]. Both the *Dietary Guidelines for Americans 2010* [49] and the Nutrition Guidelines from the American Heart Association [51] make a substantial effort to focus on strategies for implementing existing guidelines.

CONCLUSIONS

The identification of risk factors for CHD continues to evolve and is an area of great practical relevance to clinicians. Particularly given the high level of modifiable risk factors for CHD, an enormous opportunity exists for physicians and other health care workers to counsel patients on lifestyle medicine concepts to lower their risk of CHD. Specific concepts for how to integrate lifestyle measures into clinical practice will be the topic of the next chapter.

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2 Lifestyle Strategies for Risk Factor Reduction, Prevention, and Treatment of Coronary Artery Disease

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CONTENTS

Predicting Risk 20
Assessing Risk 20
Classifying Interventions for Modifiable Risk Factors 23
Class 1 Interventions 23
Lifestyle Approach to Cigarette Smoking Cessation 23
Lifestyle Approach to Management of Dyslipidemias 24
Lifestyle Management of Hypertension 25
Pharmaceutical Measures for Cardiac Protection 26
Class 2 Interventions 27
Obesity Prevention and Management 27
Diabetes/Glucose Intolerance 28
Physical Inactivity 28
Moderate Alcohol Consumption 29
Class 3 Interventions 29
Nutritional Counseling 29
Psychological Risk Factors/Counseling 29
Postmenopausal Estrogen Therapy 29
Determinants of Behavioral Change 30
Establishing a Lifestyle Medicine Emphasis in Clinical Practice 30
Summary 30
References 30

Coronary heart disease (CHD) remains the leading killer of men and women in the United States [1]. CHD also represents one of the quintessential lifestyle-related diseases since many of the risk factors for it, including cigarette smoking [2], elevated cholesterol [3], high blood pressure [4], obesity [5], and an inactive lifestyle [6], have significant lifestyle-related components.

Lifestyle strategies can play a significant role in the reduction of risk factors for CHD as well as its prevention and effective treatment. In Chapter 1, we focused on the rationale for employing lifestyle strategies for risk factor reduction. The current chapter provides practical strategies for employing these modalities in clinical practice for the prevention and treatment of CHD.

Lifestyle interventions also represent an important strategy for physicians and other health care workers to assist patients in lowering their risk factors as well as preventing CHD and treating individuals with established CHD. These lifestyle-related strategies are particularly valuable since they carry very little risk and may simultaneously reduce multiple risk factors for CHD. Furthermore, the American Heart Association has articulated a vision to pursue "primordial" risk factors meaning the prevention of risk factors in the first place. Lifestyle measures will be key components of this strategy [7].

Furthermore, lifestyle measures are already incorporated as key recommended early intervention steps in most of the major, evidence-based guidelines either prior to or in conjunction with pharmaceutical therapy to help patients lower the risk of CHD [3,4,8–15]. Unfortunately, many health care workers still do not properly emphasize these measures in their daily clinical practices. In addition, reimbursement models currently provide disincentives for using these strategies since lifestyle interventions are typically not covered by health insurance plans. It is hoped that with aspects of the Health Care Reform Act [16], particularly the Accountable Care Organizations provision, financial models will be developed to encourage these low cost, potentially high-yield lifestyle measures.

In addition to the financial disincentives, lack of time may also represent another hurdle. Delivery of those measures related to prevention of CHD recommended by the

TABLE 2.1
Evidence-Based Guidelines That Employ Lifestyle Measures to Reduce the Risk of CHD and Other Metabolic Conditions

- National Cholesterol Education Program
- JNC VII Guidelines for Prevention and Management of Hypertension
- Institute of Medicine Guidelines for Management of Obesity
- Guidelines for the American Heart Association for the Prevention and Management of Coronary Artery Disease
- Guidelines from the American Diabetes Association for the Management of Diabetes
- Dietary Guidelines for Americans
- American Heart Association Nutrition Implementation Guidelines
- Guidelines from the American Academy of Pediatrics for the Prevention and Treatment of Childhood Obesity
- Guidelines from the American Academy of Pediatrics for Heart Disease Risk Factor Reduction in Children
- Guidelines from the American Heart Association and American Academy of Pediatrics for the Prevention and Treatment of Metabolic Syndrome
- Joint statement from the American Heart Association and American Cancer Society on the Prevention of Heart Disease and Cancer

U.S. Preventive Health Services Task Force has been estimated to take the typical clinician a minimum of 1.5 h/day in non-reimbursable time [17]. Thus, it will be important in clinical practice to find ways to deliver proven lifestyle interventions with efficient strategies that are time sensitive.

A representative listing of national guidelines that incorporates lifestyle medicine emphasis in the treatment of CHD or as a strategy for lowering risk factors for related metabolic conditions are found in Table 2.1.

Health care professionals can be enormously influential in helping patients take positive lifestyle actions to lower their risk of CHD. Health care providers' recommendations to make changes in behaviors such as cigarette smoking cessation, weight loss, or improved nutrition have all been demonstrated to play important roles in lowering risk factors for CHD. Numerous studies have shown that the public perceives medical professionals as a reliable and credible source of information concerning health-related behaviors [18–24]. Often, however, health care workers underestimate how powerful their role as health counselors can be. For example, <50% of smokers report receiving advice to quit from their physician [25] and <40% of obese individuals report receiving advice about weight loss. This is unfortunate since the average adult in the United States visits a physician's office more than five times per year and it has been estimated that physicians come in contact with over 75% of adults in the United States in any given year [26]. In addition to physicians, nutritionists, nurses with an interest and background in preventive cardiology or diabetes education, and other health care professionals can play critically important roles in counseling patients on positive lifestyle behaviors to lower their risk of CHD.

It should also be noted that the majority of patients who make lifestyle behavior changes do this without formal participation in an organized program. For example, over 90% of individuals who have stopped smoking have done this without formal smoking cessation programs [27]. Furthermore, the majority of patients who lose weight also do this on their own. Nonetheless, health care professional recommendations and support can be very valuable to motivate patients to start and maintain the process of behavioral change.

It is particularly important that physicians play a proactive role in this area. At the current time, physician office visits represent a missed opportunity to promote behavioral changes. It is hoped that the advent of such organizations as the American College of Lifestyle Medicine [28] and the lifestyle medicine track in the American College of Preventive Medicine [29] will help physicians build the knowledge, basic skills, and confidence needed to make these recommendations. A recent "blue ribbon" panel of physicians representing most major medical organizations has urged physicians to become involved in lifestyle medicine and outlined a series of competencies in this area [30]. Furthermore, the Health Care Reform Act [16] including the Accountable Care Provision will increasingly mandate that physicians become active in this area.

PREDICTING RISK

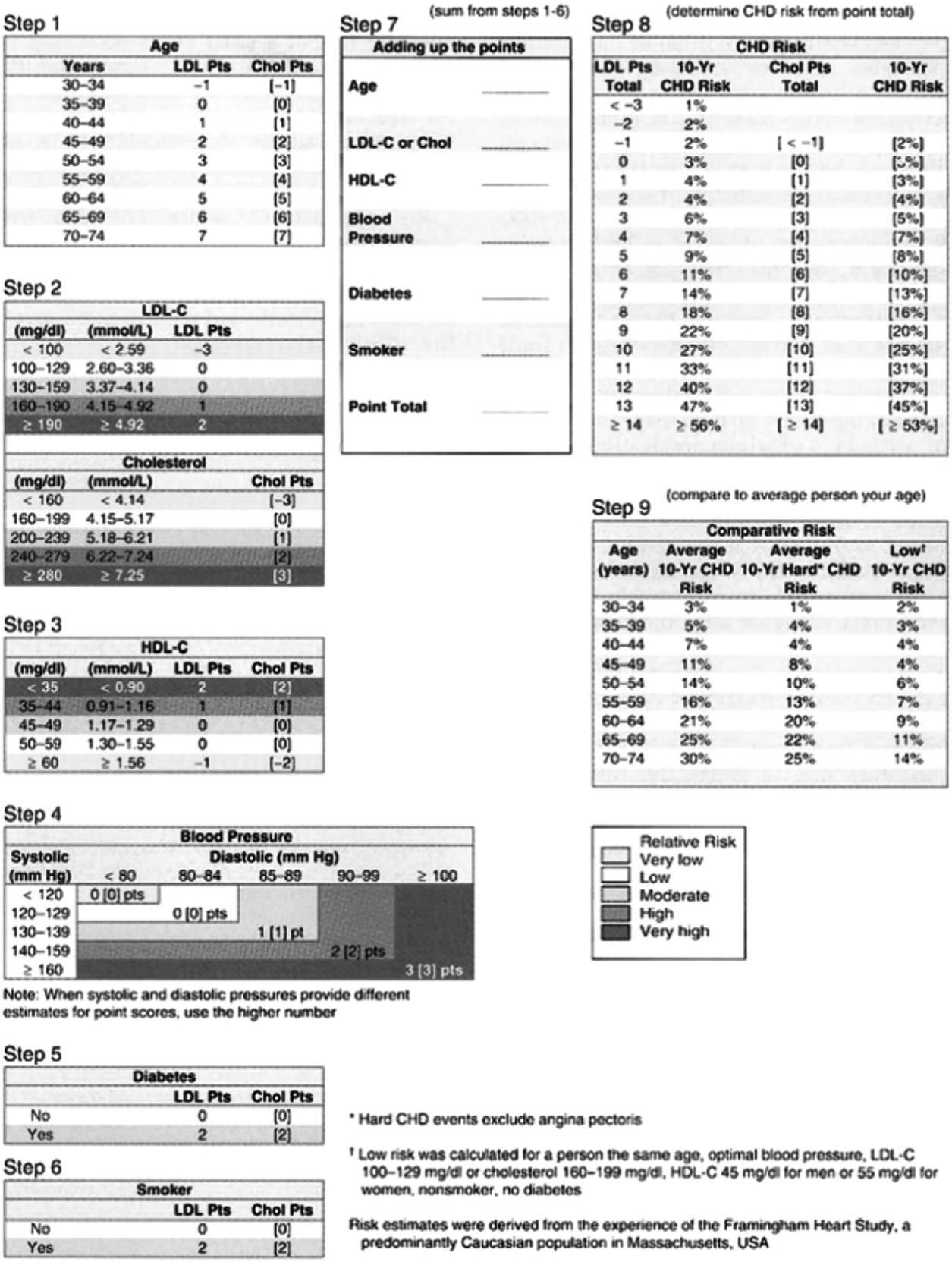
A key first step prior to using lifestyle measures to lower risk factors for CHD involves predicting risk. Risk prediction involves understanding the type and strength of evidence underlying risk factor assessment strategies as well as clearly understanding the difference between relative risk and absolute risk (see Chapter 1).

Most currently employed, evidence-based frameworks for lowering risk factors for CHD involve assessing absolute risk. For example, lowering absolute risk underlies the strategies for the National Cholesterol Education Program ATP-III Guidelines [3], the American Diabetes Association Guide of Managing Diabetes [9], and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [4].

ASSESSING RISK

Multiple frameworks are available for assessing risk of CHD. The most widely used and the one recommended by the American Heart Association is the framework developed by the Framingham Heart Study investigators [31]. This is found in Figures 2.1 and 2.2. Figure 2.1 is used to assess risk for men and Figure 2.2 is used to assess risk for women. The Framingham framework is based on estimating an individual's 10 year risk of developing CHD. The higher the 10 year risk, the more intensity of intervention is warranted.

It should be noted that there are alternatives to the Framingham score. For example, the Reynolds Risk Score provides a variation to the Framingham Score by incorporating whether a parent suffered myocardial infarction (MI) before the age of 60 years as well as high-sensitivity CRP (hs-CRP) level [32,33]. The Reynolds Score appears to be a better predictor of individuals in the middle risk category and is comparable to the Framingham Risk Score for individuals with low or high risk.



Step 1

Age		
Years	LDL Pts	Chol Pts
30–34	−1	[−1]
35–39	0	[0]
40–44	1	[1]
45–49	2	[2]
50–54	3	[3]
55–59	4	[4]
60–64	5	[5]
65–69	6	[6]
70–74	7	[7]

Step 2

LDL-C		
(mg/dl)	(mmol/L)	LDL Pts
< 100	< 2.59	−3
100–129	2.60–3.36	0
130–159	3.37–4.14	0
160–190	4.15–4.92	1
≥ 190	≥ 4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
< 160	< 4.14	[−3]
160–199	4.15–5.17	[0]
200–239	5.18–6.21	[1]
240–279	6.22–7.24	[2]
≥ 280	≥ 7.25	[3]

Step 3

HDL-C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
< 35	< 0.90	2	[2]
35–44	0.91–1.16	1	[1]
45–49	1.17–1.29	0	[0]
50–59	1.30–1.55	0	[0]
≥ 60	≥ 1.56	−1	[−2]

Step 4

Blood Pressure					
Systolic (mm Hg)	Diastolic (mm Hg) < 80	80–84	85–89	90–99	≥ 100
< 120	0 [0] pts				
120–129		0 [0] pts			
130–139			1 [1] pt		
140–159				2 [2] pts	
≥ 160					3 [3] pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 7 (sum from steps 1-6)

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL-C	_____
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point Total	_____

Step 8 (determine CHD risk from point total)

CHD Risk			
LDL Pts Total	10-Yr CHD Risk	Chol Pts Total	10-Yr CHD Risk
< −3	1%		
−2	2%		
−1	2%	[< −1]	[2%]
0	3%	[0]	[3%]
1	4%	[1]	[3%]
2	4%	[2]	[4%]
3	6%	[3]	[5%]
4	7%	[4]	[7%]
5	9%	[5]	[8%]
6	11%	[6]	[10%]
7	14%	[7]	[13%]
8	18%	[8]	[16%]
9	22%	[9]	[20%]
10	27%	[10]	[25%]
11	33%	[11]	[31%]
12	40%	[12]	[37%]
13	47%	[13]	[45%]
≥ 14	≥ 56%	[≥ 14]	[≥ 53%]

Step 9 (compare to average person your age)

Comparative Risk			
Age (years)	Average 10-Yr CHD Risk	Average 10-Yr Hard* CHD Risk	Low† 10-Yr CHD Risk
30–34	3%	1%	2%
35–39	5%	4%	3%
40–44	7%	4%	4%
45–49	11%	8%	4%
50–54	14%	10%	6%
55–59	16%	13%	7%
60–64	21%	20%	9%
65–69	25%	22%	11%
70–74	30%	25%	14%

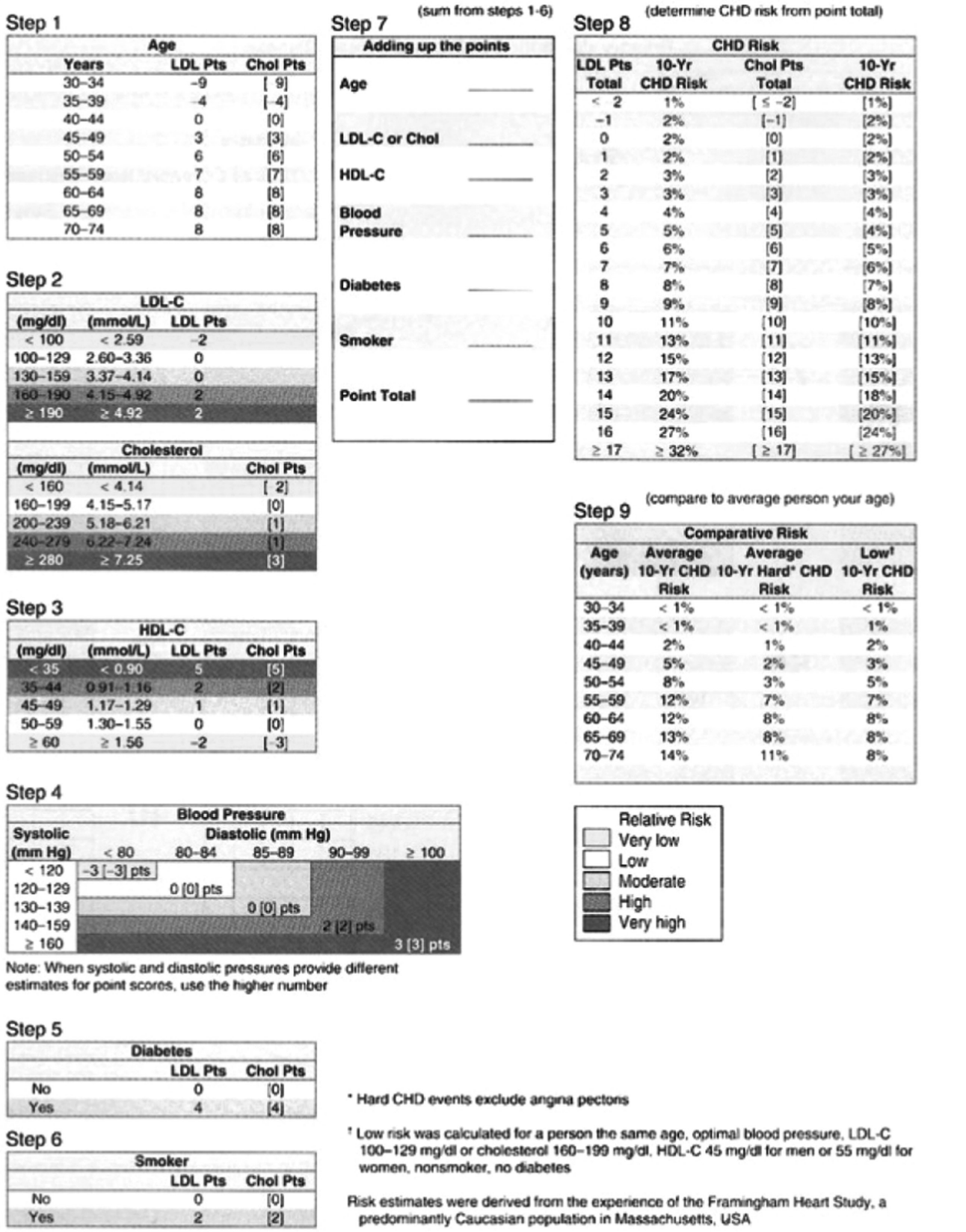
Relative Risk
Very low
Low
Moderate
High
Very high

* Hard CHD events exclude angina pectoris

† Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100–129 mg/dl or cholesterol 160–199 mg/dl, HDL-C 45 mg/dl for men or 55 mg/dl for women, nonsmoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

FIGURE 2.1 CHD score sheet for calculating 10 year CHD risk according to age, total cholesterol (TC) (or low-density lipoprotein cholesterol [LDL-C]), high-density lipoprotein cholesterol (HDL-C), blood pressure, diabetes, and smoking. Score sheet for men based on the Framingham experience in men 30–74 years at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC of 160 to 199 mg/dL (or LDL-C of 100–129 mg/dL), no diabetes, and no smoking.



Step 1

Age		
Years	LDL Pts	Chol Pts
30–34	-9	[9]
35–39	-4	[-4]
40–44	0	[0]
45–49	3	[3]
50–54	6	[6]
55–59	7	[7]
60–64	8	[8]
65–69	8	[8]
70–74	8	[8]

Step 2

LDL-C		
(mg/dl)	(mmol/L)	LDL Pts
< 100	< 2.59	-2
100–129	2.60–3.36	0
130–159	3.37–4.14	0
160–190	4.15–4.92	2
≥ 190	≥ 4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
< 160	< 4.14	[2]
160–199	4.15–5.17	[0]
200–239	5.18–6.21	[1]
240–279	6.22–7.24	[1]
≥ 280	≥ 7.25	[3]

Step 3

HDL-C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
< 35	< 0.90	5	[5]
35–44	0.91–1.16	2	[2]
45–49	1.17–1.29	1	[1]
50–59	1.30–1.55	0	[0]
≥ 60	≥ 1.56	-2	[-3]

Step 4

Blood Pressure					
Systolic (mm Hg)	Diastolic (mm Hg)				
	< 80	80–84	85–89	90–99	≥ 100
< 120	-3 [-3] pts				
120–129		0 [0] pts			
130–139			0 [0] pts		
140–159				2 [2] pts	
≥ 160					3 [3] pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	4	[4]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 7 (sum from steps 1-6)

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL-C	_____
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point Total	_____

Step 8 (determine CHD risk from point total)

CHD Risk			
LDL Pts Total	10-Yr CHD Risk	Chol Pts Total	10-Yr CHD Risk
< 2	1%	[≤ -2]	[1%]
-1	2%	[-1]	[2%]
0	2%	[0]	[2%]
1	2%	[1]	[2%]
2	3%	[2]	[3%]
3	3%	[3]	[3%]
4	4%	[4]	[4%]
5	5%	[5]	[4%]
6	6%	[6]	[5%]
7	7%	[7]	[6%]
8	8%	[8]	[7%]
9	9%	[9]	[8%]
10	11%	[10]	[10%]
11	13%	[11]	[11%]
12	15%	[12]	[13%]
13	17%	[13]	[15%]
14	20%	[14]	[18%]
15	24%	[15]	[20%]
16	27%	[16]	[24%]
≥ 17	≥ 32%	[≥ 17]	[≥ 27%]

Step 9 (compare to average person your age)

Comparative Risk			
Age (years)	Average 10-Yr CHD Risk	Average 10-Yr Hard* CHD Risk	Low† 10-Yr CHD Risk
30–34	< 1%	< 1%	< 1%
35–39	< 1%	< 1%	1%
40–44	2%	1%	2%
45–49	5%	2%	3%
50–54	8%	3%	5%
55–59	12%	7%	7%
60–64	12%	8%	8%
65–69	13%	8%	8%
70–74	14%	11%	8%

Relative Risk
Very low
Low
Moderate
High
Very high

* Hard CHD events exclude angina pectoris

† Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100–129 mg/dl or cholesterol 160–199 mg/dl, HDL-C 45 mg/dl for men or 55 mg/dl for women, nonsmoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

FIGURE 2.2 Score sheet for women based on Framingham experience in women 20–74 years of age at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, total cholesterol (TC) of 160–199 mg/dL (or low-density lipoprotein cholesterol [LDL-C] of 100–129 mg/dL), high-density lipoprotein cholesterol (HDL-C) of 55 mg/dL, no diabetes, and no smoking. Use of the LDL-C categories is appropriate when fasting LDL-C measurements are available. Pts, points. (From Wilson, P.W. et al., *Circulation*, 97, 1837, 1998.)

Other available risk scores include Systematic Coronary Risk Evaluation Project (SCORE) developed by the European Joint Task Force utilizing studies in 12 European countries involving 250,000 individuals [34]. A more recent set of guidelines was developed by the New Zealand Guidelines Committee which assesses absolute cardiovascular risk during 5 years instead of 10 years [35].

CLASSIFYING INTERVENTIONS FOR MODIFIABLE RISK FACTORS

As outlined in Chapter 1, risk factors for CHD can be conveniently divided into "modifiable" and "non-modifiable." This framework also carries practical implications and is a commonly employed classification strategy [36]. In addition, classifications employed by the American College of Cardiology and the American Heart Association divide risk factors into four categories based on the level of evidence that modifying a particular risk factor will result in lower risk of CHD. The following four classifications are typically employed:

- *Class 1 Interventions*: These interventions involve risk factor reduction strategies that have been proven to reduce risk when used.
- *Class 2 Interventions*: This classification includes risk factors where interventions are likely to lower the incidence of events but proof is less strong than Class 1 interventions.
- *Class 3 Interventions*: This classification includes risk factors that have been clearly associated with increased risk of CHD which, if modified, might lower the likelihood of a coronary event.
- *Class 4 Interventions*: This classification includes risk factors which have been associated with increased risk of CHD which, if modified, are not likely to decrease the risk of CHD or cannot be modified.

The framework for classifications is summarized in Table 2.2.

TABLE 2.2
Framework for Risk Factor Reduction Interventions (See Text for Details)

Class 1 Interventions
- Cigarette smoking cessation
- Management of dyslipidemias
- Management of hypertension
- Pharmaceutical measures for cardiac protection

Class 2 Interventions
- Obesity prevention and management
- Diabetes/glucose intolerance management
- Physical inactivity

Class 3 Interventions
- Nutritional counseling
- Psychological risk factors/counseling
- No alcohol consumption

Class 4 Interventions
- Age
- Male gender
- Low socioeconomic status
- Family history of early onset CVD

CLASS 1 INTERVENTIONS

Lifestyle Approach to Cigarette Smoking Cessation

Cigarette smoking is the leading cause of preventable death in the United States each year resulting in an estimated 440,000 deaths [37]. More than 40% of deaths from cigarette smoking result from cardiovascular disease [38]. The 1989 Surgeon General's Report showed that smoking doubles the risk of CHD and increases CHD mortality by 50% [39]. Both of these risks increase with age and the number of cigarette smoked. Worldwide, >1 million more deaths were attributable to tobacco in the year 2000 than in 1990 [40]. Worldwide, tobacco use is estimated to be responsible for 5 million deaths per year [41]. In the United States, cigarette smoking peaked in 1955 reaching 55% of men who were smokers. The peak for women came 10 years later with >33% smoking. Since that time, cigarette smoking has substantially declined; however, the rate of decline has slowed substantially in the past decade.

Currently in the United States, 21% of adults smoke [42]. Slightly more of these individuals are men than women. Eighteen percent of women over the age of 18 years smoke and approximately 23% of men over the age of 18 years old smoke [42]. If individuals do not smoke cigarettes by the time they graduate from high school, it is highly unlikely that they will adopt this habit as adults. Smoking rates among high school seniors are slightly above 30% with more female smokers slightly higher than males [43]. Smoking also tracks with socioeconomic status. Thirty-two percent of individuals living below the Federal poverty line are smokers.

The U.S. Public Health Service has published clinical practice guidelines classifying tobacco dependency as a chronic condition requiring repeated intervention [44]. These guidelines recommend that health care professionals ask every patient about tobacco use at every clinic visit [45]. Counseling and behavior therapies are based on the following:

1. Securing social support
2. Providing problem-solving skills
3. Social support outside treatment

According to the U.S. Public Health Service Guidelines, which support a combination of counseling and pharmaceutical therapy, seven pharmacotherapies reliably increase long-term smoking abstinence including bupropion hydrochloride [46], darenicline, and five nicotine replacement therapies (nasal spray, gum, patch, inhaler, and lozenges) [47]. The efficacy of smoking cessation programs ranges from 6% 1 year success with physician counseling alone to 18% with self-help programs and 20%–40% with counseling plus pharmacological intervention [48]. All individuals who smoke should, of course, be counseled

to cease this potentially deadly habit. A particularly appropriate time to encourage patients to make this effort is after a cardiac event or discovery of existing cardiovascular disease.

Lifestyle Approach to Management of Dyslipidemias

Average cholesterol levels among adult men and women in the United States have decreased to some degree since the 1960s. Currently, approximately 45% of all American adults still have cholesterol levels greater than 200 mg/dL and 16% have levels higher than 240 mg/dL [49]. In addition, both depressed HDL cholesterol levels and elevated triglyceride levels often occur together and result from different metabolic pathways than are typically involved in elevated LDL. These latter two lipid abnormalities are particularly associated with the metabolic syndrome.

Various organizations have listed somewhat different recommendations for cholesterol screenings. There is wide agreement that all patients with currently existing CVD should be periodically screened for serum cholesterol levels. The NCEP ATP-III Guidelines recommend that all adults older than 20 years should be routinely screened for serum cholesterol [3]. The American College of Physicians (ACP) provides less aggressive screening recommendations with advice that men between the ages of 35 and 65 be screened and women between the ages of 45 and 65 be screened [50]. The U.S. Preventive Services Task Force advocates screening women over the age of 45 and men over the age of 35 [45].

It is important to understand that all of the earlier referenced guidelines advocate treatment based on assessment of the patient's overall risk. The ATP-III Guidelines not only utilize LDL level but also recommend calculations based on the Framingham Risk Score (see Figures 2.1 and 2.2). A guideline algorithm presented by the ATP-III Guidelines is presented in Figure 2.3. New guidelines from the NCEP (ATP-IV) are anticipated to be published in 2012.

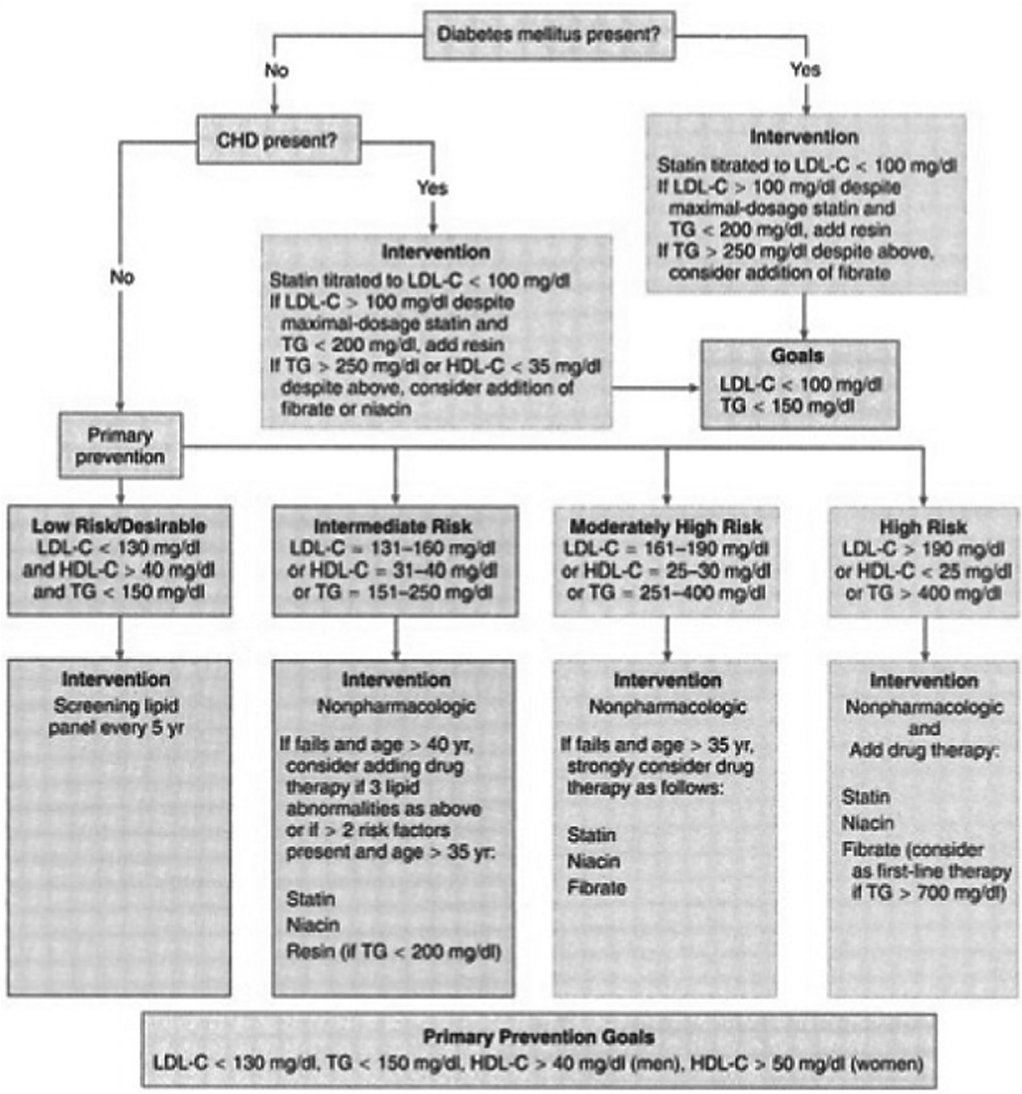


FIGURE 2.3 Algorithm for lipid-lowering therapy based on findings from intervention trials. CHD, Coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides. (From the Third Report of the National Cholesterol Education Program (NCEP), *Circulation*, 106, 3143, 2002.)

New guidelines from the NCEP (ATP-IV) are anticipated to be published in 2012. A variety of lifestyle recommendations are incorporated as recommended first-line treatment in the NCEP ATP-III Guidelines. Nutritional intervention is recommended including maintaining calories from fat between 25% and 35%, saturated fat counting for <7% with cholesterol level intake limited to <200 mg/day. Complex carbohydrates are recommended at 50%–60% of calories and protein at 15%. NCEP ATP-III Guidelines recommend consumption of 20–30 g of dietary fiber daily—an amount far more than the average American adult currently consumes [3].

In 2006, American College of Cardiology and American Heart Association updated their secondary prevention guidelines for lipid management including most of the provisions of the NCEP guidelines but also strengthening them for individuals with established CHD. The AHA/ACC Guidelines extend the option of levels of <70 mg/dL for LDL for all patients with CHD not just those at very high risk [51]. The guidelines also recommend that patients with triglyceride levels of 200–499 mg/dL should have non-HDL cholesterol level of <130 mg/dL and potentially further reduction to <100 mg/dL. Also in 2006, the AHA listed its nutritional and lifestyle recommendations [52]. A summary of these recommendations and their lifestyle interventions is found in Table 2.3. Within a clinical setting, it may be valuable for patients to receive the services of a registered dietitian to help them adhere to nutritional guidelines recommended by the AHA and NCEP ATP-III.

A variety of pharmaceutical agents have been demonstrated to lower both total and LDL cholesterol as well as reduce morbidity and mortality from CHD. Most prominent among these medicines are the statins. While statins vary according to potency, they appear to be equally efficacious. Adherence is the key issue. Other agents available include niacin, fibrates, bile acid sequestrants, and cholesterol absorption inhibitors. A complete review of pharmaceutical therapies for the management of dyslipidemia is beyond the scope of this chapter and has been well treated in a variety of other publications. All the major cholesterol management guidelines advocate that lifestyle measures be combined if pharmaceutical agents are employed to produce the most favorable outcome.

TABLE 2.3
AHA 2008 Diet and Lifestyle Recommendations for Cardiovascular Disease Risk Reduction

1. Balance caloric intake and physical activity to achieve or maintain a healthy body weight
2. Eat a diet rich in vegetables and fruits
3. Choose and prepare foods with little or no salt
4. Minimize your intake of beverages and foods with added sugars
5. Consume oily fish at least twice a week
6. Limit your intake of saturated fat to <7% of energy, *trans* fat to <1% of energy, and cholesterol to <300 mg/day by choosing lean meats and vegetable alternatives; selecting fat-free (skim), 1% fat, and low-fat dairy products and minimizing intake of partially hydrogenated fats
7. Choose whole grain, high fiber foods in your diet
8. If you consume alcohol, consume in moderation
9. When you eat food that is prepared outside of your home, follow the AHA Diet and Lifestyle Recommendations

Source: Adapted from Lichtenstein, A.H. et al., *Circulation*, 114, 82, 2006.

Lifestyle Management of Hypertension

According to the JNC 7 Report, one out of every three American adults has high blood pressure, which represents >50 million Americans [4]. Another 25% fall into the "prehypertensive" category, which represents another 45 million Americans. The JNC 7 blood pressure classification is found in Table 2.4.

According to data from the Framingham Heart Study, individuals who have a normal blood pressure at the age of 85 years still have a 90% chance of developing hypertension in their lifetime [53]. Control of high blood pressure in the United States remains abysmally low with over two-thirds of individuals with hypertension not adequately controlled [54].

A number of lifestyle measures are recommended by JNC 7 and can play significant roles in either reducing the likelihood of developing hypertension or treating it if it currently exists. These lifestyle measures include weight management, regular physical activity, proper nutrition, cessation of cigarette smoking, and moderation of alcohol—all of which represent first-line lifestyle-related measures in the treatment of high blood pressure within the JNC 7 framework [4].

Increased body weight has clearly been associated with increased risk of high blood pressure [55]. Conversely, weight reduction in overweight or obese individuals represents a highly reliable way of lowering blood pressure. In most studies, individuals who are overweight or obese can anticipate losing 1 mm Hg both systolic and diastolic blood pressure for every 2 lb of weight loss [56]. The mechanism of blood pressure lowering resulting from weight loss is not completely understood. It may represent a decrease in blood volume, an initial diuresis, or reduction in systemic vascular resistance [57,58].

Proper nutrition can also play a significant role in blood pressure control. Both the JNC 7 Guidelines [4] and the AHA Nutrition Guidelines [52] recommend that individuals with hypertension should consume a diet with no more than 2300 g of sodium per day. Recently released Dietary Guidelines for Americans 2010 [59] recommends an even lower sodium consumption of 1500 mg/day for individuals at increased risk for cardiovascular disease and all individuals over the age of 50.

Practical ways to lower salt consumption include removal of the salt shaker from the table, reduction of salt in cooking, careful label reading of processed foods (a significant and often underrecognized source of sodium), and increased consumption of whole grains and fruits and vegetables. The Dietary Approaches to Stop Hypertension (DASH) diet which emphasizes whole grains, fruits and vegetables, and low-fat dairy products has been shown to reliably lower high

TABLE 2.4
Classification and Management of Blood Pressure for Adults Aged 18 Years or Older

BP Classification	Systolic BP, mm Hg[a]		Diastolic BP, mm Hg[a]	Management[a]		
					Initial Drug Therapy	
				Lifestyle Modification	Without Compelling Indication	With Compelling Indications[b]
Normal	<120	and	<80	Encourage		
Prehypertension	120–139	or	80–89	Yes	No antihypertensive drug indicated	Drug(s) for the compelling indications[c]
Stage 1 hypertension	140–159	or	90–99	Yes	Thiazide-type diuretics for most; may consider ACE inhibitor, ARB, β-blocker, CCB, or combination	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed
Stage 2 hypertension	≥160	or	≥100	Yes	Two-drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or β-blocker or CCB)[d]	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker.

[a] Treatment determined by highest BP category.

[b] See Table 6.

[c] Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mm Hg.

[d] Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

blood pressure [60]. An addition of further sodium restriction to the DASH diet results in further reduction in blood pressure. Unfortunately, <20% of individuals with established high blood pressure are following a DASH type diet [61].

Regular physical activity also helps prevent high blood pressure and lowers blood pressure in individuals with currently existing hypertension. Physically active individuals reduce their risk of hypertension between 20% and 50% [62]. Individuals with established hypertension who start a physical activity program (emphasizing aerobic activities such as walking) may lower both systolic and diastolic blood pressure by 5–10 mm Hg by participating in such moderate-intensity physical activity [62].

Excessive alcohol consumption is a risk factor for hypertension [63]. Moderation of this habit can also contribute significantly to controlling blood pressure. Cigarette smoking and use of other tobacco products have been repeatedly shown to raise blood pressure [64,65]. Cessation of this deadly habit should be recommended for multiple reasons. Some evidence supports stress reduction as playing a role in lowering blood pressure although this effect seems to be less prominent than the other lifestyle measures already discussed [66]. A beneficial aspect of lifestyle measures in relationship to blood pressure control is that they often act synergistically with each other. It should be noted that positive lifestyle measures when practiced simultaneously appear to have additive benefits. The PREMIER trial showed that a combination of weight loss, sodium restriction, increased physical activity, and limited alcohol consumption when practiced together resulted in substantial blood pressure reductions in individuals with above optimal blood pressure, including Stage 1 hypertension (120–159 mm Hg systolic and 80–95 mm Hg diastolic) and who were not taking antihypertensive medications [67]. Further benefits were achieved by individuals who implemented a DASH diet in addition to these other lifestyle modifications.

Pharmaceutical Measures for Cardiac Protection

A detailed review of pharmacological interventions to lower the risk of heart disease is beyond the scope of this chapter. However, it is important to recognize that certain pharmacological interventions have been demonstrated to be effective in either primary or secondary prevention of cardiovascular disease.

Aspirin has been demonstrated to lower the risk of subsequent events in individuals with existing CHD, where aspirin reduces the risk of subsequent events by 25% [68]. The AHA/ACC recently lowered the recommended prophylaxic dose of aspirin in individuals with existing CHD from 75 to 325 mg/day to 75 to 162 mg/day since antiplatelet trials had showed no difference in the reduction benefit and reduced risk of bleeding at this lower dosage range [51]. Other antiplatelet agents do not offer significant benefit over aspirin. These agents such as clopidogrel should be limited to patients with aspirin allergy or intolerance [69].

The picture of aspirin usage in primary prevention is less clear [70]. The AHA guidelines issued in 2007 for women recommend aspirin for high risk women whose 10 years of a coronary event, based on Framingham criteria, exceeds 20% and for all women over the age of 65 in whom blood

pressure is controlled and the potential benefit for preventing MI or ischemic stroke outweighs the risk of bleeding or hemorrhagic stroke. The U.S. Preventative Health Services Task Force (USPHSTF) recommends aspirin for men 45–79 years of age and women 55–79 years of age for benefit in reduction of risk of MI in men and ischemic stroke in women if these benefits outweigh the risk of gastrointestinal bleeding [71].

Other potentially beneficial pharmaceutical agents include statins, β-adrenergic receptor blockers after MI, and angiotensin-converting enzyme inhibitors in individuals at high risk for CHD events. Extensive reviews of all these medications may be found elsewhere.

CLASS 2 INTERVENTIONS

Obesity Prevention and Management

Obesity [72], adult weight gain [73], and increased abdominal fat [74] are all independently associated with increased risk for CHD [75–78]. Obesity also contributes to a variety of other risk factors for CHD including hypertension, Type 2 diabetes, and dyslipidemia. The American Heart Association recognizes obesity as an independent risk factor over and above its association with other risk factors for CHD [79].

Over the last 40 years, the percentage of the U.S. population considered to be overweight (BMI ≥ 25 ≤ 29.9) and obese (BMI ≥ 30.0) has risen steadily and substantially. As depicted in Figure 2.4, over two-thirds of the adult population in the United States are now considered overweight or obese [80,81]. The prevalence of obesity has risen particularly sharply, with the most dramatic increase in individuals who are extremely obese (BMI ≥ 40.0).

The same trends have occurred in children [82] as depicted in Figure 2.5. The prevalence of overweight has more than tripled among children in the United States in the past 40 years ("overweight" in children is defined by CDC criteria as ≥95th percentile weight for height based on CDC 2000 tables) [83]. Some criteria such as those from the American Medical Association also include a description of ≥85th percentile weight for height as "overweight" and ≥95th percentile of weight for height as an appropriate definition for "obese" in children [84].

Obese individuals are particularly likely to demonstrate clustering of risk factors [85]. Framingham data have demonstrated that over two-thirds of CHD is found in individuals with two or more risk factors [86]. Moreover, obesity is the major driver of the metabolic syndrome which afflicts between 25% and 35% of the adult population in the United States and represents a potent risk factor for both CHD and diabetes [87].

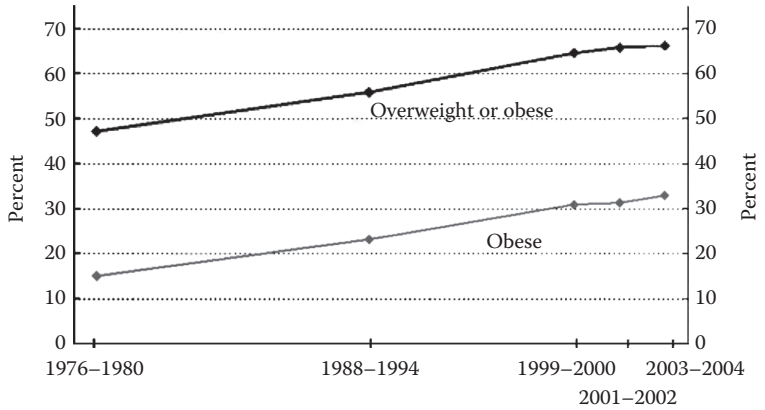


FIGURE 2.4 Trends in adult overweight and obesity ages 20–74 years. (From National Center for Health Statistics, Health, United States 1987, USDHHS Pub. No. 88-1232, U.S. Department of Health and Human Services, Public Health Service, Washington, DC, 1988.)

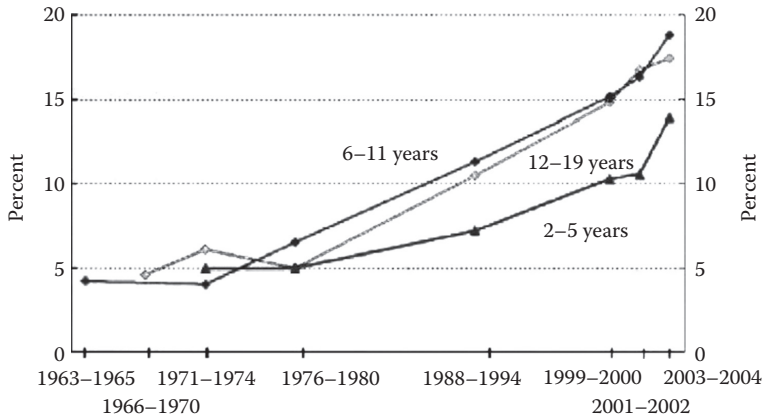


FIGURE 2.5 Trends in childhood overweight. (From National Center for Health Statistics, Health, United States 1987, USDHHS Pub. No. 88-1232, U.S. Department of Health and Human Services, Public Health Service, Washington, DC, 1988.)

Although the association between obesity and increased risk of CHD is well established, no large scale, randomized trials of weight reduction as an intervention to lower risk of CHD are available to estimate the benefits of weight loss. A number of trials, however, have shown that weight loss in obese individuals reduces risk factors for CHD and a variety of other chronic conditions. For example in the Diabetes Prevention Program, individuals who were overweight who lost 5%–7% of their body weight and adopted a program of regular physical activity reduced their risk of developing diabetes by 58% [88]. Nutritional strategies, with a particular emphasis on matching calorie intake to calorie output, have demonstrated effectiveness for weight loss. The *Dietary Guidelines for Americans 2010* [59] list overconsumption of calories and overweight/obesity as the leading nutritional problems in the United States.

In addition, regular physical activity in conjunction with attention on caloric consumption has been found in numerous studies to help in the maintenance of long-term weight loss [89,90]. The preferred form of physical activity for most overweight or obese individuals is walking. Some studies have recommended 30–60 min of moderate-intensity walking per day as a reasonable goal for individuals as a component of an effective and safe weight loss program [90]. The *Dietary Guidelines for Americans 2010* recommend 60 min or more of moderate physical activity as a component of weight management [59].

Behavioral strategies and social support are also important as components of an overall strategy for long-term weight loss [91]. Support from an individual's family and friends or from groups (e.g., from an organization such as Weight Watchers International) has been demonstrated to be helpful in long-term maintenance of weight loss [92].

Few pharmaceutical therapies are currently available for weight loss. The only agents approved in the United States at the current time are Phentermine and Orlistat. A number of other agents are in various stages of development.

It has been regularly shown that physician involvement in recommendations for weight loss represents an important predictor of both initial weight loss and maintenance of weight loss. A detailed description of available programs and therapies for weight loss is beyond the scope of the current chapter. The authors have, however, coedited a textbook on this topic and the reader is referred to this textbook for more detailed information in this area [93].

Diabetes/Glucose Intolerance

The prevalence of diabetes in the United States has grown significantly over the past decade which appears to reflect corresponding increases in the prevalence of overweight and obesity [94]. Currently, approximately 8% of the adult population in the United States—nearly 24 million people—has diabetes mellitus. The vast majority of these individuals (>90%) have Type 2 diabetes [94]. Unfortunately, approximately one-fourth of individuals with diabetes are not aware they have this condition. Another significant problem is the recent increase in Type 2 diabetes in children. It is now estimated that more new cases of Type 2 diabetes are found in children each year than Type 1 diabetes [82].

Diabetes represents a significant risk factor for CHD and is the leading cause of death for both men and women with diabetes resulting in 75% of all mortality [95,96]. A variety of lifestyle measures such as weight loss in overweight or obese individuals and regular physical activity play important roles in the management of diabetes [97,98]. These modalities are particularly important for blood sugar control in individuals with Type 2 diabetes.

Because patients with diabetes often have other risk factors for CHD, aggressive treatment of these other risk factors is imperative. For example, guidelines from the American Diabetes Association for treating high blood pressure in individuals with diabetes recommend a target of blood pressure ≤130/80 mm Hg for individuals with diabetes [99]. NCEP ATP-III Guidelines treat diabetes as a CHD equivalent and recommend reduction of LDL cholesterol in diabetic individuals to a goal of <100 mg/dL [3].

Impaired glucose tolerance often proceeds overt diabetes and is particularly common in obese individuals. Recent CDC data indicate that 35%–40% of the adult population in the United States has glucose intolerance [100]. Recent studies have shown that overweight individuals with impaired glucose tolerance who lose weight, reduce total fat intake, and increase physical activity significantly decrease their risk of developing diabetes [88,101]. Thus, lifestyle measures are highly appropriate in both diabetic and prediabetic patients.

Few data are available to address appropriate strategies for long-term reduction in CHD mortality among patients with Type 2 diabetes. It is hoped that the Look AHEAD (Action for Health in Diabetes) trial should provide some important information in this area. Initial data from this study are anticipated in 2012 [102].

Physical Inactivity

The U.S. population has become increasingly sedentary. Both the U.S. Surgeon General's Report on Physical Activity and Health [103] and data from the Behavior Risk Factor Surveillance System (BRFSS) [104] have suggested that >70% of the adult population in the United States does not achieve 30 min of moderate-intensity physical activity on most, if not all, days. Multiple studies have demonstrated that an active lifestyle substantially decreases the risk of CHD. The American Heart Association has listed the lack of physical activity as a major risk factor for CHD [105].

The recently released *Physical Activity Guidelines for Americans 2008* provides a listing of known or anticipated health benefits from increased physical activity [106]. A listing of these known benefits and the strength of the evidence supporting these relationships are found in Table 2.5. As can be seen from this table, many of the

TABLE 2.5
Health Benefits Associated with Regular Physical Activity

Children and adolescents

Strong evidence

- Improved cardiorespiratory and muscular fitness
- Improved bone health
- Improved cardiovascular and metabolic health biomarkers
- Favorable body composition

Moderate evidence

- Reduced symptoms of depression

Adults and older adults

Strong evidence

- Lower risk of early death
- Lower risk of CHD
- Lower risk of stroke
- Lower risk of high blood pressure
- Lower risk of adverse blood lipid profile
- Lower risk of Type 2 diabetes
- Lower risk of metabolic syndrome
- Lower risk of colon cancer
- Lower risk of breast cancer
- Prevention of weight gain
- Weight loss, particularly when combined with reduced
- Improved cardiorespiratory and muscular fitness
- Prevention of falls
- Reduced depression
- Better cognitive function (for older adults)

Moderate to strong evidence

- Better functional health (for older adults)
- Reduced abdominal obesity

Moderate evidence

- Lower risk of hip fracture
- Lower risk of lung cancer
- Lower risk of endometrial cancer
- Weight maintenance after weight loss
- Increased bone density
- Improved sleep quality

Source: From U.S. Department of Health & Human Services, *2008 Physical Activity Guidelines for Americans*, http://www.health.gov/PAguidelines, accessed: August 29, 2011.

known benefits from physical activity involve reduction of risk of CHD.

The *Physical Activity Guidelines for Americans 2008* recommend that individuals try to accumulate 150 min of moderate-intensity activity or 75 min of vigorous activity on a weekly basis. Moderate-intensity activities include such forms of physical activity as walking, jogging, cycling, or swimming at moderate intensity. A listing of *Physical Activity Guidelines* is beyond the scope of this chapter. The reader is referred to the *Physical Activity Guidelines for Americans 2008* for an excellent compendium of literature in this area [106].

Moderate Alcohol Consumption

A number of studies have demonstrated that moderate alcohol consumption decreases the risk of vascular diseases such as heart attack, peripheral vascular disease, and sudden cardiac death [107]. It should be noted that these studies have also demonstrated that excessive alcohol consumption increases both all-cause mortality and cardiovascular disease mortality [108]. The most reasonable course in a clinical setting is to assess risks and benefits of alcohol consumption on a case-by-case basis with each patient.

CLASS 3 INTERVENTIONS

Nutritional Counseling

Numerous studies have demonstrated that diet has an impact on CHD risk [109–112]. The U.S. Preventive Services Task Force listed nutritional counseling as having "moderate" evidence supporting its role in lowering the risk of CHD. Recent Scientific Statements from the American Heart Association [52] as well as the *Dietary Guidelines for Americans 2010* [59] both emphasize the important role of nutritional counseling to lower the risk of CHD. In particular, improved nutritional practices may help improve blood lipids, and strategies such as the DASH diet [60,113] have been demonstrated to help control high blood pressure.

Guidelines and resource materials are available in this area from the American Heart Association [114] as well as the American Dietetic Association [115] and the Preventive Cardiology Nurses Association [116] to assist patients in making nutritional choices to lower their risk of CHD. Numerous guidelines are available from various professional societies providing key components of overall health and nutritional patterns. The guidelines are all very consistent with each other, so the individual health care professional is able to choose whichever one fits most conveniently into his/her practice [117].

Psychological Risk Factors/Counseling

A number of psychological factors including depression, chronic hostility, social isolation, and lack of social support have been linked to increased risk of CHD [118]. Some studies have suggested that improved psychological support systems may improve outcome following MI. For example, one meta-analysis of 37 smaller studies showed that stress management and health education in individuals with CHD reduced recurrent MI by 29% and cardiac mortality by 34% [118]. Office visits following MI clearly represent an excellent opportunity to assess levels of depression and social isolation in individuals who have suffered recent cardiac events.

POSTMENOPAUSAL ESTROGEN THERAPY

It is well established that the risk of CHD in women increases significantly following menopause. Relatively, few women experience CHD at younger than 45 years of age in the

United States [119]. However, by the age of 60 years, CHD is the leading cause of death among women.

Multiple factors may explain the increased risk of CHD after menopause. For many years, the increase in CHD after menopause was attributed to the decline in endogenous estrogen that accompanies menopause [118]. However, the Women's Health Initiative findings did not support this concept [120–122]. For this reason, hormone therapy is no longer recommended as an approach to prevention of CVD for the USPHSTF, the American Heart Association, or other scientific organizations [121].

DETERMINANTS OF BEHAVIORAL CHANGE

The belief that it is possible to change patient's behavior provides the fundamental underpinnings to the concept of utilizing lifestyle measures to help patients adopt positive lifestyle behaviors to lower the risk of CHD or as an adjunct to the treatment of established CHD. A detailed review of the literature in this area is beyond the scope of the current chapter. However, this literature has been very well summarized in a variety of other publications [123,124].

A variety of theoretical constructs provide the foundation for behavioral therapy [125]. These include

- Cognitive behavioral therapy (which assumes that behavior is learned and can, therefore, be unlearned through cognitive and behavioral strategies)
- Social cognitive theory (this is based on the assumption that behavior is the result of interaction of personal and behavior factors as well as environmental influences)
- Transtheoretical theory (stages of change; based on accurately placing an individual along the path of various stages of change) [124]

Familiarity with these theoretical constructs, as well as technique of motivational interviewing, provides useful underpinnings and a practical framework for incorporating lifestyle change messages in clinical practice.

ESTABLISHING A LIFESTYLE MEDICINE EMPHASIS IN CLINICAL PRACTICE

As already indicated, physicians can play a particularly powerful role by recommending and monitoring lifestyle-related changes for reduction in the risk of CHD. While challenges remain including lack of time and inadequate reimbursement models, it is clear that health care professionals need to move in this direction.

The evidence supporting lifestyle therapies for reduction of risk of CHD is diverse and powerful. Moreover, an emphasis on the linkages between daily lifestyle habits and practices and the risk of CHD is incorporated in virtually all of the evidence-based guidelines for treating CHD and its risk factors as well as reducing the risk of other metabolic diseases [3–15]. The American Heart Association has also included positive lifestyle measures as a fundamental component of its strategic plan for 2020 for improving the cardiovascular health of the nation [7]. Finally, the Accountable Care Organization provision of the recent Affordable Health Care Act suggests that health care organizations and individual providers will be mandated to increase involvement in this area [126]. The recently released *Physical Activity Guidelines for Americans 2008* [106] as well as the *Dietary Guidelines for American 2010* [59] provide fundamental, evidence-based approaches to lifestyle-related issues and should be the foundation for health care workers' increasing emphasis on these strategies in their daily practice.

SUMMARY

An extensive body of scientific literature supports the concept that positive lifestyle measures are highly effective in lowering multiple risk factors for CHD as well as serving as components of therapy for individuals who already have established CHD. These interventions carry the substantial advantages of being low cost, carrying virtually no adverse side effects, and often simultaneously ameliorating multiple risk factors for CHD. The key imperative for physicians and other health care workers is to commit to learning how to incorporate counseling concerning these lifestyle measures in clinical practice and establishing strategies to bring this valuable body of information to their patients.

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3 Nutrition Interventions for Cardiovascular Disease

Behavioral and Educational Considerations

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CONTENTS

Cardiovascular Diseases and Lifestyle 35
Recommendations for "Heart Healthy Diets" 36
Environmental and Internal Factors Influencing Food Behaviors 38
The Pritikin Program and the Ornish Lifestyle Heart Diet 39
Meal Replacement or Structured Meal Plans 40
Behavioral Change Theories 40
- Cognitive Behavioral Theory 40
- Social Cognitive Theory 40
- Transtheoretical Theory (Stages of Change) 41
- Health Belief Model 41

Components of Successful Behavioral Change 41
- Goal Setting 41
- Problem Solving 42
- Self-Monitoring 42
- Feedback 42

Motivational Interviewing 42
Multicultural Counseling 42
Role of Health care Providers in Dietary Interventions 43
Effectiveness of Nutrition Interventions: The Evidence 43
- Nutrition Care Process 43
- Client/Patient and Health care Professional Contact 44
- Long-Term Dietary Change 44

Conclusion 44
References 44

CARDIOVASCULAR DISEASES AND LIFESTYLE

Death rates from cardiovascular diseases (CVD), including coronary heart disease (CHD), stroke, and heart failure, have declined; however, they remain the major cause of mortality in the United States. In 2007, CHD caused 1 in 6 deaths in the United States; stroke accounted for 1 in 18 deaths; and 1 in 9 death certificates mentioned heart failure. Traditional risk factors for CVD remain prevalent. Approximately 76,400,000 (33.5%) of the U.S. adult population had hypertension (HTN); 23.1% of men and 18.3% of women smoked cigarettes, approximately 33,600,000 (15%) adults had total serum cholesterol levels ≥240 mg/dL; 18,300,000 (8%) adults had diagnosed diabetes; and approximately 149,300,000 (67.3%) were overweight or obese [1].

In the United States, there are ethnic disparities in the prevalence of CHD and HTN. Blacks (6.7%) had the highest prevalence of CHD, followed by Whites (6.4%), Latinos (5.8%), American Indians or Alaska Natives (4.1%—figure considered unreliable), and Asians (3.9%). Blacks also had the highest prevalence of HTN (32.3%), followed by Whites (23.0%), American Indians or Alaska Natives (21.8%), and Asians (19.4%) [1]. Older and lower socioeconomic status individuals also have an increased prevalence of CVD and they are more likely to have risk factors associated with CVD, including sedentary behavior, overweight, and unhealthy dietary habits [2].

The American Heart Association has projected that direct and indirect costs of CVD in the United States will increase from $252.5 and $171.7 billion dollars in 2010 to $818.1 and $275.8 billion in 2030, respectively. These cost estimates do not include all costs related to obesity, diabetes mellitus, and tobacco use [3]—all major risk factors for CVD.

Although death rates from CVD have fallen, the prevalence and severity of risk factors associated with these diseases has increased [4]. Thus, reduction of incident cases of CVD is a primary public health goal. "To improve cardiovascular health and quality of life through prevention, detection, and treatment of risk factors for heart attack and stroke; early identification and treatment of heart attacks and strokes; and prevention of repeat cardiovascular events" is a goal for Healthy People 2020 (HP 2020) [5]. To meet this goal, HP 2020 has 24 specific objectives related to increasing the overall cardiovascular health in the U.S. population. These objectives include those related to lifestyle changes, including Heart Disease & Stroke goal (HDS-10): (Developmental): "Increase the proportion of adults with hypertension who meet the recommended guidelines" which includes reducing saturated fatty acid (SFA) and sodium intake, and moderating alcohol intake. Another goal related to reducing CVD using lifestyle changes is HDS-13 goal: (Developmental) "Increase the proportion of adults with elevated low-density lipoprotein cholesterol (LDL-C) who have been advised by a health care provider regarding cholesterol lowering management including lifestyle changes and, if indicated, medication." Components of this goal include lowering serum cholesterol levels and weight control through diet.

The potential impact of diet and other lifestyle factors on the risk of CHD was shown by Ancel Keys in the Seven Countries study [6] and by a study that looked at heart disease in Japanese men living in Japan, Hawaii, and California [7]. Although these studies are older, and have been criticized for design and analyses issues, they provide an historical basis for the link between diet and CHD.

Modifiable risk factors for CVD accounted for 90% and 94% of the Population Attributable Risk (PAR) factors in males and females, respectively. Smoking and abnormal lipids were shown to be the most important risk factors, accounting for approximately two-thirds of the PAR of an acute myocardial infarction. These were followed by psychosocial factors, abdominal obesity, diabetes, and HTN [8]. The severity of dyslipidemia, abdominal obesity, diabetes, and HTN can be modified by lifestyle changes, including diet.

RECOMMENDATIONS FOR "HEART HEALTHY DIETS"

Overall nutrient and food consumption patterns play a central role in the prevention of CHD in individuals and population [9,10]. A meta-analysis of dietary trials showed that lowering of serum cholesterol levels by diet produced as much CHD risk reduction as did lipid-lowering drugs—corresponding to their respective degree of cholesterol lowering [11]. Diets, and other lifestyle measures, designed for primary or secondary prevention of CHD, should be designed not only to reduce serum total cholesterol, LDL-C, and triglycerides in those individuals with dyslipidemia and to increase high-density lipoprotein cholesterol (HDL-C) but also to control other risk factors for CHD, including overweight/obesity, blood pressure, and blood glucose levels.

Dietary and physical activity recommendations for prevention and treatment of CHD, as well as other chronic diseases, including HTN, stroke, type 2 diabetes, cancer, are remarkably consistent [12–18]. Recommendations are for total healthy diet patterns, which are generally rich in whole grains, fruit and vegetables, low-fat dairy, and lean proteins; some agencies also recommend consumption of nuts. Nutrient recommendations include high intakes of poly-UFA (PUFA) and mono-unsaturated fatty acids (MUFA) and potassium, and low intakes of added sugars, SFA, *trans*-fats, and sodium.

It is also important that individuals balance energy intake with physical activity to maintain a healthy weight [16]. The Department of Health and Human Services recommends specifically that adults (18–64 years of age) should do 150 min of moderate-intensity weekly, or 75 min of vigorous-intensity, aerobic physical activity weekly, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 min, preferably spread throughout the week. Additional health benefits are seen from increasing physical activity to 300 min/week. Adults should also do muscle-strengthening activities that involve all major muscle groups performed on 2 or more days per week. Adults older than 64 years should follow these recommendations unless limited by chronic conditions, and if present, individuals should be as physically active as they can. Few Americans meet the recommendations for either diet or physical activity [18].

The U.S. Preventive Services Task Force (USPSTF) recommends intensive behavioral dietary counseling for adult patients with hyperlipidemia and other known risk factors for CVD and diet-related chronic disease [19]. Such secondary prevention of CVD can be conducted by a physician or a Registered Dietitian (RD) via nutrition education or counseling. The USPSTF, however, failed to find sufficient evidence to recommend for or against behavioral counseling for primary prevention of CVD in unselected patients [19]. A Cochrane Review found that education or counseling in the general population did lower risk factors modestly, but did not lower CHD events or total or CHD mortality and were not recommended. It did find that high risk patients could, however, benefit from these efforts [20].

Dietary recommendations for secondary prevention of CHD or HTN are similar to those for the general public, although they are somewhat more restrictive [11,21] (Table 3.1). For example, population-wide recommendations for SFA are <10% of energy, whereas the recommendation for those with dyslipidemia or who have had a coronary event is <7% of energy from SFA [11]. Dietary changes are recommended as the first-line treatment for mild to moderate dyslipidemia [22]. The principal goal of the National Cholesterol Education Program's Adult Treatment Panel III's goal is to lower serum LDL-C levels [11]. With the reduction in serum LDL-C levels comes a concomitant decrease in CHD mortality [23]. Dietary changes can reduce serum cholesterol levels by up to 30% [24]; however, in practice, reductions of 5%–15% are more common [25]. The principal dietary modifications to reduce serum LDL-C levels are to reduce the intake of SFA and increase the intake of PUFA and MUFA.

TABLE 3.1
Nutrient Recommendations for Primary and Secondary Prevention of CVD

	Primary Prevention			Secondary Prevention	
	IOM[a]	2010 DGA	AHA	ATP III	DASH
Energy	Energy intake should be balanced with energy expenditure to achieve and maintain an appropriate weight				
Protein	10%–35% of energy	N/A	N/A	~15% of energy	18% of energy
Carbohydrates	45%–65% of energy	N/A	N/A	50%–60% of energy	55% of energy
Refined grains	N/A	No more than 3 oz eq[b]	"Choose whole grain foods"	N/A	N/A
Added sugar	<25% of energy[c]	Reduce Intake	<10% of energy	N/A	N/A
Fiber	38–21 g/day[d]	14 g/1000 kcal	N/A	20–30 g/day; 10–25 g/day viscous fiber	30 g/day
Total fat	20%–35% of energy	20%–35% of energy	25%–35% of energy	25%–35% of energy	27% of energy
SFA[e]	As low as possible	<10% of energy	<7% of energy	<7% of energy	6% of energy
trans-fat	As low as possible	As low as possible	<1% of energy	"Low intake"	N/A
Solid fat	N/A	Reduce intake	Minimize	N/A	N/A
MUFA	N/A	N/A	N/A	Up to 20% of energy	N/A
PUFA	N/A[f]	N/A	N/A	Up to 10% of energy	N/A
Cholesterol	As low as possible	<300 mg/day	<300 mg/day	<200 mg/day	150 mg/day
Potassium	4700 mg	4700 mg	N/A	90 mmol[g]	4700 mg
Sodium	19–50 years 1500 mg; 51–70 years 1300 mg; >70 years 1200 mg	<2300 mg[h]	Moderation	2400 mg[g]	2300 mg[g]
Magnesium	Males: 19–30 years 330 mg; ≥31 years 350 mg Females >19 years 265 mg	N/A	N/A	Enough for good health[g]	500 mg
Calcium	Males: 19–70 years 800 mg; ≥71 years 1000 mg Females: 19–50 years 800 mg; ≥51 years 1000 mg	N/A	N/A	Enough for good health[g]	1250 mg
Alcohol[i]	N/A	1 drink/day females; 2 drinks/day males	Moderation		Limit

Sources: IOM, *Dietary Reference Intakes (DRI)*, http://www.iom.edu/Activities/Nutrition/SummaryDRIs/~/media/Files/Activity%20Files/Nutrition/DRIs/New%20Material/5DRI%20Values%20SummaryTables%2014.pdf, accessed August 10, 2011; United States Department of Agriculture, *2010 Dietary Guidelines for Americans (DGA)*, http://www.cnpp.usda.gov/DGAs2010-PolicyDocument.htm, accessed August 10, 2011; National Institutes of Health, National Heart, Lung, and Blood Institute, Detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III), http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf, accessed August 10, 2011; *DASH Eating Plan*, http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/new-dash.pdf, accessed August 10, 2011.

N/A, no specific recommendation; however, this will revert to the DGA or the IOM's DRI values. American Heart Association (AHA): Lichtenstein, A.H. et al., *Arterioscler. Thromb. Vasc. Biol*., 26, 2186, 2006; the AHA added sugars recommendation is from Van Horn, L. et al., *Circulation*, 122, 2470, 2010.

[a] Unless otherwise noted, recommendations are for adults 19+ years; pregnant and lactating females excluded. Institute of Medicine (IOM) acceptable macronutrient distribution ranges are presented for protein, carbohydrates, and total fat.

[b] Based on a 2000 kcal diet.

[c] Acceptable macronutrient distribution range, not the recommended intake.

[d] Fiber recommendations are age- and gender-dependent: males 19–50 years 38 g/day, 51+ years 30 g/day; females 19–50 years 25 g/day, 51+ years 21 g/day.

[e] Saturated fatty acids (SFA) in the diet should be replaced by monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA).

[f] IOM acceptable macronutrient distribution range for *n*-6 polyunsaturated fatty acids (linoleic acid) is 5%–10% of energy and for *n*-3 polyunsaturated fatty acids (α-linolenic acid) is 0.6%–1.2% of energy.

[g] Referenced from JNC VI.

[h] Intake should be reduced to 1500 mg among 51+ years, African Americans, or individuals with hypertension, diabetes, or chronic kidney disease.

[i] If alcohol is consumed, intake should be moderate, as defined earlier; this is not a specific recommendation for alcohol consumption.

When counseling patients to reduce SFA intake, it is important to consider this reduction in the context of the macronutrients that replace it. Replacement of SFA with PUFA or MUFA has shown to reduce both LDL-C and HDL-C and may lessen CHD risk. Generally, MUFA has a slight positive effect on HDL and LDL levels and improves insulin sensitivity [26,27]. Olive oil, a MUFA, has also been shown to have a positive effect on lipid levels, but it is unclear if this is due to the fatty acid profile or to the polyphenolic content of the oil [28]. However, if the energy from SFA is replaced by carbohydrates, particularly refined

carbohydrates, this can increase triglycerides and small LDL-C particles, as well as reduce HDL-C. Other dietary interventions, as described later, can reduce the risk of CVD.

Nutrient recommendations may be difficult for the public to follow, so either the recommendations need to be in food, as they have been for MyPlate [29], the interpretation of the DGA for the consumer, or the DASH diet [21]. These are recommendations for whole diets rather than individual foods or nutrients. Health providers, including RDs, can help individuals make appropriate food and diet choices to reduce CVD risk (Table 3.2). Consumption of fruit and vegetables may lead to a reduced intake of SFA and dietary cholesterol. These foods also contribute dietary fiber, antioxidant vitamins, potassium, magnesium, and phytochemicals to the diet that may be cardioprotective [30]. Adults that consume fruit and vegetables tend to have a lower body weight than those that do not, although the association was weak [31]. Whole grains contribute dietary fiber, vitamin E, B vitamins, folate, and magnesium and may enhance satiety and displace refined carbohydrates in the body. Nuts provide unsaturated fatty acids (some [walnuts] are high in omega-3 fatty acids), phosphorus, magnesium, and phytochemicals; nut consumers also have lower body weights than nonconsumers. Fish, especially fatty fish, provide omega-3 fatty acids, selenium, magnesium, and vitamin D. Moderate alcohol intake is associated with some cardioprotective factors, notably elevating HDL-C levels, reducing systemic inflammation, and improving insulin resistance. Heavy habitual alcohol intake, on the other hand, is associated with ventricular dysfunction and a higher risk of atrial fibrillation [30].

Additional therapeutic dietary options for individuals with dyslipidemia that cannot meet LDL-C goals, with or without lipid-lowering medication, include plant stanols/sterols (2 g/day) [11,32] and increased viscous (soluble) fiber (10–25 g/day) [11]. Other lifestyle variables that can be modified by behavioral interventions are increasing physical activity and smoking cessation. However, the efficacy and availability of statins and other cholesterol-lowering drugs has reduced enthusiasm for behavioral modifications.

ENVIRONMENTAL AND INTERNAL FACTORS INFLUENCING FOOD BEHAVIORS

Despite the consistency of dietary recommendations across agencies and across time, the majority of Americans do not meet them [33]. On average, adults consume 11% of energy from SFA, 12%–13% of energy from MUFA, and 6%–8% of energy from PUFA [34]. Intake of whole grain [35], fruit and vegetables [36,37], and low-fat dairy [38] is also well below current recommendations.

Dietary behaviors are complex issues, and for interventions to be effective, they must not only be based on sound

TABLE 3.2
Food Recommendations (2000 kcal Diet) for Primary (MyPlate) and Secondary (DASH) Prevention of Cardiovascular Disease

	MyPlate	DASH Diet	Components that Reduce CVD Risk Factors
Total grain/whole grain	6/3 oz	6–8 servings	Whole grains contribute dietary fiber, vitamin E, B vitamins, folate, and magnesium and may enhance satiety and displace refined carbohydrates in the body. Whole grains are generally low in total fat and saturated fatty acids and sodium; no cholesterol
Fruit	2 cups	4–5 servings	High in dietary fiber, antioxidant vitamins, potassium, magnesium, and phytochemicals; low in total fat and saturated fatty acids and sodium; no cholesterol
Vegetables	2.5 cups	4–5 servings	High in dietary fiber, antioxidant vitamins, potassium, magnesium, and phytochemicals; low in total fat and saturated fatty acids and sodium; no cholesterol
Low-fat dairy	3 cups	2–3 cups	High in vitamin D, calcium, and potassium; low in total and saturated fatty acids
Lean protein[a]	5.5 oz	≤6 oz	Low in total and saturated fatty acids; fatty fish are high in omega-3 fatty acids, selenium, magnesium, and vitamin D
Nuts, seeds, legumes[b]	N/A	4–5/week	Nuts and seeds provide unsaturated fatty acids (some [walnuts] are high in omega-3 fatty acids), phosphorus, magnesium, and phytochemicals; low in sodium. Legumes are high in dietary fiber, low in total fat and saturated fatty acids and sodium; no cholesterol
Oils	6 t	2–3 servings	High in monounsaturated fatty acids

Sources: United States Department of Agriculture, MyPlate, http://www.choosemyplate.gov, accessed August 10, 2011; National Institutes of Health, National Heart, Lung, and Blood Institute, *Your Guide to Lowering Your Blood Pressure with DASH*, http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf, accessed August 10, 2011.

All recommendations are per day except as noted. DASH servings of grain: 1 slice of bread, ½ cup cooked cereal, pasta, or rice, 1 oz ready-to-eat cereal; fruit: 1 piece of fruit, ½ cup cut fruit, ¼ cup dried, ½ cup juice; vegetables: 1 cup leafy green, ½ cup cooked; nuts: 1½ oz, 2 T peanut butter, ½ oz seeds, ½ cup legumes; oils: 1 t soft margarine, 1 t vegetable oil, 1 T mayonnaise, 2 T salad dressing. Sugars should be limited in both eating plans.

[a] Protein foods should be prepared using methods that minimize addition of added fats: baking, broiling, and grilling are recommended.

[b] MyPlate does not have a specific recommendation for nuts, seeds, or legumes; however, these are included in the category of protein foods.

theoretical theories and learning principles but be individualized to patients' specific environmental and behavioral factors influencing their food behaviors and food choices. Taste, cost, nutrition, convenience, and weight control have been shown to be the most important factors influencing food choice. Other contributing factors are socioeconomic status and level of education, interpersonal and cultural influences, and family influences.

Although it is assumed that individuals have the freedom to choose a healthy lifestyle, food choices are often constrained by economic factors which can lead to unhealthy dietary practices [39,40]. Grains, oils, and sugar have been shown to be cheaper than vegetables and fruit [41,42]. Overall, the cost of nutritious diets was higher than less nutritious diets [43]; cost or the perceived cost of healthy foods may limit individuals' ability to consume these foods [44]. Often the cheapest easiest to prepare "convenience" foods are high in SFA, added sugars, and sodium, which are nutrients to limit in a healthy diet [45]. Supermarket availability [45], food accessibility [45], and lack of nutrition knowledge and food preparation skills [44] also affect the ability of individuals to consume a healthful diet.

Nutrition knowledge, especially as it relates to diet–disease relationships, can help promote more healthful dietary choices. Declarative and procedural knowledge are both necessary components of a nutrition intervention program [46], but neither is sufficient without the motivation and support to elicit a behavioral change. An example of declarative knowledge would be knowing the number of grams of SFA in butter or olive oil, but not knowing how to incorporate olive oil (or other oils high in MUFA) into the diet. Procedural knowledge is needed to transform declarative knowledge into behavior. Important knowledge for individuals seeking to change dietary behaviors includes shopping skills, reading nutrition labels, and food preparation skills. Knowledge of food and food sources of nutrients is also needed [47] to help improve the diet.

Nutrition labels have been referred to as "a cost-effective population-level intervention with unparalleled reach." However, it is important to ensure that the information presented is accessible and understandable to all population. Although controversial [48], front of package labels may help those individuals with time constraints [49].

Other than understanding the potential link with dietary SFA and CVD, consumers appear confused about dietary fat and the health implications of consuming dietary fats [50,51]. Consumer education has been shown to increase the knowledge of some types of fat that may increase the risk of CVD; however, knowledge of food sources remained low [52]. The SFA and *trans*-fat content of foods are provided on the Nutrition Facts label and it is important for health professionals to help individuals understand how to read these labels and to know that foods low in these fats are not necessarily healthy foods. In a survey, American consumers were asked "which types of the following specific information that relate to heart health do you look for on food or beverage labels or packages?" Responses were sodium (60%), total fat (58%), cholesterol (54%), *trans*-fat (53%), SFA (50%), and statements about heart health benefits (41%). These findings did not always translate into heart healthy behaviors; for example, only 37% of individuals surveyed used more healthful fats than *trans*-fats and only 27% reviewed information on *trans*-fats and SFA together before purchasing the product. Some consumers also substituted tropical oils for products with *trans*-fats or SFA [52].

Nutrition education has been shown to improve knowledge of the food label in a variety of populations [53,54]. Individuals with type 2 diabetes, hypertension, or hyperlipidemia who read food labels consumed less sugar and more fiber than those who did not. Also, individuals with these health problems read food labels more frequently than those without them [55]. Additional education is needed to help the general consumer and those with chronic nutrition-related diseases to read Nutrition Facts labels.

Meal structure and patterning is changing with more convenience and prepared foods consumed and fewer fresh foods used in meals. Although lack of time has been cited as a principal reason for this, use of convenience foods also depends on economic and social factors and lack of self-efficacy [47,56]. A lack of cooking or food preparation skills has also been associated with consumption of pre-prepared foods [57] where an individual has no control over the sodium content or the type or amount of fat used. Food preparation has been associated with a better diet quality and less frequent fast food intake; those who prepared food frequently were more likely to meet dietary recommendations for fat, calcium, fruit, vegetables, and whole grains than those who did not [58].

Dietary modifications for CVD can include highly restrictive and highly supervised programs, like the Pritikin Program or the Ornish Lifestyle Heart Diet or be those that are behaviorally driven, including meal replacement plans, and nutrition education, or counseling.

THE PRITIKIN PROGRAM AND THE ORNISH LIFESTYLE HEART DIET

Making successful small, stepwise changes to improve diet and physical activity can increase the confidence and motivation of most individuals. Other individuals become frustrated and lose motivation if the results of their changes are minimal. The alternative for them may be to begin with a highly restrictive diet, such as the Pritikin Program [59,60] or the Ornish Lifestyle Heart Diet [23]. The Pritikin Program is provided in a physician's office and incorporates diet (10%–15% of energy from fat, 15%–20% from protein, 65%–75% from carbohydrates), exercise, and counseling lasting 21–26 days; there is an optional residential component available for participants. The Ornish lifestyle change approach incorporates comprehensive lifestyle modifications, including exercise, a very low-fat diet (10% energy from fat), smoking cessation, stress management, and group support which is available at several centers in the United States. The Ornish Program has been demonstrated to reverse coronary atherosclerosis and reduce the number of coronary events when compared with more traditional diets [23].

Diets that focus on macronutrient content, such as the Pritikin and Ornish diets, may be deficient in micronutrients and it is important that counselors also focus on helping individuals obtain nutrient adequacy. A recent study showed that after 8 weeks on the Ornish diet, intakes of >25% of females were below the Estimated Average Requirement for vitamins A, E, and B12, magnesium, and zinc [60].

In August 2010, the Centers for Medicare and Medicaid Services approved both programs for inclusion in the list of approved intensive cardiac rehabilitation programs for Medicaid and Medicare reimbursement. To qualify for reimbursement, these programs had to demonstrate through peer-reviewed, published research that they improved patients' CVD through specific outcomes and that they significantly influenced one or more of these elements: (1) positively affected the progression of CHD, (2) reduced the need for coronary bypass surgery, and (3) reduced the need for percutaneous coronary interventions. Finally, the programs had to demonstrate significant reductions (from baseline) in five or more of the following measures: (1) LDL-C, (2) triglycerides, (3) body mass index (BMI), (4) systolic blood pressure, (5) diastolic blood pressure, and (6) the need for cholesterol, blood pressure, and diabetes medications. Intensive cardiac rehabilitation sessions are limited to 72 one hour sessions, up to 6 sessions/day, over a period of up to 18 weeks [61]. It should be noted that, per patient, the Ornish Program costs four times as much as some traditional cardiac rehabilitation programs [62], thus may not be a suitable option for all patients.

MEAL REPLACEMENT OR STRUCTURED MEAL PLANS

These are considered as nutrition counseling strategies since meal replacements help participants control food portions while attempting to modify their eating patterns. Meal replacements include over-the-counter shakes, bars, or portion-controlled frozen meals; they can be purchased in a supermarket or can be ordered by mail. They have the advantage of simplifying food choice, reducing the time planning or preparing food, reducing the temptation to overeat, and controlling portion sizes [63]. The disadvantage is that using them does not teach the patient/client meal planning or food selection or preparation skills.

Meal replacements are most commonly used for weight loss, blood sugar control in conjunction with weight loss in individuals with diabetes, or reducing dietary fat. Short-term studies have shown that prepared meal plans have shown improved cardiovascular risk factors, quality of life, dietary compliance, and nutritional adequacy [64]. One study that compared meal replacements with a self-selected diet accompanied by nutrition education information and the ability of participants to follow the National Cholesterol Education Step Diets showed a higher prevalence of those receiving meal replacements were able to meet recommendations for both Step 1 and Step 2 diets* [65].

BEHAVIORAL CHANGE THEORIES

It is important to consider the personal and environmental factors that affect consumer choices; however, these factors do not explain how patients make decisions to change behaviors. Behavioral change is based on the assumption that behavior is learned, and can be unlearned and replaced by other behaviors. Behavioral change theories and models have been proposed that account for how individuals make decisions and should be used when designing and implementing nutrition counseling programs. Three variables have been identified as key determinants of behavior [66–68]: (1) the person has committed to performing the behavior; (2) there are no environmental constraints making it impossible for the behavioral change to occur; and (3) the person has the necessary skills to make the behavioral change. These variables are common to behavioral change theories. Other factors that influence the strength and direction of the intention of the behavior include the person's attitude that the advantages of performing the behavior outweigh the disadvantages and that the person believes that he or she has the capability to perform the behavior under a variety of circumstances (self-efficacy).

Interventions that are based on a behavioral theory are more likely to be successful than those that are not and strategies that combine multiple theories are more likely to have a larger effect [2,69]. The three principal behavioral change theories used in nutritional counseling are the cognitive behavioral theory (CBT) [70–72], the transtheoretical theory [73], and the social cognitive theory (SCT) [74].

Cognitive Behavioral Theory

This theory assumes that behavior is learned and can, therefore, be unlearned through cognitive and behavioral strategies taught to patients. The CBT focuses on external factors (environmental and reinforcement) and internal factors (thoughts) [63]. The CBT uses strategies to promote dietary change that may include goal setting, self-monitoring, problem solving, cognitive restructuring, social support, relapse prevention, and contingency management [75].

Social Cognitive Theory

The basis of the SCT is that behavior is the result of the complex interaction of personal and behavioral factors, and environmental influences; the theory also acknowledges

* Step diets were the previously recommended dietary programs to reduce serum LDL-C levels and reduce the risk of CHD. They have been replaced by the Therapeutic Lifestyle Change (TLC) diet recommended by the Adult Treatment Panel III. Step 2 diets were more restrictive than Step 1 diets and were employed if patients were unable to meet their LDL-C goals on a Step 1 diet.

the ability of the individuals to alter and construct their environments to fit their needs [69]. A basic premise of SCT is that people learn not only through their own experiences but also by observing the actions of others and the results of those actions [74]. Key constructs of SCT that are relevant to health behavioral change interventions include observational learning (acquiring behaviors by watching others), reinforcement (responses to the behavior that can increase or decrease the likelihood of repeating the behavior), self-control (personal regulation of behavior), and self-efficacy (the personal confidence in the ability to perform a behavior and overcome barriers to that behavior under any circumstance) [69].

Self-efficacy can facilitate or hinder behavioral change since individuals are more likely to engage in behaviors they believe they can successfully perform and avoid behaviors in which they believe that they will be unsuccessful. Nutrition counseling strategies can strengthen patient's self-efficacy by setting goals, using demonstrations and modeling, developing skills, and providing social support and reinforcements—including self-monitoring records [63,69]. Because of its broad appeal, the concept of self-efficacy has been incorporated in several other behavioral change models, including health belief model, theory of planned behavior, and transtheoretical model [76].

Transtheoretical Theory (Stages of Change)

Introduced in 1981 to explain smoking cessation behaviors, the transtheoretical model of health behavioral change has also been used to guide a wide variety of health behavioral changes, including dietary changes. The model's core concept includes five stages of change that people pass through over time with change most likely to occur when individuals engage in the right activities for the right stage [77]. The early stages of behavioral change are precontemplation (unaware a change is needed or not planning to make any changes) and contemplation (thinking about making a change within the next 6 months). In preparation, individuals are planning to take action in the near future (within 30 days) and are taking steps to change behaviors. In the action stage, individuals have made overt change and in maintenance (usually defined as 6 months), the behavior is sustained. Individuals usually do not progress linearly through these changes of change and relapses are common depending on the motivation and self-efficacy of the patient.

It is important that clinicians working with patients tailor their message to the specific stage [78], since determining the readiness to change is a key element of effecting dietary change. This should be a standard element of nutritional counseling [78,79]; unfortunately, few clinicians do this. Patients can be categorized into a specific stage by asking questions and listening to the replies. Statements in pre-contemplation that a patient may make could include "I don't need to change the way I eat" or "I tried eating more fruit and vegetables, but I just can't." In contemplation, they might say "I've been thinking about eating healthy for awhile now." In preparation, the statement might be "I bought a new cookbook on low-fat cooking." In action, "I'm using my new cookbook and including more fruit and vegetables in the family's meals. It wasn't as hard as I thought it would be." For the patient to be in maintenance, they would need to say something like "I've been eating healthy for about 6 months, and it's become my standard now." Understanding a patient's stage of change can also help to understand barriers and enablers to dietary change.

Health Belief Model

This model is widely used in nutrition education and counseling. This model is based on the theory that patients have choices and can make appropriate decisions regarding health behaviors. In the health belief model, patients must perceive themselves as susceptible to a health threat or disease that has the potential to impact them or their lifestyle. They must also perceive that the benefits to making changes outweigh the effort of making behavioral changes. Internal and external cues motivate patients to take action and patients have the self-efficacy to accomplish these actions [80].

COMPONENTS OF SUCCESSFUL BEHAVIORAL CHANGE

Many of the behavioral theories outlined earlier have common components including goal setting, problem solving, self-monitoring, and feedback.

Goal Setting

Goal setting is appropriate for patients ready to make a change or in action or maintenance stages. Measurable goals that focus on a behavior (e.g., increasing fruit and vegetable intake) rather than a physiological target (e.g., improving LDL-C levels) are preferable since behaviors, not outcomes, are under an individual's control [2]. Setting a challenging goal, but one that can be achieved, is better than setting one that cannot be reached or is so easy that it does not provide a sense of accomplishment when it is achieved [2]. Goals should be defined in terms of a measureable outcome. Goal setting will only work if the person accepts the challenge and has the experience, self-efficacy, and necessary feedback to accomplish the behavioral changes [81]. One to three goals, depending on the needs and skills of the patient, should be set, so as not to overwhelm an individual [80]. Ideally, goals should be established jointly by the health care provider and patient; however, goals set by either can elicit the desired outcomes [2].

Common to the success of any intervention is setting reasonable and achievable specific goals rather than having either vague goals or no goals at all. An example of an appropriate goal for the end result of lowering serum cholesterol levels would be: eat oatmeal for breakfast three times a week, not increase dietary fiber [80]. As much as possible, approach

goal setting as what the client can have, not what they cannot have. Regular feedback on goal attainment is important to reinforce self-efficacy. The need for feedback typically diminishes as the patient's skills improve.

Problem Solving

Problem-solving skills provided to and practiced by the patient should address specific barriers to behavioral change related to chronic illness. It is especially important part of self-management for patients with diabetes. Glasgow et al. [82] described a specific technique for analyzing problems and developing solutions: "S—specify the problem; T—think of options; O—opt for the best solution; and P—put the solution into action." It is also suggested that patients look beyond the obvious solution and brainstorm to find multiple solutions to barriers to behavioral change [75].

Self-Monitoring

Self-monitoring is associated with improved treatment outcomes. It increases awareness of behaviors and helps to identify barriers to change; self-monitoring also identifies behavioral patterns and facilitates recognition of program progress made toward achieving a goal [2]. This entails keeping a detailed record of behaviors that influence diet or physical activity. The record may include what foods were eaten and where they were eaten; frequency, duration, and intensity of physical activity; any physical measurements, for example glucose levels; and thoughts associated with the behavior. Self-monitoring strategies can reflect the patient's self-response or external prompts, such as e-mail reminders or personal digital assistant programs can be used to help motivate patients.

Feedback

Feedback is effective in reinforcing positive behavioral changes and increasing self-efficacy [80]. Those at high risk for CVD are more likely to respond to feedback than those not receiving it [83].

MOTIVATIONAL INTERVIEWING

Lack of motivation is a major reason for backsliding on the readiness to change continuum outlined earlier in the transtheoretical model and can result in a lack of long-term behavioral change. Motivational interviewing was shown to be a highly effective strategy, especially when coupled with CBT. Goal setting, problem solving, and self-monitoring were effective strategies in helping individuals maintain behavioral changes. Motivational interviewing is a technique used by counselors to help individuals build motivation. It has been described as "a client-centered, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence" [84]. Motivational interviewing is used to identify and resolve discrepancies between desired and actual behaviors and to increase the motivation to change behaviors. It is client-centered and adheres to the concept that behavioral change is a shared responsibility of the client and practitioner and practitioners can enhance motivation to change or contribute to resistance [85].

The principles of motivational interviewing include expressing empathy, which suggests an acceptance and understanding of the client's perspective and situation; developing discrepancy, which emphasizes the discrepancy between present behavior and goals can facilitate change; avoiding escalating resistance from the client and, if present, changing strategies to assist change; rolling with resistance or provide a comfortable atmosphere for change; and supporting self-efficacy since confidence in the ability to make changes or achieve goals is a powerful motivator [80,84].

Motivational interviewing is an evidence-based counseling strategy that builds on several behavioral theory models, including the transtheoretical model of change, and is best applied to individuals who are not ready to change behaviors (pre-contemplation, contemplation, or preparation) or are unwilling or are ambivalent about changing diet or lifestyle. Reflective listening, eliciting self-motivational statements, and asking open-ended questions to elicit self-motivational statements are specific strategies that can be used [80]. Although developed originally for individuals with substance abuse, motivational interviewing has been used effectively to reduce energy [86] and sodium [87] intake and to increase intake of fruit and vegetables [88]—all of which would be important in counseling patients with CVD. It is less clear if behavioral changes can be sustained over time and what the overall effect on health is. Motivational interviewing and health-promoting behaviors have been recently reviewed [89].

MULTICULTURAL COUNSELING

The majority of conventional theories that guide behavioral change strategies were developed by white males of European descent; they may have gender and cultural limitations and may not consider the influence the family has on the patient. Although all counseling occurs in a cultural context, counseling is only considered multicultural or cross-cultural when the counselor is of a different racial/ethnic group than the individual receiving the counseling. Effective multicultural counseling requires flexible techniques and training in cultural sensitivity and cultural norms [80]. This issue becomes more complex when individuals indentify with more than one culture. As the United States moves to a racial/ethnic plurality, it is critical that more individuals be competent in cross-cultural counseling and that more individuals from different races/ethnicities become health professionals.

It is vital to develop cultural strategies to address the needs of specific groups. It is also important to consider all patients as individuals. For example, Latinos in the United States come primarily from Mexico, but they also come from all Central and South American countries and the countries of the Caribbean. Knowledge, attitudes, and beliefs, as well

as food, the role of the family in food and health norms, and languages spoken and understood may be different. The level of literacy, including health literacy, and acculturation, or the process by which immigrants adopt the attitudes, beliefs, and dietary practices of the host country, must be considered and how complete any acculturation is [90].

Latinos are the largest ethnic minority in the United States; they are at high risk for developing diet-related chronic diseases, including CVD. A recent review suggested that there was no relationship between intake of dietary fat and percent energy from fat and that less acculturated individuals consumed more fruit, rice, beans, and whole milk and less sugar, sugar-sweetened beverages, snacks, and added fats [91]. Dietary acculturation may have a negative effect on the diet and health of immigrants and places them at higher risk for developing diet-related chronic diseases [90–92]. Although it is important for counselors to develop cultural sensitivity, this was not sufficient for a successful intervention and it needed to be combined with behavioral change strategies and awareness of the individuals' socioeconomic status [90].

ROLE OF HEALTH CARE PROVIDERS IN DIETARY INTERVENTIONS

The majority of individuals seeking to change dietary behaviors to reduce the risk of CVD do not choose either highly restrictive programs or meal replacement programs. Many of those interested in dietary change rely on group or individual education or counseling by health professionals, including physicians and RDs.

Healthy People 2020 [5] has as a goal to "Increase the proportion of physician office visits made by patients with a diagnosis of cardiovascular disease, diabetes, or hyperlipidemia that include counseling or education related to diet and nutrition" from 20.8% to 22.9% (+10%). Physician advice is highly valued by patients [93], presenting an ideal opportunity to provide counseling to patients about reducing risk factors of CVD. Those receiving advice about dietary change from a physician were more likely to report a healthy diet than those not receiving this advice [94].

Family physicians and general internal medicine physicians screen for CVD risk factors and may provide initial advice on lifestyle changes to patients who present with risk factors, such as high LDL-C or low HDL-C levels. Sixty-one percent of individuals surveyed by the Academy of Nutrition and Dietetics (AND) [95] cited physicians as very credible sources on nutrition. Paradoxically, the same survey showed that only 10% of respondents used physicians as a source of nutrition information—physicians ranked lower on this question than the Internet (~25%) or family and friends (~20%).

The link between nutrition and chronic disease is widely understood by physicians and they can be effective counselors for patients with CVD [96]. However, many physicians do not feel prepared to do nutrition counseling with their patients [97] or do not believe that nutrition counseling is one of their responsibilities [98]. Most physicians have not been trained in nutrition counseling, and barriers to physician counseling for CVD and CVD risk factors include lack of time and compensation [98], nutrition knowledge [97,98], low self-efficacy [97], lack of knowledge of the guidelines [99], ineffective communication between doctors and patients [99], and "clinical inertia" [100].

During an office visit, a patient spends only about 10 min with a physician [101], suggesting that time is a principal barrier to effective nutrition counseling. Referral of patients with dyslipidemia, CHD, or hypertension to an RD can expand the time available for a counselor to spend with a patient. Implementing the nutrition care process [102], the RD can provide quality theory-driven interventions and provide patients with effective nutrition interventions to reduce CVD risk [103]. Overall, however, providing nutrition information is a shared responsibility among physicians, RDs, and other health professionals [11].

EFFECTIVENESS OF NUTRITION INTERVENTIONS: THE EVIDENCE

The AND's Evidence Analysis Library (EAL) Nutrition Counseling Workgroup recently conducted a systematic review of the literature related to behavioral change theories and strategies used in nutrition counseling [63]. They found that there was strong evidence to support the use of a combination of behavioral theory and CBT in facilitating behavioral change targeted to dietary habits, weight, and cardiovascular risk factors. The evidence was fair that problem-solving strategies were effective for diet management and weight loss, but the EAL noted that the studies available were small and limited to women. The effectiveness of client self-selected behavioral goal setting and goal attainment intervention was also validated. There was little evidence that cognitive restructuring was effective in patients without eating disorders and there was no evidence that stress management or stimulus control were effective strategies in eliciting behavioral change. The EAL also found that the evidence was fair that group counseling was more effective than individual counseling and that short-term CBT (less than 6 months) could result in long-term behavioral changes.

Nutrition Care Process

In 2003, the AND published the Nutrition Care Process, which they termed "a road map to quality care and outcomes management" [102]. The four steps of the nutrition care process are (1) nutrition assessment, (2) nutrition diagnosis, (3) nutrition intervention, and (4) nutrition monitoring and evaluation. Nutrition assessment has five domains: food/nutrition-related history; anthropometric measurements; biochemical data, medical testing, and procedures; nutrition-focused physical findings; and client history. It is essential that a counselor understands these components for effective counseling and to be able to help the client/patient be able to set the behavior goals that will help

them meet the ultimate health outcome goals, such as weight loss or lowering LDL-C levels. Nutrition diagnosis has three domains within which the problems fall: intake, clinical, and behavioral/environmental. From the standpoint of behavioral counseling, understanding behavioral/environmental aspects of the client, their family, and their living situation will help the client address potential barriers and find unique solutions to these barriers. There are four domains of nutrition intervention: food or nutrient delivery, nutrition education, nutrition counseling, and the coordination of nutrition care. Nutrition monitoring and evaluation terms are coupled with the first four domains of nutrition assessment [102,104].

The nutrition education domain is further divided into content with instruction intended to lead to nutrition knowledge, and application, with "training intended to lead to nutrition-related result interpretation or skills." Nutrition counseling, on the other hand, is defined as "a supportive process, characterized by a collaborative counselor-patient/client relationship, to set priorities, establish goals, and create individualized action plans that acknowledge and foster responsibility for self-care to treat an existing condition and promote health." This domain is divided into a theoretical basis approach and strategies [104]. Nutrition education or counseling is critical to elicit long-term dietary change.

Client/Patient and Health care Professional Contact

Nutrition counseling can be provided to individuals or groups and in single or multiple sessions. The advantage to group counseling is that individuals can learn from each other and provide support to group members. The disadvantage is that less time is available to address individual problems. Group counseling tends to be more effective than individual counseling [63].

Multiple sessions tend to be more effective than single sessions since frequent contact helps to establish trust between the patient and provider, which is especially important among racial/ethnic minorities. Continued contact can also help patients progress through stages of change, provide patients with multiple skills, and allow for follow-up that can reinforce positive behavioral change. Ongoing contact can be face-to-face, via the telephone, e-mail, or the Internet. As contact decreases, new behaviors may wane and actually cease if contact stops. The majority of interventions that induce long-term behavioral changes involved multiple contacts [2].

Long-Term Dietary Change

Despite consistent health messages, the general public may not make dietary changes to improve their health; thus, nutrition interventions are critical, especially for those with chronic disease or risk factors for chronic disease [105]. To be effective in reducing CVD risk factors, nutrition interventions need to influence behaviors that are sustainable. When patients and health professionals are setting goals, it is important to consider short-term, as well as long-term goals. For most patients that follow a diet to reduce CVD risk factors, significant reductions have been shown within 4–6 weeks and cholesterol reduction goals can be met within 3 to 6 months [106]. With a well-designed intervention, highly motivated individuals can sustain reduced fat intake and increased intake of fruit, vegetables, and fiber for 12 months, but for most, sustaining changes over longer periods was less successful [105].

It is clear, however, that long-term dietary changes to reduce CVD risk factors can be made by population and by individuals. Perhaps the most dramatic example of a population change was the 80% decline in coronary mortality in Finland. This reflects principally the "great" reduction in risk factors, including declines in serum cholesterol levels, blood pressure, and smoking prevalence. The greatest change in health behaviors was diet—including the type and amount of fat consumed and the intake of fresh fruit and vegetables. These changes were associated with long-term chronic disease prevention and health promotion interventions. It is unclear why the change in risk factors among the Finns is so much better than in other population, although it may be related to the collaboration among health services, nongovernmental organizations, and industry [107].

CONCLUSION

Facilitating dietary changes that reduce the risk of CVD can reduce the disease and cost burden to the United States. Dietary changes should be theory driven and individuals should be provided with the knowledge and skills to facilitate and maintain these changes. Self-efficacy and sustained motivation must compliment the knowledge and skills provided to the patient.

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4 Physical Activity and Fitness in the Prevention of Cardiovascular Disease

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CONTENTS

Physical Fitness versus Physical Activity 50
General Recommendations for Physical Activity 51
Women and CHD 51
Stroke 52
Hypertension 52
Resistance Exercise Training and Blood Pressure 53
Heart Failure 53
Diabetes 53
Metabolic Syndrome, CVD, and T2DM 53
Glycemic Control 54
Strength Training 54
Obesity 54
Central Adiposity, Inflammation, and CVD 54
"Fitness versus Fatness" Debate 55
Preventing Weight Gain 55
Physical Activity and Sustained Weight Loss 55
How Much Physical Activity Is Required for Sustained Weight Loss? 56
Resistance Training and Weight Loss 56
Lipids 56
Metabolic Syndrome 57
Different Medical Society Definitions of the Metabolic Syndrome 57
Current Prevalence Estimates 58
Physical Activity and Prevalence of the Metabolic Syndrome 58
Cardiorespiratory Fitness and the Metabolic Syndrome 58
Muscular Strength and the Metabolic Syndrome 58
Conclusion 58
References 59

Cardiovascular disease (CVD), as defined by the Centers for Disease Control and Prevention (CDC), encompasses coronary heart disease (CHD), stroke, hypertension, and heart failure (HF).[1] Nearly 2400 Americans die from some manifestation of CVD every day; approximately one in every 37s.[1] CVD has been the leading cause of death since 1900 and remains so despite a decade-long decline in CVD mortality.[1]

Data from the National Heart, Lung, and Blood Institute predict that some 785,000 Americans will experience a first myocardial infarction this year and approximately 470,000 will be the victim of a reinfarction.[1] Of these, it is estimated that 21% will be "silent" with no symptoms or symptoms other than angina which are missed or ignored.[1] The relative risk of CHD attributable to physical inactivity ranges from 1.5 to 2.4, an increase in risk similar to that estimated for high cholesterol, hypertension, or cigarette smoking.[1] Given that more than half of all Americans do not engage in regular physical activity of even moderate intensity with nearly 1 in 4 reporting no leisure-time physical activity (LTPA)[2] and that the greatest reduction in risk for CHD appears to be for those engaging in even modest amounts of physical activity compared with the most physically inactive,[3] even relatively small increases in physical activity could potentially result in a significant decrease in CHD for a large portion of the American population. For example, epidemiological data suggest that the estimated 2.3% decline in physical inactivity between 1980 and 2000 prevented or at least postponed 17,445 deaths due to CHD in the United States.[4]

In spite of the overwhelming evidence implicating physical inactivity as an important and significant risk factor for CHD, fewer than half of adults meet even the minimum recommendation for aerobic exercise.[5] Statistics for young people are even more alarming with fewer than 20% of adolescents performing the recommended ≥60 min of daily physical activity.[6]

Despite the documented lack of physical activity in the United States, and the well-established benefits of regular exercise, many physicians are not encouraging their patients to exercise and lose weight.[7–9] Of equal importance, they do not appear to be adequately prepared to provide recommendations for exercise and physical activity. For example, a survey of 175 primary care physicians revealed that only 12% were aware of the recommendations of the American College of Sports Medicine (ACSM) for physical activity.[9] An evaluation of 51 internal medicine residents reported that while 88% were confident in their knowledge of the benefits of exercise, only about 25% demonstrated adequate knowledge useful for patient counseling.[10]

Health care professionals need to promote physical activity with all of their patients. In that regard, an understanding of the health benefits associated with physical fitness and regular physical activity is fundamental. This chapter reviews the evidence linking greater physical activity and fitness with primary prevention of cardiovascular and metabolic disease through effective risk factor management. Recommendations for exercise are also provided both in general terms and for specific conditions.

PHYSICAL FITNESS VERSUS PHYSICAL ACTIVITY

Physical fitness, specifically cardiorespiratory fitness, is defined here as the ability to deliver and utilize oxygen during sustained activity and typically quantified as maximal oxygen uptake (VO_{2max}). When respiratory gases are measured with a metabolic cart during a maximal graded exercise test, VO_{2max} is valid and reliable. However, submaximal tests or those relying on indirect measures such as time to exhaustion are subject to considerable error. Measures of physical activity, on the other hand, usually rely on retrospective self-reported data (i.e., physical activity questionnaires). Nonvocational or LTPA is most commonly assessed. Vocational physical activity, household chores, and biking or walking to work are also sometimes quantified but less often. The definitions of physical activity vary greatly from study to study and the components of physical activity or exercise such as intensity, duration, and frequency are often not reported or inadequately assessed.

The categorization of physical activity (i.e., low, moderate, or high) also varies from study to study. Many studies use different criteria for moderate- and vigorous-intensity exercise or activity. ACSM defines moderate physical activity as any activity requiring 50%–70% of VO_{2max} or maximal heart rate.[11] Vigorous physical activity is anything greater than 70% VO_{2max} or maximal heart rate.[11] Walking or brisk walking is generally recommended as the type of exercise that meets the criteria for moderate physical activity. However, it is important to understand that the intensity of walking, or any exercise for that matter, is relative to an individual's age, physical condition, and fitness level. For example, based on the ACSM Guidelines for Exercise Testing and Prescription,[11] even brisk walking may not be of sufficient intensity to meet the minimum criteria for moderate physical activity in a normal, healthy individual of college age. Conversely, brisk walking might be considered vigorous activity for someone over the age of 65 years. As such, any exercise recommendations should be applied relative to the individual's capabilities and limitations.

Surprisingly, physical fitness has been shown to be only modestly correlated with physical activity with correlations ranging from 0.09[12] to 0.60.[13] In a meta-analysis of 7 physical fitness and 16 physical activity cohorts cited in the 1996 Surgeon General's Report,[14] Williams[3] found that the risk of CHD or CVD decreased linearly with increasing percentiles of physical activity. He also found that the reduction in risk for CHD or CVD associated with increasing percentiles of physical fitness demonstrated a precipitous decrease occurring just before the 25th percentile of the physical fitness distribution. Further, at all ≥25th percentiles, the reduction in risk for CHD and CVD was significantly greater for physical fitness compared to physical activity (Figure 4.1).

These findings are supported in a more recent comparison of fitness versus physical activity in predicting all-cause mortality in a cohort of 842 men referred for exercise testing.[12] While both physical activity and fitness were strong predictors of all-cause mortality, physical fitness was a stronger predictor of mortality than activity level. A 1000 kcal/week increase in physical activity was found to be similar to a 1 MET (metabolic equivalent; oxygen uptake of 3.5 mL/kg/min) improvement in fitness with both conferring a 15%–20% reduction in mortality. Of equal, if not greater, interest, these data also demonstrated that 40% of the reduction in mortality occurred between the least active or fit and the next least fit or active groups suggesting that even modest increases in physical activity or fitness, especially in those who are inactive, may result in a significant reduction in mortality.

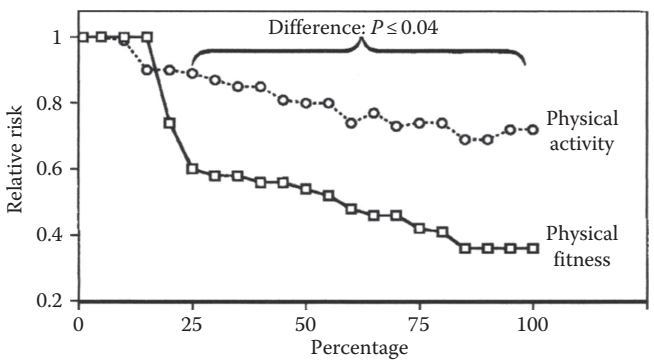


FIGURE 4.1 Estimated dose–response curve for the relative risk of either CHD or CVD by sample percentages of fitness and physical activity. Studies weighted by person-years of experience.

GENERAL RECOMMENDATIONS FOR PHYSICAL ACTIVITY

In 1996, the Surgeon General's Report on Physical Activity and Health recommended "people of all ages to include a minimum of 30 min of physical activity of moderate intensity (such as brisk walking) on most, if not all, days of the week. It is also acknowledged that for most people, greater health benefits can be obtained by engaging in physical activity of more vigorous intensity or of longer duration."[14] More recently, the 2008 Physical Activity Guidelines for Americans[15] provide updated and more specific recommendations for different age groups and some clinical population. Following is a very brief summary of their recommendations:

Adults

- All adults should avoid inactivity. Some physical activity is better than none, and adults who participate in any amount of physical activity gain some health benefits.
- For substantial health benefits, adults should do at least 150 min/week of moderate-intensity, or 75 min/week of vigorous-intensity, aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity.
- Adults should also do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on ≥2 days a week, as these activities provide additional health benefits.

Children and Adolescents

- Children and adolescents should do 60 min (1 h) or more of physical activity daily.
- *Aerobic*: Most of the ≥60 min a day should be either moderate- or vigorous-intensity aerobic physical activity and should include vigorous-intensity physical activity at least 3 days a week.
- It is important to encourage young people to participate in physical activities that are appropriate for their age, that are enjoyable, and that offer variety.

Older Adults

- When older adults cannot do 150 min of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow.
- Older adults should do exercises that maintain or improve balance if they are at risk of falling.
- Older adults should determine their level of effort for physical activity relative to their level of fitness.
- Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely.

WOMEN AND CHD

About 8.4 million women in the United States have a history of heart attack, angina pectoris, or both. Of these, 3.5 million have a history of myocardial infarction.[1] Each year over 350,000 women will have a new or recurrent MI.[1] Twenty-three percent of women age 40 and older die within a year after their first MI compared with 18% of men.[1] Because women typically have heart attacks at older ages than men do, they are more likely to die from them within a few weeks.[1]

Despite these overwhelming statistics, surveys indicate that some 43% of women still do not know that CHD is by far the number one killer of women in the United States.[1] And while regular physical activity has been demonstrated to significantly reduce the risk of CVD in women, they are on average less physically active than men with only 53.1% of women compared with 60.3% of men engaging in moderate to vigorous activity ≥3 days/week.[5]

Although a greater exercise volume and/or intensity appears to produce greater health benefits for most people, the literature examining the relationship between exercise intensity and risk for CHD is not unequivocal.[3] A meta-analysis of 16 gender-specific physical activity cohorts found that the risk for CHD decreased linearly with increasing percentiles of physical activity but examination of the individual cohorts revealed considerable variation in the outcomes.[3] This inconsistency in findings has been observed elsewhere[17] and may reflect real differences in study cohorts differing in age, gender, level of fitness, and other important factors but has also been ascribed to differences in study design. For example, in the 16 studies he examined, Williams[3] found that the intervals (tertiles, quartiles, etc.) reported, differed greatly with nine studies using three levels, six using four levels, and one study using six levels.

Despite issues related to study design, there is evidence to suggest that the dose–response relationship between exercise intensity and risk for CHD or mortality may differ between men and women.[16–20] For example, based on data from the Nurses Health Study, a cohort of 72,488 female nurses 40–65 years old, Manson et al.[17] concluded that "the reduction in risk for CHD for women who walked at a brisk pace ≥3 h/week was similar to those women who engaged in regular vigorous (≥6 MET) exercise." Data from the Women's Health Study[16] showed that walking 1–1.5 h/week was associated with a 51% reduction in risk for CHD but walking ≥2 h/week conferred no greater reduction in risk. More vigorous activity was not associated with a lower risk for CHD, comparing highest with lowest. Similarly, the relationship between walking pace and risk for CHD did not demonstrate a linear trend.

Other studies have not demonstrated an association between physical activity/inactivity and CHD and/or mortality in women with one review reporting no relationship between physical inactivity and CHD in 10 of 14 studies.[18] More recently, Blair et al.[19] found that all-cause mortality rates in women did not differ across the range of physical activity levels. The Framingham

Study also found no association between physical activity level and mortality in women.[20]

Therefore, it would seem that the risk reduction associated with physical activity is variable, depending on the study population. As such, the apparent gender differences in the response to physical activity may be mediated by the physical activity levels of the study participants. As an example, the most active 20% of women in the Women's Health Study expended ≥1500 kcal/week in LTPA whereas men in highest quintile of physical activity in the Harvard Alumni Health Study reported expending ≥3129 kcal/week in LTPA.[3]

The relatively limited data on the relation between physical fitness, and risk for CVD and/or mortality in women suggests a greater similarity with studies of men, when compared with studies of physical activity. For example, data from the St. James Women Take Heart Project demonstrated a 17% reduction in mortality for every 1 MET increase in exercise capacity.[21] As such, it would appear that women who engage in exercise vigorous enough to improve aerobic fitness gain health benefits comparable to their male counterparts.

STROKE

While the incidence of stroke has been declining, it is estimated that 795,000 people in the United States experience a new (~610,000) or recurrent (~185,000) stroke each year.[1] Of these, the large majority are ischemic (~87%) with the remainder being hemorrhagic in nature.[1] The risk of a stroke for African Americans is nearly double that for Caucasians and tends to occur at a younger age.[1] Hispanics, particularly Mexican Americans, have significantly higher rates of ischemic stroke and at a younger age.[1] Annually, 55,000 more women than men have a stroke with the incidence in women aged 45–54 years especially high.[1]

Some 200,000–500,000 transient ischemic attacks (TIAs) are estimated to occur in the United States each year and the incidence is higher in men, African and Mexican Americans.[1] The occurrence of a TIA increases the risk of a stroke both short term and long term.[1] Approximately 15% of all strokes are preceded by a TIA and about 12%–13% of individuals will die within a year of a TIA.[1]

The most important risk factors for stroke include history of TIA, preexisting CHD, age, hypertension, diabetes mellitus (DM), cigarette smoking, and atrial fibrillation.[1] Physical inactivity has also been shown to increase the risk of a stroke and stroke mortality but its relationship to cerebral events is less well understood than that for CHD.[1] Meta-analyses have shown that the reduction in risk for stroke associated with aerobic exercise/activity ranges between 20% and 40% depending on the type of stroke and study design.[22,23] The benefit for women is less clear and may not be as great as that for men.[22] It remains unresolved as to whether or not a dose–response relationship exists between level of physical activity and stroke risk. While those studies that looked at different levels of physical activity generally found a greater benefit for higher levels of physical activity, there was a real lack of consistency in their findings.[22] In addition, the criteria for different levels of physical activity are not uniform, varying from study to study and often poorly quantified. As such, an exercise prescription to optimize the reduction in risk for stroke remains undetermined. Currently, the American Heart Association (AHA) recommends moderately intense aerobic physical activity for *at least* 30 min/day to reduce the risk of ischemic stroke.[24] While there is evidence that greater muscular strength in youth is associated with a modestly reduced risk (~5%–10%) for stroke later in life,[25] the relationship between muscular strength, strength training, and stroke risk remains virtually unexplored.

HYPERTENSION

Based on data from the National Health and Nutrition Examination Survey (NHANES), the AHA estimates that over 76 million adults or almost 1 in 3 American adults suffer from hypertension (systolic blood pressure [SBP] ≥140 mm Hg and/or diastolic blood pressure [DBP] ≥90 mm Hg).[1] Approximately 69% of individuals who have a first myocardial infarction, 77% of those who suffer a first stroke, and 74% of those who have HF are hypertensive.[1] A meta-analysis of 61 studies involving more than 1 million individuals demonstrated that mortality associated with both ischemic heart disease (IHD) and stroke increases linearly from levels as low as 115 mm Hg SBP and 75 mm Hg DBP.[26] For every 20 mm Hg SBP or 10 mm Hg DBP increase in blood pressure, there is a doubling of mortality from both IHD and stroke.[26] Those with hypertension have a shorter life expectancy, shorter life expectancy free of CVD, and can expect to live more years with CVD compared with those who are normotensive.[1]

Regular physical activity has been shown to be an effective way to lower blood pressure in 75% of persons with hypertension.[27,28] Compared with sedentary adults, those who are physically active have a lower incidence of hypertension,[29–31] with blood pressures that average 5 mm Hg lower.[32] Higher levels of occupational and/or LTPA are associated with lower BP.[27,31,33] These data have led to recommendations for regular physical activity as lifestyle therapy for the prevention and management of hypertension.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)[33] recommends regular aerobic physical activity such as brisk walking at least 30 min/day, most days of the week for the prevention and management of hypertension. In a meta-analysis of 44 trials of at least 4 weeks duration and after controlling for other factors, increased physical activity was associated with a small but significant decrease of 3/2 mm Hg in normotensive subjects and 7/6 mm Hg in hypertensive subjects.[34] The training intensity in these studies averaged 65% of heart rate or VO_2 reserve. However, the characteristics of the training programs (intensity, duration, and frequency) explained less than 5% of variance in blood pressure response. Weekly energy expenditure was not significantly related to the changes in SBP or DBP. Vigorous exercise was not found to be different from moderate-intensity exercise in its ability

to reduce blood pressure, with some studies showing that exercise at 40% of VO_2 reserve to produce a greater reduction in SBP than exercise at 65%–75% of VO_2 reserve.[35,36] As such, and per JNC VII, regular moderate-intensity exercise is recommended for the prevention and management of hypertension.

Resistance Exercise Training and Blood Pressure

Resistance training is generally recommended as an adjunct to aerobic activity. On average, studies have reported 3 mm Hg reductions in resting SBP and DBP following progressive weight-lifting programs.[30,37–39] Although this decrease may seem small, a 3 mm Hg reduction lowers the risk of CHD, stroke, and all-cause mortality.[30] Two to three days per week of total body resistance training is generally recommended.[16,40–42] However, as with aerobic exercise, the "optimal" exercise prescription for strength training is not known. More specifically, low- to moderate-intensity strength training (30%–40% of a 1 repetition maximum [1RM] for upper body exercises, and 50%–60% 1RM for lower body exercises) is currently recommended by some for the prevention and management of high blood pressure.[27,42] Rezk et al.[43] showed that both single bouts of high- or low-intensity resistance exercise lower SBP, but only low-intensity training lowered DBP. Other studies reported that high-intensity resistance training reduced neither SBP nor DBP, and actually raised SBP in some individuals.[44]

The currently recommended strength training program to optimize BP reduction is 1–3 sets of 10–15 repetitions for each of the major muscle groups (thighs [hamstrings and quadriceps], hips, back, chest, arms, and abdominals), 2–3 days/week.[30,42]

HEART FAILURE

It is estimated that some 5 million Americans suffer from HF (also known as congestive heart failure).[1] The risk of developing HF increases with age; by the age of 40 years, both men and women have a one in five risk of developing HF some time in their lives.[1] Both the incidence and prevalence of HF are particularly high in minorities, especially African Americans.[1] HF occurs earlier and mortality is higher in African Americans, compared to Caucasians.[1]

Surprisingly, few studies have examined the relationship between physical activity and primary prevention of HF. Two large longitudinal studies exploring this association found that compared to sedentary individuals, those who engaged in regular vigorous exercise had a 15%–35% lower risk for developing HF.[45,46] Vigorous activity was defined as activities "vigorous enough to work up a sweat"[45] such as running, jogging, swimming, heavy gardening, or competitive sports.[46] The reduction in risk was correlated with the frequency of vigorous exercise in a dose–response manner.[45] Activity of a moderate intensity, defined as >4 h/week of walking, cycling, or light gardening was associated with ~15% reduction in risk.

DIABETES

The latest available data from NHANES estimates that 12.9% of Americans over the age of 19 years have DM, of which >90% are classified as Type II (T2DM).[47] Insulin resistance (IR) often precedes the onset of T2DMM and is prevalent in the prediabetic states of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Nearly 30% of Americans are classified as prediabetic with IFG and/or IGT.[47] This means that more than 40% of all adults have some degree of abnormal glycoregulation.[47] The prevalence of CHD has been estimated to be as high as 55% in adult diabetics and T2DM is an independent risk factor for myocardial infarction and CVD in both men and women.[48,49] T2DM is a predictor of ischemic stroke and HF, and DM increases the overall CV risk in patients with preexisting HF.[50,51] Compared to nondiabetics, mortality from CHD has been reported to be twice as great in diabetic men and four to five times greater in diabetic women.[52] CVD is responsible for at least two-thirds of deaths in adults with DM.[52]

Metabolic Syndrome, CVD, and T2DM

The clustering of risk factors known as the metabolic syndrome (see section later for definition and more information) is predictive of both T2DM and CVD. It is associated with a twofold increase in the risk for cardiovascular events and a fourfold increase in the development of T2DM.[53] Abdominal obesity in particular is an independent risk factor for IR[54,55] and T2DM.[56] Much of the increased risk of CHD and CVD associated with T2DM can be attributed to the presence of the metabolic syndrome.[57] One study reported 10 year cardiovascular mortality to be 3.55 times greater in men with metabolic syndrome compared to those without the condition.[58]

Numerous studies have demonstrated an inverse relationship between physical activity and/or fitness and the risk for developing T2DM.[59–67] Men of low fitness have a two to three times greater risk of developing T2DM compared to those in the higher fitness categories.[59,60] Similarly, physical activity shares an inverse relationship with the risk for T2DM in a dose–response manner. Even just daily walking for more than 30 min has been shown to reduce the risk of developing T2DM by 20%–45%.[63,66–69] Brisk/faster walking was associated with a lower risk independent of time spent walking.[63,66,67] In an interventional trial involving 18 previously sedentary middle-aged men and women, 6 months of walking (minimum of 3 days/week for 30 min) resulted in improved insulin sensitivity.[70] Sedentary behaviors such as excessive television watching have been demonstrated to increase the risk for T2DM even after – controlling for diet and physical activity levels. It has been estimated that 43% of new cases of diabetes could be prevented by watching TV less than 10 h/week and engaging in brisk walking for ≥30 min/day.[68] Modest improvements in diet and exercise habits have been shown to reduce the incidence of T2DM even in those at highest risk for developing it—those with IFG and/or IGT.[71–73]

Glycemic Control

Studies of aerobic exercise training have shown significant but modest reductions in glycosylated hemoglobin (HbA1C, long-term index of glycemic control) of about 8% from baseline.[74,75] The exercise intensity in these studies accounted for almost 83% of the differences in post-intervention HbA1C compared to 21% determined by exercise volume. Those interventions with an intensity >65% of VO_{2max} demonstrated the greatest improvement in HbA1C. As such, exercise interventions for glycemic control should include some vigorous exercise.[76]

Strength Training

Resistance training, especially in combination with aerobic exercise training, can significantly improve HbA1C levels, fasting blood glucose, and insulin sensitivity.[77] Additionally, other risk factors, such as blood pressure, have been shown to be significantly reduced in diabetics with a program combining strength and aerobic training compared with either aerobic or resistance training alone.[77] As such, The American Diabetes Association now recommends strength training, in addition to aerobic exercise training as part of a program to prevent or manage T2DM.[78] Weight training has been found to be safe in persons with CVD, ST depression, myocardial ischemia, ventricular dysrhythmias, and other cardiovascular complications.[78] The myocardial demands of high-intensity weight training are comparable to activities such as stair-climbing, walking uphill, or carrying 20–30 lb of groceries.[78]

Following are some of the specific recommendations from the American Diabetes Association Consensus Statement on Physical Activity/Exercise and Type II Diabetes[78]:

- People with IGT should begin and continue a program of weight control, including at least 150 min/week of moderate to vigorous physical activity and a healthful diet with modest energy restriction.
- To improve glycemic control, assist with weight maintenance, and reduce risk for CVD, the panel recommends 150 min/week or more of moderate-intensity aerobic physical activity and/or 90 min/week or more of vigorous aerobic exercise. The physical activity should be distributed over at least 3 days/week, with no more than two consecutive days without physical activity.
- Compared with lower volumes of activity, performing at least 4 h/week of moderate to vigorous aerobic and/or resistance exercise is associated with greater CVD risk reduction.
- For long-term maintenance of major weight loss (≥13.6 kg or 30 lb), larger volumes of exercise (7 h/week of moderate or vigorous aerobic physical activity) may be helpful.
- Unless contraindicated, people with type 2 diabetes should be encouraged to perform resistance exercise three times per week, targeting all major muscle groups. This should progress to 3 sets of 8–10 repetitions at a weight that cannot be lifted more than 8–10 times. Initial supervision and periodic reassessments by a qualified exercise specialist are recommended to ensure that resistance exercises are performed correctly, to maximize health benefits, and to minimize the risk of injury.

OBESITY

Based on the most recent data from the NHANES, and using body mass index (BMI, body weight in kg/(height in m)^2) as the criterion measure, the prevalence of overweight and obesity in the United States continues to rise and has increased significantly just from 1999 to 2008.[79] In adults, overweight is defined as a BMI of 25–29.9 kg/m^2. Obesity is defined as a BMI ≥ 30; extreme (formerly morbid) obesity is defined as a BMI ≥ 40. Among men, the prevalence of obesity increased from 27.5% in 1999–2000 to 31.1% in 2003–2004 to 32.2% in 2007–2008.[79] In women, the prevalence of obesity was even higher: 33.4% in 1999–2000 to 33.2% in 2003–2004 to 35.5% in 2007–2008.[79] The prevalence of extreme obesity also rose from 2003–2004 (2.8% for men and 6.9% in women) to 2007–2008 (4.2% for men and 7.2% for women).[79] Finally, differences in the prevalence of obesity by race/ethnicity continued with 44.1% and 39.3% reported for non-Hispanic blacks and Mexican Americans, respectively.[79]

Over the last two decades, it has become increasingly apparent that abdominal adipose tissue has unique metabolic properties and may be more predictive of CVD, metabolic syndrome, and diabetes than BMI or measures of overall adiposity.[80–84] Abdominal or central obesity is most commonly assessed by measuring waist circumference or waist-to-hip ratio (WHR). From 1988–1994 to 1999–2000 (most recent data available), mean waist circumference of adult Americans increased from 95.3 to 98.6 cm in males and from 88.7 to 92.2 cm in females.[85]

Despite these rather alarming trends, only 40.3% of obese patients were advised to lose weight by their family physician in 2004, down from 42.3% in 1994.[86] An evaluation of an academic pediatric hospital found that only little more than half (53%) of the children who met the NHANES criteria for overweight (≥95th percentile for BMI) were identified as such by their primary care physician.[87] Interestingly, while a majority (69%) of the children's charts contained an "adequate" dietary history, only 15% included information regarding physical activity and/or television watching.

Central Adiposity, Inflammation, and CVD

Atherosclerosis has now come to be understood as an inflammatory disease.[88–91] A growing body of evidence further demonstrates that greater adipose tissue mass, especially visceral adipose tissue, directly contributes to systemic inflammation.[92–94] The proinflammatory state associated with abdominal obesity has been proposed as a common

underlying condition linking CVD, IR/type 2 diabetes, and the metabolic syndrome.[95–97] While a complete discussion of the complex physiology and mechanisms of adipose-related inflammation is beyond the scope of this chapter, it is increasingly evident that visceral adipose tissue secretes a veritable host of proinflammatory cytokines. Greater levels of central adiposity have been shown to be associated with higher circulating levels of these proinflammatory proteins such as interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and C-reactive protein (CRP).[98–100]

A published review of lifestyle interventions and systemic inflammation observed that 9 of 12 studies reviewed demonstrated an inverse relationship between physical activity or fitness and markers of inflammation, after controlling for BMI or other measures of adiposity.[101] For example, in a 20 year follow-up of 4252 elderly men (aged 40–59 at baseline), Wannamethee et al.[102] found that physical activity level was inversely associated with levels of CRP and other inflammatory markers, even after adjusting for BMI and other covariates. In those men who went from "at least lightly active" to inactive, the levels of these markers were similar to those men who had been inactive throughout the follow-up period. Those who were inactive at baseline but increased their level of activity had levels similar to those men who had remained continuously active.

The HERITAGE Family Study examined the effects of 20 weeks of exercise training on CRP levels in 652 sedentary, but healthy, adults.[103] The training program was performed on cycle ergometers 3 days/week progressing to 50 min at 75% of baseline VO_{2max}. This protocol resulted in a substantial (17.8%) increase in VO_{2max}. However, reduction in CRP levels occurred only in the individuals with high baseline levels of CRP. The positive relationship between baseline CRP levels and exercise-induced changes has been observed elsewhere[104] and may explain, at least in part, why some studies have not found that an exercise intervention reduces levels of inflammatory markers.[105–110]

"Fitness versus Fatness" Debate

While it is well established that both increased body fat and low levels of physical activity and/or fitness are associated with increased mortality, T2DM, and CVD, it is not precisely clear as to their relative importance or how they interact. An extensive review of the literature addressing the fitness versus fatness debate as it pertains to CHD and/or CVD concluded "… physically active lifestyle and/or a moderately high fitness level (i.e., not in the bottom 20% of the population) reduces the risk of CVD/CHD in overweight or obese persons."[111] While they suggest that overweight or obese individuals who are physically fit or active have levels of risk that approach those associated with those of lean, unfit persons, they also concede that their risk is still greater than those who are fit/active and of normal weight. The authors further observed that the risk reduction associated with increased fitness or activity is greater in those who are overweight or obese compared with those of normal weight. Finally, they recommend that physical activity should be encouraged regardless of whether or not that activity induces weight loss. This recommendation is supported by the majority of the studies reviewed that found physical activity/fitness to be independent risk factors for CHD/CVD.

Addressing obesity begins with the understanding that weight gain is caused by a cumulative positive energy balance where energy intake exceeds energy expenditure. As such, weight loss can *only* occur in the presence of a negative energy balance. Maintenance of body weight, therefore, requires that energy intake matches energy expenditure. While the concept of energy balance or imbalance is conceptually simple, the respective role of diet and exercise in weight loss and management is less clear. Following is a brief summary of recent and relevant investigations of the role of physical activity in (1) preventing weight gain, (2) weight loss, and (3) weight loss maintenance.

Preventing Weight Gain

In 2003, the International Association for the Study of Obesity (IASO) released the following statement regarding physical activity and prevention of unhealthy weight gain:

> The current physical activity guideline for adults of 30 minutes of moderate intensity activity daily, preferably all days of the week, is of importance for limiting health risks for a number of chronic diseases including coronary heart disease and diabetes. However for preventing weight gain or regain this guideline is likely to be insufficient for many individuals in the current environment. There is compelling evidence that prevention of weight regain in formerly obese individuals requires 60–90 minutes of moderate intensity activity or lesser amounts of vigorous intensity activity … For children, even more activity time is recommended. A good approach for many individuals to obtain the recommended level of physical activity is to reduce sedentary behaviour by incorporating more incidental and leisure-time activity into the daily routine …[112]

Physical Activity and Sustained Weight Loss

Unfortunately, most studies do not support increasing physical activity, either alone or in combination with a calorie-restrictive diet, to be an effective means to produce short-term weight loss.[113–115] However, physical activity appears to play a major role in long-term maintenance of weight loss.[113–116] An extensive review of the role of exercise in promoting weight loss combined data sets and used weighted mean differences (WMD) to explore the efficacy of exercise interventions.[116] The randomized clinical trials (RCTs) in this review only included studies that incorporated a follow-up of at least 12 months duration to assess long-term maintenance of weight loss. A summary of their findings follows:

- Compared to diet alone, diet plus exercise produced significantly greater weight loss at 12 months (WMD = −1.95 kg), 18 months (WMD = −7.83 kg), and 36 months (WMD = −8.22 kg). In addition, there were small but significantly greater differences/improvements in high-density lipoprotein (HDL) and triglycerides (TG) at 12 months.

At 18 months, diet plus exercise demonstrated large and significantly greater reductions in SBP (WMD = −8.90 mm Hg) and DBP (WMD = −12.10 mm Hg).
- A separate analysis in this review compared diet plus behavior therapy with diet plus behavior therapy and exercise. The addition of exercise produced significantly greater weight loss at 12 months (WMD = −3.02 kg) and at 24 months (WMD = −2.16 kg). There were no significant differences between groups for cholesterol, blood pressure, or glucose.

These data suggest that regular physical activity is advantageous for sustained weight loss.

How Much Physical Activity Is Required for Sustained Weight Loss?

There is a general consensus that 2500–2800 kcal/week (60–90 min/day of moderate-intensity physical activity) is required for long-term weight loss as reflected in the recommendations and consensus statements of the U.S. Department of Health,[117] ACSM,[118] and IASO.[112] These recommendations are supported by data from the National Weight Control Registry (NWCR), a database of approximately 5000 individuals who have minimally lost 30 lbs for at least 1 year (average weight loss is about 30 kg for an average of 5.5 years).[119] Data collected on these "successful losers" indicate that more than 90% of participants expend ~2800 kcal/week in physical activity.

Resistance Training and Weight Loss

Despite claims in the popular literature, strength training is not recommended as the primary mode of exercise for weight loss.[118] While strength/resistance training has been shown to preserve fat-free mass when coupled with a calorie-restrictive diet, it has not been shown to enhance weight loss either alone or in combination with a dietary intervention.[113,115,116,118] Despite the apparent ability of resistance training to maintain muscle mass in the presence of calorie deficit, it does not appear to be able to prevent the decrease in resting energy expenditure associated with weight loss.[118,120] In the absence of a dietary intervention, some studies have shown that high-intensity resistance training can significantly increase resting energy expenditure for 16 h or more.[121–125] However, these findings are based on a very small number of subjects and are not supported by the results of other investigations.[126–128] As such, in the absence of stronger evidence, resistance training is not recommended as the primary form of exercise to promote or enhance weight loss.[118] However, weight training may provide an advantage in maintaining fat-free mass and enhancing body composition with a weight loss intervention.[118]

LIPIDS

The role of blood lipids in the pathology of atherosclerosis is well established and dyslipidemia is understood to be an important contributing factor for CHD.[129] Dyslipidemia includes elevations in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and low levels of HDL cholesterol (HDL-C).[129] In addition, newer lipid and lipoprotein measures such as lipoprotein particle size and number, apolipoproteins, and TG-rich lipoproteins (TRL) are emerging as risk factors that may also increase CVD risk.[130] The National Cholesterol Education Program Adult Treatment Panel III has published guidelines establishing lipid and lipoprotein modification goals for both primary and secondary prevention.[129] However, data from NHANES indicates that many Americans have not achieved recommended levels for all lipids and lipoproteins.[131]

One of the proposed mechanisms by which regular physical activity reduces the risk for CHD is its effect on blood lipids, especially the increases in HDL-C and reduction in TG levels.[132–134] Cross-sectional studies have consistently shown a positive association between the volume and intensity of aerobic activities and HDL-C levels and a negative association with TG levels.[135] However, reviews of the literature reveal a surprisingly inconsistent response of other blood lipids to regular aerobic exercise.[135,136] These findings may be further confounded by concurrent changes in body weight or composition. In studies without a dietary intervention, the most commonly reported change in lipids was an increase in HDL averaging 4.6%, ranging from a decrease of 5.8% to an increase of 25%. Simultaneous reductions in TG (3.7%), LDL-C (5.0%), but not TC, were also observed.[135] Changes in TC and LDL-C are much less frequently reported, are modest when they do occur, and may be more attributable to weight loss than the exercise intervention per se. As such, regular exercise alone cannot be recommended as an effective strategy to lower TC or LDL-C.[134]

Relatively few studies have attempted to evaluate the effect of the exercise prescription (intensity, volume, etc.) on blood lipids and, as such, there is no consensus on the optimal exercise regime for improving cholesterol profile. In most of the studies reviewed, the exercise intervention was performed at moderate to high intensity, three to five times per week for at least 30 min per session. Total caloric expenditure, as opposed to exercise intensity, has been proposed to be of greatest importance for blood lipids, and a threshold of between 1200 and 2500 kcal/week has been proposed.[137]

A meta-analysis of studies that explored the effect of strength training on blood lipids and dating back to 1955 found that strength training resulted in modest but significant improvements in blood lipid profiles (but not HDL-C).[138] However, while earlier studies generally demonstrated an improvement in blood lipid profile with resistance training, at least some suffered from design flaws including no or poor dietary control,[139–142] no control group,[139–141] or no control for fat loss.[140,141,143] Better designed and/or more recent studies have not found an improvement in lipoprotein profiles with resistance/strength training.[144–148]

METABOLIC SYNDROME

The clustering of established risk factors for CVD and T2DM has been recognized for decades.[149–165] In 1988, Gerald Reaven drew immense attention to risk factor clustering and CVD in his now famous "Banting Lecture" at the annual meeting of the American Diabetes Association.[153] He described a constellation of risk factors leading to development of T2DM and CVD which he termed *Syndrome X*. Reaven postulated the etiology and clinical course of three major related diseases—T2DM, CVD, and hypertension—all having a common foundation of IR and hyperinsulinemia. However, at that time, adiposity was not considered a major etiological factor.

The metabolic syndrome has been recognized as a global public health problem that is strongly linked as a seminal cause of CVD and T2DM, both of which are responsible for premature mortality and morbidity worldwide.[166–169] The metabolic syndrome is characterized by the clustering of specific cardiovascular risk factors including IR, central obesity, hypertension, and atherogenic dyslipidemia (specifically elevated triglycerides and low levels of HDL-C).[169–174] Also, depending on the medical society definition applied, microalbuminuria may also be considered another risk factor.[174]

Different Medical Society Definitions of the Metabolic Syndrome

In establishing an *official diagnosis* for the metabolic syndrome, the American Association of Clinical Endocrinologists (AACE) championed the creation of the International Classification of Disease 9th revision (ICD-9) Code 277.7 for the metabolic syndrome.[171] Currently, there are five working medical society definitions proposed for the diagnosis of the metabolic syndrome. Table 4.1 summarizes the various definitions published by the following medical societies: (1) World Health Organization (WHO),[174] (2) European Group for the study of Insulin Resistance (EGIR),[170] (3) AHA and the National Heart, Lung, and Blood Institute (NHLBI) definition[175] which refers to the updated National Cholesterol Education Program (NCEP) (2001) definition, (4) the American College of Endocrinology (ACE) and AACE consensus definition for epidemiological research,[171] and (5) the International Diabetes Federation (IDF).[172]

TABLE 4.1
Metabolic Syndrome Definitions Issued by Various Medical Societies

	WHO (1999)	EGIR (1999)	ACE/AACE (2003)	IDF (2005)	AHA/NHLBI (2005)
Requisite criteria	IGT, IFG, type 2 diabetes, insulin in top quartile of population	Insulin in top quartile of population	High risk[a]; BM1 >25 kg/m^2 or WC >102 cm (men) or >88 cm (women)	WC ≥94 cm (men) and ≥80 cm (women), and population specific for ethnic groups[b]	N/A
Other criteria—plus ≥2 of:					
Glucose	N/A	≥100 mg/dL, 2 h post-OGTT ≥140 mg/dL but not diabetes	≥100 mg/dL, 2 h post-OGTT ≥140 mg/dL but not diabetes	≥100 mg/dL, diabetes	≥100 mg/dL, diabetes or Rx
Obesity	W:H ratio >0.9 (men) or >0.85 (women); BMI >30 kg/m^2	WC ≥94 cm (men) or ≥80 cm (women)	N/A	N/A	WC ≥102 cm (men) or ≥88 cm (women)
Lipids	TG ≥150 mg/dL and/or HDL-C <35 mg/dL (men) or <39 mg/dL (women)	TG >180 mg/dL and/or HDL-C <39 mg/dL in men or women or Rx	TG>150 mg/dL or HDL-C <40 mg/dL (men) or <50 mg/dL (women)	TG ≥150 mg/dL or Rx or HDL-C <40 mg/dL (men) or <50 mg/dL (women) or Rx	TG ≥150 mg/dL or HDL-C <40 mg/dL (men) or <50 mg/dL (women) or Rx
Hypertension	≥140/90 mm Hg or Rx	≥140/90 mm Hg or Rx	>130/85 mm Hg or Rx	≥130/85 mm Hg or Rx	≥130/85 mm Hg or Rx
Other	Microalbuminuria ACR ≥30 mg/g				

WC, waist circumference; *W:*H, waist:hip; TG, triglycerides; OGTT, oral glucose tolerance test; Rx, medication; ACR, albumin:creatinine ratio; others designated in text. WHO, World Health Organization; EGIR, European Group for the study of Insulin Resistance; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; ACE/AACE, American College of Endocrinology/American Association of Clinical Endocrinologists; IDF, International Diabetes Federation.

[a] Family history of type 2 or gestational diabetes, known CVD, polycystic ovary syndrome, physically inactive lifestyle, >40 years of age, and ethnic population at high risk for a type 2 diabetes.

[b] In this analysis, Mexican American men were classified using a WC cutoff value of ≥90 cm and Mexican American women ≥80 cm.[9]

The majority of the recent research focusing on the metabolic syndrome involved the use of the NCEP definition because of its clinical utility (see Table 4.1). The NCEP definition requires that three of the following five criteria be present for a diagnosis of the metabolic syndrome: IFG represented by a fasting blood sugar ≥110 mg/dL, including T2DM; HDL-C <40 mg/dL in men and <50 mg/dL in women; triglycerides ≥150 mg/dL; an augmented waist circumference (WC) of ≥102 cm in men and ≥88 cm in women; or a blood pressure value of ≥130/85 mm Hg.

Current Prevalence Estimates

It is estimated that close to 1 billion people worldwide have the metabolic syndrome.[176] Global prevalence estimates of the metabolic syndrome vary considerably, depending on the population under study, definition applied, and study design utilized. Using the NCEP definition, the age-adjusted prevalence for the metabolic syndrome in the United States is estimated to be 34.6%. These data also showed a 10% increase in the prevalence of the metabolic syndrome in U.S. adults, from 1988 to 2002. With the metabolic syndrome becoming more common in Western societies,[176] the prevalence and incidence are anticipated to increase in line with the prevalence and incidence of obesity[177] and T2DM.[178]

Physical Activity and Prevalence of the Metabolic Syndrome

The association between physical activity or inactivity and prevalence of the metabolic syndrome is not clear, at least based on cross-sectional studies.[179–187] In most studies, the initial analysis often shows a negative relationship between physical activity level and the prevalence or risk of metabolic syndrome but this association typically disappears after controlling for other factors such as gender, age, education, socioeconomic status, or other risk factors (i.e., smoking).

Several longitudinal studies showed that increased levels of physical activity, especially of vigorous intensity, were associated with significantly and dramatically reduced risk for developing the metabolic syndrome and in a dose–response manner. Interventional studies are fewer in number but at least one study showed that 20 weeks of vigorous exercise performed for 30 min, three times per week resulted in a decreased prevalence of the metabolic syndrome (16.9%–11.8%) in 621 men and women aged 17–65 years.[188] That is, of the 105 participants with the metabolic syndrome at baseline, 32 no longer had the syndrome at the end of the study.

Cardiorespiratory Fitness and the Metabolic Syndrome

The relationship between cardiorespiratory fitness, as measured by VO_{2max}, and the metabolic syndrome has not been studied as extensively as that with physical activity. However, cardiorespiratory fitness can be more objectively measured and may be more predictive of the metabolic syndrome than physical activity per se. Cardiorespiratory fitness has been shown to be predictive of the metabolic syndrome with men of low fitness (VO_{2max} < 29.1 mL/kg/min) being almost seven times more likely to have metabolic syndrome compared with those men with a VO_{2max} ≥ 35.5 mL/kg/min.[183] Over a 4 year period, and after controlling for age, BMI, socioeconomic status, presence of CVD, smoking, and alcohol consumption, the incidence of metabolic syndrome was found to be 47% and 75% lower in middle-aged men with a VO_{2max} of 29.0–35.6 and ≥37.0 mL/kg/min, respectively, compared with those men whose VO_{2max} was less than 28.9 mL/kg/min.

The relationship between aerobic fitness and the prevalence of the metabolic syndrome appears to hold for women as well. Women with a VO_{2max} of 11 METs or greater had a prevalence of the metabolic syndrome that was one-third to one-fourth that of women of lower fitness.[189]

The precise amount and intensity of physical activity required to prevent or reverse the clustering of risk factors known as the metabolic syndrome has yet to be definitely determined. While there is evidence to suggest that regular, moderate-intensity, physical activity (such as walking 30 min on most if not every day of the week) may be preventive of the metabolic syndrome, other evidence suggests that activity of greater intensity may be required to optimally minimize risk. Greater cardiorespiratory fitness has demonstrated an even stronger negative association with the metabolic syndrome. Attainment of higher levels of fitness requires more vigorous physical activity.[11]

Muscular Strength and the Metabolic Syndrome

Evidence from the Aerobics Center Longitudinal Study (ACLS) suggests that even after controlling for age, examination date, smoking status, alcohol intake, number of metabolic syndrome risk factors at baseline, family history of diabetes, hypertension, and early onset coronary artery, men above the 75th percentile for muscular strength have a 24% lower risk for developing the metabolic syndrome compared to men in the lowest strength category.[190] Others have also illustrated the benefits of resistance training and increases in muscular strength on metabolic risk.[191–195] Muscular fitness appears to add another level of protection against the metabolic syndrome in men and may help with daily and long-term glycemic control. However, strength training is recommended as an adjunct to regular aerobic exercise, but not the sole or primary form of activity to prevent or manage the metabolic syndrome.[196]

CONCLUSION

CVD, in all its forms, represents the greatest threat by far to health and longevity in the United States and the world. The major risk factors for CVD are well known and their prevention and/or management are crucial in reducing the prevalence of CHD, stroke, hypertension, and HF. Greater physical activity and especially greater cardiovascular fitness have been shown to significantly reduce the risk for these

manifestations of CVD. The reduction in risk is largely mediated via the risk factors as described in this chapter. As such, an appropriate and individually prescribed program of regular physical activity or exercise should be a standard lifestyle intervention for individuals of all ages and abilities.

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5 Clinical Strategies for Managing Dyslipidemias

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CONTENTS

Introduction 65
Elevated Total and LDL Cholesterol 65
HDL 65
Triglycerides 66
Non-HDL Cholesterol and Apo B 66
Lipid Classification and Treatment Targets 66
Role of Lifestyle in the Management of Dyslipidemia 68
Impact of Diet 68
Weight Management 70
Exercise Effects 70
Smoking Effects 71
Conclusions and Recommendations 71
References 71

INTRODUCTION

Dyslipidemia is defined as elevated fasting blood levels of total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides (TG) and/or a reduced level of high-density lipoprotein (HDL), alone or in combination. A high prevalence of dyslipidemia exists in the United States, in particular elevated TC and LDL cholesterol (LDL-C).[1] There is generally a strong environmental/lifestyle contribution to dyslipidemia with a polygenic mode of inheritance. Familial hypercholesterolemia, an inherited monogenic, autosomal dominant form, is much less common.[2] Although lipids contribute to many vital functions in the body, an abnormal blood level of lipids and their lipoprotein carriers contributes significantly to the pathophysiology of atherosclerosis and the development and progression of coronary heart disease (CHD).

ELEVATED TOTAL AND LDL CHOLESTEROL

Large-scale, long-term, longitudinal, observational studies[3–7] have demonstrated a continuous, positive association of TC (from >180 mg/dL, a 2% increase in CHD risk for every 1% increase), even in the presence of other major risk factors.[3] Other observational studies have indicated that a concentration of apolipoprotein B-100 (apo B-100) is an even stronger predictor of CHD than LDL-C.[8,9] There also have been a number of studies that have shown an association of lipoprotein (α) (Lp (α)) with increased risk of CHD.[8,10,11] Randomized, controlled clinical trials using cholesterol-lowering drugs such as HMG-CoA reductase inhibitors (statins), cholestyramine, niacin, and fibrates have all been successful in reducing CHD risk.[10,11]

A landmark meta-analysis included results of large-scale, placebo-controlled, statin trials, involving >30,000 participants over an average of 5.4 years, indicated that statin use resulted in a mean reduction of 30% in initial or recurrent CHD events.[12] Further analysis indicated that this CHD reduction was primarily related to a 28% reduction in LDL-C, with some benefits being derived from 20% reduction in TG and an increase of 5% in HDL-C. In addition, it should be noted that statin drugs have pleiotropic antiatherosclerotic effects, contributing to the reduction in the development and progression of CHD.[13,14]

HDL

Low HDL-C is also associated with development and progression of atherosclerosis and is generally considered a secondary target for therapeutic intervention. A clear inverse association of HDL-C to CHD has been shown by a number of major prospective cohort studies. Gordon et al. reported in 1989 (based on four prospective studies) that a 1 mg/dL decrease in HDL-C was associated with a 2%–3% increased CHD risk. Interestingly, for each 1 mg/dL increase in HDL-C there appears to be a 6% lower risk of fatal CHD events.[15] Support for the protective role of HDL against CHD has been shown by numerous randomized, controlled trials through several cardioprotective effects including antioxidant effects, improved endothelial function, anti-inflammatory effects, reduction in endothelial-derived adhesive proteins, antithrombotic and profibrinolytic effects, reverse cholesterol transport from

foam cells to the liver, and even regression of atherosclerotic plaques.[12,15–18] HDL functions in the body to remove cholesterol from cell membrane and transport it to the liver for disposal in the bile as cholesterol or as bile acids.[19] Cholesterol acyltransferase (LCAT), an enzyme carried by HDL and activated by HDL's apo A-I, acts by esterifying HDL's newly acquired cholesterol and the resulting cholesterol ester (CE) is drawn into the core of HDL. Cholesterol ester transfer protein (CEPT) is another enzyme involved in reversed cholesterol transfer by catalyzing the transfer of CE from HDL to other lipoproteins in exchange for TG. If CEPT is inhibited via pharmacological measures or inherited, there is a resultant increase in HDL-C levels postulated to result in a reduction in atherogenesis. However, it appears that recently developed drugs that impair the function of CEPT result in an increase level of HDL-C as designed, but in contrast to a hypothesized reduction in atherogenesis, this does not protect against CHD and may even promote progression of CHD.[20–22] These studies suggest that very high levels of large HDL particles laden with cholesterol may lose their cardioprotective properties and may even be atherogenic.[23] Interestingly, individuals who has a specific genetic variant of apo A-I (i.e., apo A-I Milano) have low levels of HDL-C and a very low risk of CHD, and vegetarians also generally have reduced levels of HDL-C (and LDL-C) and have a low risk of CHD.[24,25] Measurement of nascent or newly formed HDL particles, cholesterol, and apo A-I levels apparently better reflects the cardioprotective effects of HDL. It is clear that additional research is needed to elucidate the cardioprotective effect of HDL and to develop techniques to better reflect the antiatherogenic functions of HDL.

TRIGLYCERIDES

TG levels in the blood are elevated for about an hour following a meal, primarily as part of TG-rich chylomicrons, and in the fasting state they are primarily carried by very-low-density lipoprotein (VLDL). Apo C-II (carried by chylomicrons and VLDL) activates lipoprotein lipase (LPL) found in the capillaries of skeletal and heart muscle, and in the adipose tissue. Associated LPL then acts on the TG of the lipoproteins to release free fatty acids and glycerol.[19] Hypertriglyceridemia does not appear to be as strong a risk factor for CHD as LDL-C. This may in part be due to a greater biological and laboratory measurement variability, as compared to the other dyslipidemia components, as well the other atherogenic risk factors that commonly accompany hypertriglyceridemia.[26] It should also be noted that TG-rich VLDL is the precursor of circulating LDL via intermediate-density lipoprotein (IDL), which (together with other apo B-100-containing remnants of VLDL) and appears to be able to cross the arterial endothelium and contribute to atherogenesis.[27] Numerous epidemiological studies have suggested that elevated TG is predictive of CHD, although this association appears to be lost (in some studies) following multivariate analysis that included HDL-C and other CHD risk factors.[28] For example, a meta-analysis of six cohorts involving 46,000 men and 10,000 women indicated that each 1 mmol/L (88.5 mg/dL) increment in TG level was associated with an increase in risk of CHD of 76% in women and 32% in men. However, after adjusting for HDL-C, the increased risk was reduced to 37% and 14% for women and men, respectively.[29] It has further been postulated that nonfasting TG may give a more accurate assessment of risk of CHD because postprandial TG-rich remnant lipoproteins can penetrate the endothelial cell layer and contribute in the subendothelial space to development of atherosclerosis. Although there have not been any intervention trials specifically targeting TG, subgroup analysis of trials using fibrate or statin drugs indicated ~1% reduction in incidence of CHD associated with each 1% reduction in TG level.[30]

NON-HDL CHOLESTEROL AND APO B

Reduction of the concentration of cholesterol within all apo B-containing lipoprotein particles (i.e., non-HDL-C, TC – HDL-C) has been proposed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) as a secondary therapeutic goal in the presence of elevated TG following primary targeting of LDL-C.[31] In fact, non-HDL-C appears in observational studies to be an even better predictor of cardiovascular disease (CVD) than LDL-C or HDL-C alone.[32] Since LDL and VLDL and its remnants following TG lipolysis each contain 1 molecule of apo B, it is postulated that plasma level of apo B represents the total atherogenic particle number.[32–34] A strong correlation (0.8–0.9) exists between non-HDL-C and apo B; however, they are only modestly concordant.[34]

LIPID CLASSIFICATION AND TREATMENT TARGETS

The screening battery for blood lipids consists of TC, LDL-C, HDL-C, and TG. LDL is usually estimated using the Friedewald formula (LDL-C = TC – TG/5).[35] If TG levels are >400 mg/dL, isolation of the LDL fraction and direct quantification of its cholesterol content are required. ATP III guidelines recommend classifying patients with dyslipidemia by their relative overall/global risk of an initial or recurrent major CHD event. This is done to stratify those with elevated LDL-C by a recommended intensity of intervention and to set target level (Table 5.1). Those with CHD equivalent conditions (e.g., diabetes) or prior CVD diagnosis are automatically classified as being at high risk.

All patients with elevated LDL-C should be screened for the presence of five additional major risk factors (in addition to elevated LDL-C), i.e., cigarette smoking, age >45 years in men or >55 years in women, family history of premature CHD events in first-degree relatives (i.e., <55 years of age in men or <65 years of age in women), and treated or untreated hypertension. If two or more of these risk factors are present, the patient's global risk score for probability of nonfatal or fatal CHD events over 10 years should be determined using ATP III-modified tables, based on an algorithm derived from Framingham Heart Study data.[24,37] Patients should

TABLE 5.1
ATP III Blood Lipid and Lipoprotein Classification

Total cholesterol (mg/dL)	
<150	Optimal
<200	Desirable
200–239	Borderline high
≥240	High
LDL cholesterol (mg/dL)—Primary target of therapy	
<100	Optimal
100–120	Near optimal/above optimal
130–159	Borderline high
160–189	High
≥190	Very high
HDL cholesterol (mg/dL)	
<50 (for women)	Low
<40 (for men)	Low
≥60	High
Triglycerides (mg/dL)	
<100	Optimal
<150	Normal
150–199	Borderline high
200–499	High
≥500	Very high

Sources: Adult Treatment Panel III, Executive summary of the third report of the National Cholesterol Education Program (NCEP), *JAMA*, 285, 2486, 2001; Grundy, S.M. et al., *Circulation*, 110, 2142, 2004.

Notes: Lipid classification based on values after a 12 h or longer fast and the values shown are in mg/dL. Values for non-HDL cholesterol are 30 mg/dL higher than the value for LDL-C. To convert mg/dL to International Unit mmol/L, divide cholesterol values by 38.7 and triglycerides by 88.54.

be classified according to ATP III guidelines as high risk (10 year risk probability of CHD >20%), moderately high risk (10 year probability of 10%–20%), moderate risk (a 10 year probability of <10%), or lower risk (0–1 additional risk factor). Clinicians may upgrade a person at moderately high risk if additional clinical findings or biomarkers are available (e.g., elevated C-reactive protein [CRP] or a high coronary calcium CT scan risk score). Elevated LDL-C is designated as the primary target by NCEP ATP III guidelines for lipid management (Table 5.2).

ATP III guidelines were revised in 2004[36] and current advise considering a therapeutic intervention goal of <70 mg/dL for high risk patients and a goal of <100 mg/dL for moderately high risk patients. TLC are indicated for patients in all risk categories and are recommended initial treatment option for patients in the lower risk category for 6–12 months prior to initiation of pharmacological management. For those in the high risk category, initiation of TLC is recommended as an adjunct concurrent with LDL-C-lowering drug therapy. An HMG-CoA reductase inhibitor or statin drug therapy is currently recommended by ATP III for all patients with CHD or a CVD equivalent (e.g., diabetes), unless contraindications

TABLE 5.2
Risk Category and Recommended LDL Levels

Risk Category	LDL Goal	TLC Initiation	Drug Consideration
High risk			
CHD or CHD equivalent (10 year risk >20%)	<100 (option <70)	>100	≥100
Moderately high			
2+ risk factors (10 year risk 10%–20%)	<130 (option <100)	>130	>130
Moderate			
(10 year risk <10%)	<160	<130	>160
Lower risk			
(0–1 risk factor)	<160	>160	>190 (160–189: lipid-lowering drug optional)

exist, due to their beneficial pleiotropic effects (independent of LDL-C lowering) on reducing atherogenesis.

If target LDL-C level is not achieved using the recommended maximal levels of a statin drug, another LDL-C-lowering drug should be considered as an adjunct treatment option. ATP III guidelines further recommends using a combination of statin therapy, and fibrate or nicotinic acid, or fish oil supplement (1–4 g/day) in addition to TLC to help control low HDL-C or high TG levels (Table 5.3).

ATP III considers elevated TG and low HDL-C levels as secondary lipid targets. It should be noted that a TG level

TABLE 5.3
Percent Changes in Blood Lipid/Lipoprotein Levels for Each Specific Class of Drugs

Class	LDL-C (%)	HDL-C (%)	TG (%)
HMG-CoA reductase inhibitors (statins, e.g., atorvastatin)	↓20–63	↑5–15	↓10–37
Bile acid sequestrants (e.g., cholestyramine)	↓15–30	↑5	±
Fibric acid derivatives (e.g., gemfibrozil)	↓10–15	↑5–20	↓20–50
Niacin (e.g., sustained release)	↓5–25	↑15–35	↓20–50
Cholesterol absorption inhibitor (eczetimide)	↓20	↑5	±

Sources: Adapted from Gotto, A.M., Jr., *Contemporary Diagnosis and Management of Lipid Disorders*, 3rd edn., Handbooks in Health Care, Newton, PA, 2004, pp. 7–42.

Notes: ↑, increase; ↓, decrease; ±, variable if any. For more details and precautions in use of these lipid management drugs, the reader is referred to Bettridge and Morrell [38].

>500 mg/dL requires immediate attention due to increased risk of acute pancreatitis. Treatment guidelines specify the addition of a fibrate drug or nicotinic acid, in addition to a very-low-fat diet (<15% of calories), weight reduction, and increased physical activity. For a moderate elevation of TG (200–499 mg/dL), a recommended goal is a reduction in non-HDL-C levels to at least 30 mg/dL below the LDL-C goal for the patient's risk status. Intensive TLC is considered first choice of treatment if HDL-C is low (i.e., <40 mg/dL) after achieving LDL-C and non-HDL-C targets or for management of an isolated low HDL-C level, followed by the addition of a nicotinic acid or a fibrate drug if target treatment is not achieved.[39]

ROLE OF LIFESTYLE IN THE MANAGEMENT OF DYSLIPIDEMIA

Lifestyle, particularly dietary habits, body weight, physical activity, alcohol consumption, and smoking, accounts for the major differences in blood lipid levels in the population (although heritability can make a substantial contribution as well). These lifestyle habits are considered major TLC targets for the management of dyslipidemia.

Impact of Diet

The primary dietary targets for a cholesterol-reducing program are to reduce intake of animal food sources, specifically red meat, dairy products, butter, hard margarines, and commercial baked goods[25] that contain saturated fatty acids (SFAs), since these are the principal environmental/lifestyle contributors to elevated levels of blood lipid/lipoprotein levels. In addition, intake of *trans*-fatty acids (TFAs) should be minimized because they raise LDL-C and lower HDL-C. Observations from the seven countries study indicated that 60%–80% of the variance among the population in mean TC levels could be accounted for by variation in mean percentage of energy from SFAs; specifically the cohorts who consumed 17%–22% of their daily energy intake from foods high in SFAs had elevated mean TC levels, which was associated with a high incidence of CHD, whereas those with a lower SFA intake (3%–14% of daily energy) displayed a lower CHD rate. This observation has been confirmed in the past two decades by both observational studies and controlled intervention trials.[4,25,40,41] Metabolic ward studies have shown that omega-6 PUFAs, particularly linoleic acid (18:1, n-6), have a cholesterol-lowering effect, which is illustrated by the so-called Keys' equation[42]: $\Delta TC = 1.3(2\Delta S - \Delta P) + 1.5\Delta Z$ (ΔTC is the change in TC; ΔS is the change in percent of total calories provided by SFAs; ΔP is the change in percent of energy from omega-6 PUFAs; and ΔZ is the square root of the dietary cholesterol expressed in milligrams per 1000 kcal of dietary energy). This equation shows that for every 1% reduction in SFAs, serum TC is expected to be reduced 2%. The relatively small impact of dietary cholesterol on blood cholesterol levels is due to the limited absorption of dietary cholesterol with about two-thirds of circulating cholesterol synthesized de novo by the liver from acetyl coenzyme A products of metabolism.[43] It should be noted that only three long carbon-chained SFAs have been shown experimentally to be responsible for increasing TC (i.e., lauric [12:0], muristic [14:0], and palmitic [16:0] acid). These SFAs appear to markedly downregulate hepatic synthesis of LDL apo B/E cell receptors, which reduces the removal of circulating LDL, as well as VLDL, IDL, and apo B-100 containing lipoprotein remnants and results in a significant increase in cholesterol level.[43,44] Stearic acid (18:0) and SFAs with 10 or less carbons have no effect on TC and are not included in Keys' equation.[42] Omega-6 PUFAs, in contrast, lower cholesterol levels by upregulating hepatic LDL receptors and increasing the removal of lipoproteins and reduce the rate of conversion of VLDL to LDL. The current ATP III recommendation is to keep intake of omega-6 PUFAs to 10% or less of daily energy intake, since a higher intake appears to lower HDL-C levels. Linoleic acid (18:2, n-6), the parent compound for the omega-6 family of PUFAs, is found in sunflower, corn, and soybean oils, seeds, and nuts. Linoleic acid forms arachidonic acid (AA; 20:4, n-6) via enzymatic stepwise elongation of its carbon chain. AA is the precursor of prostaglandins and eicosanoids via cyclooxygenase (COX) enzyme activity and is essential for regulation of blood circulation, blood clotting, and inflammatory responses.[19]

Omega-3 PUFAs are a family of long-chained, essential fatty acids required in the diet. They have an initial double bond/unsaturated carbon atom at the third rather than the sixth position from the methyl end of the molecule for omega-6 PUFA. There has been a steady increase in the interest in omega-3 PUFA due to their apparent importance for eye and brain health through the lifecycle, and their postulated contribution to primary and secondary prevention of CHD.[44,45] The parent compound of this family is α-linolenic acid (ALA; 18:3, n-3). Its carbon chain is enzymatically converted to longer chain and eventually become the more unsaturated fatty acids, eicosapentaenoic acid (EPA; 20:5, n-3) and docosahexaenoic acid (DHA; 22:5, n-3). It should be noted that DHA competes with AA for conversion via COX enzyme to alternative eicosanoids and prostaglandins, which are believed to be cardioprotective. Because of the limited conversion of ALA to EPA and DHA, all three are currently considered essential dietary nutrients; however, DHA appears to be the most biologically active form of the omega-3 PUFAs.[46] ALA is primarily present in vegetable oils, in particular canola and soybean oils, whereas fatty fish such as salmon, mackerel, herring, and sardines are rich sources of EPA and DHA. The apparent relationship of omega-3 fatty acids to cardiovascular health was first observed during studies of the unique dietary habits in Greenland Inuits.[47] Despite a diet consisting primarily of very fatty meat from sea mammals, they had a surprisingly low rate of CVD. This was eventually attributed to their high intake of EPA and DHA from these food sources. Other epidemiological observational studies have consistently reported an inverse association between consumption of fish or fish oil supplements, with morbidity and mortality from CVD.[48] The cardioprotective effects of these fatty acids have further been confirmed in animal models and by primary and secondary

TABLE 5.4
Experimentally Identified Mechanisms Postulated to Contribute to the Apparent Cardioprotective Effects of Omega-3 PUFAs

- Reduced dyslipidemia (decreased TG and VLDL-C and increased HDL-C)
- A moderate reduction in elevated blood pressure
- Improved endothelial function and endothelial-dependent and endothelial-independent vasoreactivity
- Anti-inflammatory effects, inhibiting progression of atherosclerosis
- Antithrombotic effects
- Increased parasympathetic activity, as evidenced by increased heart rate variability
- Improved myocardial electrical stability, reducing risk of a fatal ventricular arrhythmia

Sources: Von Schacky, C., *Am. J. Clin. Nutr*., 71, 224S, 2000; Harris, W.S., *Lipids*, 31, 243, 1996; Holub, B.U., *CMAJ*, 116, 608, 2002.

CHD prevention trials, indicating a 20%–30% reduction in fatal and nonfatal CHD events.[49,50] It appears that a modest intake of fatty fish, i.e., two to three portions per week or a daily fish oil capsule, can reduce risk of CHD, whereas consumption of ALA from vegetable oils does not appear to be as cardioprotective (Table 5.4).

DHA and EPA fish oil–based supplements appear to result in a reduction in TG (6%–10%/g of EPA and DHA), VLDL-C, VLDL-TG, and non-HDL-C and an increase in HDL-C.[52] Thus, large doses of EPA–DHA-based fish oil supplements in combination with a statin drug appear to be an effective therapeutic approach for treatment of mixed dyslipidemia.[38]

Attention was first directed to the benign relationship of monounsaturated fatty acids (MUFAs) in the diet to risk of CHD by the Seven Countries Study.[4] Approximately 80% of the fatty acids contained in olive oil are MUFAs, particularly oleic acid (18:1, n-9). Oleic acid either has no effect on blood lipids or, as reported in some studies, it reduces TC levels, but appears to have no effect on HDL-C or TG levels.[53] However, the presence of MUFAs in LDL makes it less susceptible to oxidation. MUFAs are plentiful in olive oil, canola and peanut oil, avocados, nuts, and fish.

TFAs have attracted attention in recent years due to their adverse effects on blood lipids. In fact, the FDA now mandates inclusion of quantities of TFAs on food labels along with that of SFAs and PUSFs. New York City and California even banned the use of TFAs in restaurants for food preparation. It should be noted that only a limited quantity of TFAs occurs naturally in meat and dairy products, while essentially all of the reported 2.6% of usual daily energy intake of TFAs results from intake of margarines and shortenings used in food preparation. This is due to the formation of TFAs by the partial hydrogenation of the double bonds of unsaturated fatty acids in liquid vegetable oils to solidify them since this makes products more heat stable and increases shelf life.[54] TFAs appear to promote an increase in cholesterol synthesis and a concomitant increase in LDL-C levels, but more importantly in contrast to SFAs they increase Lp (α) and lower HDL-C levels.[55] Currently, it is recommended that dietary intake is limited to less than 1% of total energy intake.

A diet high in nondigestible fiber may have a modest beneficial effect on TC and LDL-C levels.[25,38] Soluble fiber components, in particular β-glycans and pectin, contribute to blood cholesterol reduction. Soluble fibers are found in whole grains (especially oats), fruits and vegetables, and beans and legumes. Soluble fibers bind and thus prevent reabsorption of bile salts in the small intestine, which results in upregulation of hepatic LDL receptors, thereby enhancing LDL removal and reducing LDL-C levels. An intake of 30 g/day of soluble fiber has been reported to be associated with a 5 mg/dL reduction in total LDL-C levels and especially the smaller, dense, atherogenic LDL particles thereby reducing fatal and nonfatal CHD events.[25,56–59] It should also be noted that dietary fiber slows gastric emptying and glucose absorption, which decreases insulin response and thus reduces hepatic lipogenesis and promotes satiety.

Plant sterols and stanols (when esterified with a fatty acid or when emulsified such as Benacol) are plentiful in vegetable oils, seeds, and nuts.[60] It appears that PUFA margarines with or without the addition of 2 g/day of sterols/stanols to the diet may result in a reduction of 21 mg/dL in LDL-C (a 9%–27% reduction) and non-HDL-C levels.[60,61] LDL-C removal is enhanced via an upregulation of LDL receptors in the liver, in part due to competitive inhibition of dietary and biliary cholesterol uptake in the small intestine.[25] ATP III has endorsed the use of stanol-enriched margarines, as an adjunct for lowering LDL.

Plant-derived antioxidants such as lipid-soluble vitamin E and β and other carotenes, water-soluble vitamin C, and a large variety of non-nutrient phytochemicals are postulated to reduce the development and progression of CHD by preventing oxidative stress and reducing LDL oxidation, and endothelial dysfunction.[38,62] Vitamin E, found in vegetable oil, nuts, and seeds, is transported by LDL and has been associated with a reduction of CHD risk and reduction of oxidized LDL.[38,62] However, it should be noted that numerous large-scale randomized controlled clinical trials have failed to demonstrate any protective effect against CVD mortality by supplementation of antioxidant vitamins (vitamin E, vitamin C, or β-carotene).[38,62,63] Another type of plant chemicals (phytochemicals) of significant health-promoting interest in recent years has been flavonoids, found in fruits, vegetables, tea, red wine (and grape juice from which wine is derived), and cocoa bean products. These phytochemicals have been demonstrated in in vitro studies to be potent inhibitors of LDL oxidation.[38] However, there have been inconsistent results from clinical trials and current evidence does not clearly support their use in a clinical setting.[38]

A moderate alcohol intake of —one to two drinks per day has been associated with about one-third lower risk of mortality from CHD when compared to either no alcohol or heavy alcohol consumption, possibly due to both antithrombotic effects and ethanol-involved increased HDL-C levels by ~12%.[38,64] However, it should be noted that alcohol also produces a concomitant increase in TG and VLDL production and therefore raises non-HDL-C

levels. Moreover, excessive use of alcohol raises blood pressure, is potentially addictive, and can contribute to major health problems, in addition to increasing risk of accidents and violent death. Thus, it is considered unethical to encourage nondrinkers to start using alcohol for prevention of CHD.

WEIGHT MANAGEMENT

Health consequences associated with excess body weight include dyslipidemia, all components of the metabolic syndrome, and thereby an increased risk of type 2 diabetes and CHD.[65] Thus, weight reduction is a critical component in the management of dyslipidemia. Obesity results generally from a combination of overeating and sedentary lifestyle, causing a positive energy balance and thus an increase in lipogenesis and fat storage. In order to lose weight, a sustained negative energy balance must be achieved. The ATP III,[31] the AHA,[66] and the American College of Sports Medicine[79] recommend a sustained weight reduction by achieving a modest negative energy balance of 500–1000 kcal/day. This is expected to result in a 1–2 lb (0.45–0.99 kg) weight loss per week. The initial goal is to achieve a 5%–10% weight loss over a 6 month period. If this weight loss is achieved via dietary changes only, about 75% of this loss is generally from fat and 25% fat-free mass (FFM). If exercise is combined with a reduced energy intake, FFM is generally better preserved during weight reduction and weight regain appears to be less likely.[65–67]

It is essential to include behavioral modification of eating habits and regular PA to successfully achieve and maintain a more desirable body weight.[65–67] Bariatric surgery commonly results in a substantial weight loss; however, there are serious risks associated with the surgical procedures, including postsurgical complications related to the induced nutrient malabsorption.

Numerous dietary approaches have been promoted for weight reduction. These diets often target a specific macronutrient (i.e., fat, carbohydrates, or protein). However, it should be noted that the greatest impact on the initial amount of weight loss is the level of energy deficit achieved, irrespective of the dietary approach. Current guidelines specify that daily energy intake should not be lower than 1000–1500 kcal/day, in order to provide all essential nutrients while achieving an adequate negative energy balance.[56–67] The approach that is most commonly recommended by authoritative sources for successful long-term weight loss and maintenance includes limitation of dietary fat intake (since fat provides 9 kcal/g compared to 4 kcal/g for carbohydrates and protein).

It appears that a successful 10% weight loss may result in a significant decrease in TC of 30.5 mg/dL (–13.2%), LDL-C 15.1 mg/dL (–11.3%), VLDL-C 15.5 mg/dL (–36.5%), and TG 58.4 mg/dL (–32.2%); HDL-C initially declines during the active weight loss phase and then increases 5.5 mg/dL (+12.6%) after weight stabilization. This represents about a 0.35 mg/dL increase in HDL-C for every kilogram of weight lost.[68] In a recent meta-analysis, Nordmann et al.[69] compared the effects of a reduced-fat and a low-carbohydrate diet (i.e., the Atkin's diet) on weight loss and cardiovascular risk factors. The fat content of the reduced-fat diets was limited to 25%–35% (current recommendation) of daily energy in four of these studies and to 10% in one study. The low-carbohydrate diet was unlimited in protein and fat intake. The mean weight loss at 6 months was significantly greater on the low-carbohydrate diet, while at 12 months there was no statistically significant difference between the low-carbohydrate and the reduced-fat diets. However, the reduction in TC and LDL-C was more favorable on the low-fat diets compared to the low-carbohydrate diets (mean difference in LDL-C between diets was –5.4 mg/dL). Interestingly, changes in HDL-C (+4.6 mg/dL) and TG (–22.1 mg/dL) were significantly more favorable on the low-carbohydrate diets.

A recent randomized study[70] investigated the effects of weight loss and blood lipid changes between a low-carbohydrate, non-restricted-calorie diet and a reduced-fat (<35% of daily energy), restricted-calorie diet, following AHA guidelines, and a restricted-calorie Mediterranean-type diet. The mean weight loss after the 2-year follow-up was 2.9 kg for the AHA diet, 4.4 kg for the Mediterranean diet, and 4.7 kg for the low-carbohydrate diet. There was a mean increase in HDL-C of 8.4 (+22.4%), 6.3, and 6.4 (+16%) mg/dL for the low-carbohydrate, AHA, and Mediterranean diets, respectively. TG reduction (23.7 mg/dL) was also significantly more favorable with the low-carbohydrate diet. Surprisingly, in this study there was no significant change in LDL-C in any group.

The combination of dietary modification and regular exercise has consistently been shown to be the most effective approach for achieving and maintaining long-term weight reduction (~1 kg/week greater weight loss than dieting alone).[65–67] Aerobic exercise (as well as resistance exercise) may attenuate FFM loss that will occur with weight loss.[67] Regular aerobic exercise for 60–90 min/day is critical for preventing weight regain.[71,72] However, exercise alone is generally not effective for inducing sizable weight loss, unless one performs supervised, large-volume, prolonged aerobic exercise 5–7 days/week.[67]

EXERCISE EFFECTS

It has been well established that increased physical activity and exercise training reduce morbidity and mortality from CHD through multiple cardioprotective effects including reducing dyslipidemia.[73–76] Studies have consistently shown that aerobic exercise training results on the average a modest increase in HDL-C of 2–3 mg/dL, or about 4%–5% with an associated increase in apo A-I and LPL activity.[77–80] However, it should be noted that there is a great deal of variability in the response of HDL-C following exercise training,[81] which appears to be related to genetic factors as well as to weight change.[82–86] Additionally, individuals with a low baseline level of HDL-C or sedentary women with genetically high HDL-C levels appear less likely to respond to exercise training.[84] Exercise-induced reductions in LDL-C and TG have appeared to be rare in the absence of an associated weight loss.[77–80] The majority of well-controlled studies on the effect of exercise on blood lipids have used a standard exercise prescription of a moderate- to high-intensity aerobic exercise for 30–60 min, three times per week with a weekly energy expenditure of 900–2000 kcal (or about 10–20 MET h) for at least 12 weeks (about 15–20 miles/week of walking).[77–80]

Smoking Effects

Cigarette smoking has been associated with reduced apo A-I and HDL-C levels about 4–6 mg/dL or 11%–14% lower than nonsmokers.[87–89] These findings are despite the fact that smokers tend to weigh less and drink more alcohol. More importantly, smoking cessation appears to result in a rapid improvement in HDL-C (an average 6–8 mg/dL increase).[90] In addition, smokers have been reported to have slightly higher LDL-C levels than nonsmokers. These adverse effects of smoking on blood lipids are postulated to be due both to nicotine and carbon monoxide exposure.[91]

CONCLUSIONS AND RECOMMENDATIONS

Therapeutic lifestyle components are major contributors to dyslipidemia and resulting CHD, in particular eating habits and low levels of physical activity. The high consumption of red and processed meat, high-fat milk and dairy products, fried and salty foods, refined grain products, and sugar-laden desserts and soft drinks is principally responsible for the obesity epidemic and associated dyslipidemia in this country.[92–95] It has been well established that eating patterns associated with reduced rates of dyslipidemia and CVD include

- Vegetarian and near-vegetarian diets[96,97]
- Mediterranean-style diets[4,40,41,98,99]
- The Dietary Approach to Reduce Hypertension (DASH) diet[100–102]
- The "Prudent Heart Healthy Diet" advocated by the AHA (formerly the AHA Step II Diet), ATP III, and the U.S. Departments of Agriculture (USDA) and Health and Human Dietary (DHHS) Guidelines for Americans 2010[31,102–104]

Successful dietary patterns to improve blood lipid profile should be characterized by a low intake of saturated and *trans*-fat and dietary cholesterol via a reduction of red meat, hard fats, full-fat milk; an increased intake of whole grains, legumes, fruits, and vegetables; and a moderate intake of fish and poultry and low-fat or fat-free milk and dairy products. The recommended macronutrient content of this eating pattern, as a percentage of daily energy intake, is as follows[31,105]:

Total fat	25%–35%
Saturated fat	<7%
trans-fats	<1%
Monounsaturated fats	15%
Polyunsaturated fats (with an omega-6 to omega-3 ratio of 3-4:1)	10% or less
Cholesterol	≤200 mg/day
Protein	About 15%
Carbohydrates	50%–60%

The combination of a proper dietary plan and regular aerobic exercise has been reported to lower TC, LDL-C by 7%–18% and TG by 4%–18%, respectively, while increasing HDL-C by 2%–18%.[106] Weight management is critically important in improving blood lipid profile. Table 5.5 summarizes the effects of specific dietary components and other TLC reviewed in this chapter on dyslipidemia.

TABLE 5.5
Effects of Specific Dietary Components and Other TLC on Dyslipidemia

Dietary Component or TLC Change	TC	LDL-C	HDL-C	TG (and Non-HDL-C)
Decrease SFAs, *trans*-fats, and cholesterol	↓↓	↓↓	↓	↓
Increase omega-6 PUFAs	↓	↓	→	→
			↓	
Increase omega-3 PUFAs	→	→	↑	↓↓
		↑	→	
Increase MUFAs	→	→	↑	↓
	↓	↓	→	
Increase soluble fiber	↓	↓	→	→
Moderate alcohol	→	→	↑↑	↑↑
Phytosterols	↓	↓	→	→
Soy proteins	↓	↓	→	↓
Vitamin E (recycled by vitamin C)	—	↓ OxLDL	—	—
Negative energy balance (weight loss)	↓	↓	↑	↓↓
Aerobic exercise	↓	↓	↑	→
	→	→		
Smoking cessation	→	→	↑	↓

Notes: ↑, increase; ↓, decrease; →, no change.

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6 Lifestyle Management and Prevention of Hypertension

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CONTENTS

Introduction 75
Etiology of Hypertension and Relationship to CVD 75
Physical Activity, Exercise, and Hypertension 76
Dietary Modifications in the Prevention and Management of Hypertension 77
Effect of Sodium Restriction 78
Effects of Increased Dietary Potassium Intake 78
Effect of Alcohol Consumption 78
Effect of Omega-3 Polyunsaturated Fatty Acids 78
Weight Management 78
Pharmacological Management of Hypertension 79
Summary of Conclusions 79
References 79

INTRODUCTION

Hypertension is a well-established major risk factor for cardiovascular disease (CVD) morbidity and mortality.[1–4] Despite the fact that major advances have been made in our understanding of hypertension and pharmacological therapy, it continues to be poorly controlled in the over 50 million U.S. adults diagnosed with hypertension, including ~70% of all adults >50 years of age, with blacks having an even higher incidence than nonblacks.[5–7] Pharmacotherapy has traditionally served as the primary treatment modality for hypertension. This is despite strong evidence of the benefit of lifestyle modifications to reduce both incidence of hypertension and blood pressure levels in individuals with established hypertension.

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Seventh Report (JNC-7)[1] highlights the importance of therapeutic lifestyle changes (TLC) by recommending five TLC for both the prevention and initial treatment of pre- and stage 1 hypertension, which include the following : (1) weight loss to achieve a BMI <25 kg/m^2; (2) a minimum of 30 min of moderate-intensity aerobic exercise ≥5 days/week; (3) if consuming alcohol, limiting consumption to no more than two drinks (2 oz) per day for men and no more than one drink per day for women; (4) eating a healthy diet, rich in fruit, vegetables, and whole grains, moderate in fat-free and low-fat dairy products, and low in saturated and total fat (e.g., Dietary Approaches to Stop Hypertension [DASH] diet); and (5) lower sodium/salt intake ≤100 mEq/L/day. These measures have been shown to reduce systolic blood pressure levels (2–20 mm Hg) and potentiate antihypertensive drug therapy.[1] Target blood pressure levels should be <140/90 or <130/80 mm Hg in the presence of diabetes, chronic kidney disease, or CVD, with the initial goal to lower the systolic blood pressure (Table 6.1).[1] Currently, a BP level of <115/75 mm Hg is considered optimal for health promotion.[1]

ETIOLOGY OF HYPERTENSION AND RELATIONSHIP TO CVD

Primary or essential hypertension, the most common cause of hypertension in the United States, (90%–95%) has no specific known underlying cause, while secondary hypertension results from medical conditions such as chronic kidney disease, renal artery stenosis, or adrenal tumors (e.g., pheochromocytoma, primary aldosteronism, and Cushing's disease).[8,9] Essential hypertension cannot be cured, but it can be controlled with TLC and/or pharmacotherapy.[1,8,9] Nonmodifiable risk factors for essential hypertension include a positive family history (generally via a polygenic mode of inheritance), age (>30 years old in men), sex (more common in men than women), and ethnicity (more common in blacks than in nonblacks). Modifiable risk factors are excess weight (BMI > 25 kg/m^2); excess alcohol consumption; a sodium-rich diet, low in calcium, potassium, and magnesium; and physical inactivity.[1,8,9,10–13] Any physiological factor that increases cardiac output or total peripheral vascular resistance can result in an elevation of blood pressure, since blood pressure level is determined hemodynamically by the product of these two variables. Other contributing factors that increase blood pressure levels include endothelial dysfunction, increased sympathetic nervous system activation,

TABLE 6.1
Adapted from JNC-7: Classification of Blood Pressure for Adults 18 or Older

BP Classification	SBP	DBP	Lifestyle Modification	Drug Treatment
Optimal	<115	<75	Encourage	None
Normal	<120	<80	Encourage	None
Prehypertension	120–139	80–89	Yes	Usually not indicated[a]
Stage 1 hypertension	140–159	90–99	Yes	Indicated[b]
Stage 2 hypertension	>160	>100	Yes	Indicated[c]

Source: Adapted from Chobanian, A.V. et al., *JAMA*, 289, 2560, 2003.

[a] Initiate pharmacological treatment if compelling indications such as chronic kidney disease, diabetes, or CVD with a blood pressure goal <130/80 mm Hg.

[b] Thiazide diuretic for most (if therapeutic lifestyle modifications have failed to reduced blood pressure within 6–12 months), add other drugs as indicated if blood pressure is more than 20/10 mm Hg above the blood pressure goal.

[c] Two-drug combination, usually consisting of a thiazide diuretic plus another, may be needed as indicated.

and renin–angiotensin–aldosterone system (RAA) activity. It is postulated that a sustained elevation in blood pressure from any of these physiological disturbances results in a resetting of the baroreceptors, hypertrophy of the arteriolar smooth muscle, and an increase in peripheral vascular resistance, the principal hemodynamic disturbances associated with essential hypertension.[8] Hypertension-induced LVH (a major cardiac consequence of hypertension) is postulated to be related to both an increase in preload and afterload (i.e., chronic volume and pressure overload) resulting in eccentric or concentric volumetric ventricular changes associated with dysfunctional systolic contraction.[8–11] The reader is referred to a recent review by Rosendorff et al.[8]

PHYSICAL ACTIVITY, EXERCISE, AND HYPERTENSION

Observational studies also have reported an inverse association between leisure time physical activity, physical fitness (relative risk 1.5–1.9), and development and severity of hypertension even after adjusting for other risk factors.[14–26] For example, Kokkinos et al.[27] reported in a cross-sectional study an 8–9 mm Hg lower systolic and 4–5 mm Hg diastolic mean 24 h ambulatory blood pressure in individuals with high and moderate physical fitness, compared to persons with a low fitness levels. These studies suggest that increased levels of physical activity and moderate physical fitness result in ~5 mm Hg lower systolic blood pressure level, compared to age- and sex-matched individuals who are less active and less fit.[26]

The effect of exercise training on blood pressure levels have been well-established in over 70 randomized, controlled trials and over 15 meta-analyses.[28–43] In general, these studies have shown that a moderate-intensity aerobic exercise training program 30–60 min per session, three times per week, for 12–16 weeks lowers elevated blood pressure levels.[44,45] These studies have indicated a mean reduction in resting blood pressure levels in normotensive individuals of 2.6–4.7 mm Hg in systolic and 1.8–3.1 mm Hg in diastolic blood pressure and a reduction in systolic of 6–10 mm Hg and diastolic blood pressure of 2.4–7.6 mm Hg in patients with diagnosed hypertension. There also appears to be a significant difference in blood pressure reduction between moderate or vigorous exercise intensity training, and based on BMI, sex, and age.[28–46]

Aerobic exercise training also appears to reduce mean 24 h systolic blood pressure of 6–10 mm Hg and diastolic blood pressure of 5–8 mm Hg in hypertensive participants, and 3.0–3.3 mm Hg systolic blood pressure and 3.3–3.5 mm Hg diastolic blood pressure in normotensive individuals[30,44,45] although no change was found in overnight blood pressure.[44] It is concluded from these data that moderate-intensity (40%–70% of maximal aerobic capacity) aerobic exercise training 30–60 min 3–5 days/week is effective for both prevention and management of hypertension. Moreover, immediately following cessation of each bout of aerobic exercise there is a temporary reduction in systolic (5–15 mm Hg) and diastolic (4–6 mm Hg) blood pressure that appears to last several hours (up to 24 h).[45,47–49] The mean acute post-exercise reduction in blood pressure levels of hypertensive individuals has been reported to be higher in controlled settings (15/4 mm Hg) than in uncontrolled settings (~5/4 mm Hg).[45] It is postulated that the mechanism of this acute blood pressure reduction following each exercise session includes the following:

- Immediate decrease in sympathetic adrenergic stimulation of the precapillary vessels
- Attenuated response to α-adrenergic stimulation
- Laminar flow-mediated release of endothelial-derived vasodilatory chemicals (e.g., nitric oxide, prostacyclin, and adenosine)
- Resetting of the arterial and cardiopulmonary baroreceptor operating points
- Neural adaptations involving central vasopressin V_1 receptors and substance P receptors[48–53]

Resistance exercise training has been reported in some studies to result in a reduction in blood pressure ~7/6 mm Hg, while in other studies it failed to result in a blood pressure reduction.[44,45,54] However, meta-analyses on the effect of resistance training on mean resting blood pressure have reported a blood pressure reduction of approximately 3/3.5 mm Hg in normotensive individuals.[44,54] However, it should be noted that only the diastolic pressure reduction reached statistical significance in the largest meta-analysis. The current recommendation for resistance exercise training is that it should only be used as a supplement and not a substitute for aerobic exercise training. It is advised that resistance exercise in the management of pre- or stage 1 hypertension should be performed at a moderate intensity with 1–3 sets

of 10–15 repetitions per session, 2–3 times/week involving 8–10 exercises of the large muscle groups.[45,55] Limited available evidence suggests that combined aerobic and resistance exercise training may result in a reduction of 5.6 mm Hg in systolic and 5.5 mm Hg in diastolic blood pressure levels in hypertensive individuals. The reader is referred to the American College of Sports Medicine's guidelines and contraindications to exercise testing and training in patients with hypertension.[56]

There have been many postulated and plausible mechanisms for the blood pressure–reducing effects of exercise training. Poiseuille's law explains that a small change in vessel diameter has a large effect on resistance to fluid flow (i.e., inversely proportional to the fourth power of the vessel radius).[45] Therefore, it appears that a reduction in total peripheral vascular resistance, specifically by a change in small vessel diameter, is responsible for at least one part of the observed blood pressure reduction with exercise training (7.1% reduction).[44] The exercise-induced reduction in peripheral vascular resistance is postulated to be mediated by several factors including

1. Improved vascular endothelial function and arterial elasticity/compliance
   a. Due to increased nitric oxide (NO) synthase activity from exercise-induced laminar shear stress and prolonged NO activity via reduced oxidative deactivation of NO, and reduction of collagen deposition on the media of the arteries
2. Reduction in endothelial-derived endothelin-1
3. Attenuation of α-adrenergic receptor-responsive and reduced sympathetic tone
4. Reduction in peripheral vascular resistance
5. Improved baroreceptor reflex sensitivity
6. Reduced circulating catecholamines[44,57–64]

The effects of exercise training on the RAA system are less well known. There have been a few reports of an exercise training-induced reduction in renin activity[44] and angiotensin II activity in normotensive persons, but not in hypertensive persons.[45] There is also an exercise training-induced improvement in insulin sensitivity, which has been associated with increased renal sodium excretion.[45,65] In addition, exercise training-induced vascular adaptations also include an increase in skeletal muscle precapillary and capillary vessel numbers (i.e., angiogenesis), and adaptations in vascular structure including vascular remodeling (arteriogenesis) resulting in a larger conduit artery lumen diameter, which further contributes to reduced vascular resistance.[45,66]

The genetic impact on the exercise-induced reduction in blood pressure is not well known and the interactions between genes and environment are complex. It is plausible that genes affecting NO synthase activity are involved in the blood pressure response to exercise training, as shown by the *He*alth *Ri*sk Factors Exercise *Tra*ining and *Ge*netics (HERITAGE) Family Study.[67,68]

DIETARY MODIFICATIONS IN THE PREVENTION AND MANAGEMENT OF HYPERTENSION

Dietary-induced prevention and management of hypertension through a combination of sodium intake reduction; increased intake of potassium, calcium, and magnesium; and moderation of alcohol consumption have been shown to very effective and is strongly supported by evidence from randomized, controlled trials.[69–72] The most effective dietary intervention for blood pressure control and reduction to date is known as the DASH diet, which is rich in fruit and vegetables, moderate in low-fat dairy products (and hence, low in sodium and high in potassium, calcium, and magnesium), and low in total and saturated fat (Table 6.2).[70]

The DASH diet was shown in a controlled randomized study to be very effective in reducing blood pressure levels ~11.4/5.5 mm Hg hypertensive participants versus 3.5/2.2 mm Hg in prehypertensive participants. Interestingly, it appeared to be more effective in lowering BP in black as compared to white study participants (6.9/3.7 and 3.3/2.4 mm Hg, respectively).[70]

TABLE 6.2
Dietary Approaches to Stop Hypertension (DASH) Dietary Plan

Nutrient	Percentage of Total Caloric Intake
Total fat (% of total kcal)	25–35
Saturated fat	<7
trans-fats	<1
Monounsaturated fats	15
Polyunsaturated fats (with an omega-6 to -3 ratio of 3-4:1)	10 or less
Cholesterol	≤200 mg/day
Protein (% of total kcal)	About 18
Carbohydrates (% of total kcal)	50–60
Dietary fiber (g/day)	31
Potassium (mg/day)	4700
Calcium (mg/day)	500
Sodium (mg/day)	1500–2400
Number of servings per day based on 2000 kcal diet	Daily servings
Fruit	7–8
Vegetables	4–5
Grains	4–5
Low-fat dairy products	2–3
Meats, poultry, fish	≤2
Nuts, seeds, dry beans	4–5
Fats, oils	2–3
Sweets	≤5 per week

Source: Adapted from Appel, L.J. et al., *Hypertension*, 47, 296, 2006.

Note: Total effect of blood pressure reduction using the DASH diet is approximately 11/6 mm Hg.

Other dietary studies have reported a 6–10 mm Hg blood pressure reduction in normotensive participants versus a 12–16 mm Hg reduction in participants with hypertension following a diet high in fruit and plants, as well as diets high in carbohydrate, protein, or unsaturated fat.[69,72] Moreover, an increased dietary fiber intake of 11.5–14 g/day intake found in whole grains, fruit and vegetables, beans, nuts, and legumes is associated with a small reduction in systolic (1.1–1.6 mm Hg) and diastolic blood pressure levels (1.3–2.0 mm Hg).[73–75] Currently, it is recommended that for BP management, an appropriate diet is one rich in fruit and vegetables, and whole grains, as found in the DASH dietary eating pattern.

Effect of Sodium Restriction

Observational prospective and cross-sectional studies, animal studies, clinical trials, and meta-analyses have established a positive independent association between sodium (and table salt) intake and blood pressure levels.[35,76–78] The largest dose–response sodium restriction blood pressure trial to date was the DASH-Sodium Trial. This randomized study compared three levels of reduced sodium intake (150, 100, 50 mmol/day) with changes in blood pressure levels. This study found an apparent dose–response relationship between reduced sodium intake and systolic blood pressure reduction.[71]

Generally, sodium restriction reduces elevated systolic blood pressure levels by 4.7–7 mm Hg and elevated diastolic blood pressure levels by 2.5–2.7 mm Hg, and reduces the risk of progression of prehypertension to hypertension (a relative risk reduction of 20%). Further, it potentiates pharmacological treatment.[35,69,76–81] It is important to note that there is a great interindividual variability in blood pressure response to sodium restriction. In general, black, middle-aged, older individuals, and patients with over activity of the RAA system appear to respond best to sodium restriction with large reductions in blood pressure.[69,71,80,81] The current American diet is high in sodium levels, mostly from commonly used processed foods, therefore making it difficult for many Americans to achieve a lower sodium goal. The AHA therefore recommends 2.3 g/day as the upper limit of sodium intake for blood pressure control,[1,69] whereas the JNC-7 recommendations are to reduce sodium chloride intake to 1.5 g/day.[69]

Effects of Increased Dietary Potassium Intake

Fluid homeostasis in the body is in part controlled via sodium and potassium balance. In general, serum sodium levels increase to promote fluid retention in response to a reduction in serum potassium levels, whereas increased serum potassium levels lead to an increase in renal sodium excretion (natriuresis) and an associated diuresis. Although clinical trials have reported mixed blood pressure response to increased dietary potassium intake, there is in general a trend between increased potassium intake from 1.3 to 4.7 g/day and reduced systolic blood pressure (2.42–4.4 mm Hg) and diastolic blood pressure (1.5–2.5 mm Hg) in patients with hypertension. In general, a greater blood pressure–reducing effect of increased potassium intake is observed in black as compared to matched white hypertensive individuals.[35,69,70,82–84] However, the combination of a diet rich in potassium and low in sodium does not appear to be additive.[69] Currently, it is recommended that a 4.7 g/day dietary intake of potassium should be consumed via a dietary eating pattern similar to that of the DASH diet, instead of potassium supplement use.[69,70] However, patients with medical conditions that are associated with impaired urinary excretion of potassium (e.g., renal disease) or are using medications that reduce potassium excretion (e.g., angiotensin-converting enzyme [ACE] inhibitors) should consume a lower daily potassium intake to avoid hyperkalemia.[1,69]

Effect of Alcohol Consumption

A J-shaped dose-dependent association between alcohol consumption and blood pressure levels has been demonstrated in clinical trials. It appears that relatively light alcohol consumption has no effect on blood pressure, whereas higher daily alcohol consumption increases blood pressure levels.[76,85–88] Controlled trials have demonstrated that 50%–70% reduction of daily alcohol consumption independently reduces blood pressure levels approximately 3.5/3 mm Hg. On the other hand, a 10 g/day increase in alcohol consumption is associated with an increase in blood pressure of 2/1 mm Hg.[35,88] Current recommendations are for individuals who consume alcohol to limit their intake to no more than two drinks per day for men and no more than one drink per day for women to reduce the risk of adverse effects of alcohol on blood pressure levels. A drink is defined as a serving of either a 12 oz beer, 5 oz wine, or 1.5 oz of 80-proof distilled spirits.[1,69]

Effect of Omega-3 Polyunsaturated Fatty Acids

Fatty fish and fish oil supplements are rich in long-chain omega-3 polyunsaturated fatty acids, which are postulated to play an essential role in blood pressure regulation via the production of eicosanoids and prostaglandins. Small-scale studies in patients with hypertension using large doses of fish oil supplements (>3 g/day) have reported an associated blood pressure reduction of 2.3–4.0 and 2.2–2.5 mm Hg in systolic and diastolic blood pressure, respectively.[35,89–91] The current recommendations is to consume fatty fish (or use of fish oil supplements) two or more times per week for blood pressure management and other cardioprotective effects.[69]

WEIGHT MANAGEMENT

The association of obesity and hypertension had been well-established by both observational studies and clinical trials.[69,92] In general, it appears that a reduction in body weight of 5–10 kg in overweight individuals reduces blood pressure levels approximately 6–12/5–8 mm Hg.[35,69,93–97] Exercise training remains an important component for weight management, although exercise training alone generally only results in a 2 kg weight loss. Regular exercise training

improves maintenance of lost weight as well as reduces the loss of lean body mass as associated with weight loss.[98–100] Exercise training appears to selectively reduce visceral abdominal fat, thereby potentiating blood pressure reduction. In fact, it appears that the combination of exercise and a reduction in energy intake generally results in a greater blood pressure reduction than either alone.[100,101] Currently, it is recommended that in order to achieve and maintain a significant weight loss and lower blood pressure, 60–90 min/day of moderate-intensity aerobic exercise should be combined with a reduced-calorie DASH diet.[69]

Intervention trials that utilized comprehensive lifestyle modification programs to lower blood pressure levels have in general had very encouraging results. The most notable large-scale trials are the PREMIER[102] and the *E*xercise and *N*utritional Interventions for *C*ardi*o*vascula*r* H*e*alth (ENCORE)[103] studies. These controlled, randomized studies have reported a mean reduction in blood pressure in hypertensive individuals of 11–16 and 6–10 mm Hg in systolic and diastolic blood pressure, respectively, following comprehensive lifestyle intervention (including weight reduction). In addition, the ENCORE trial reported a significant reduction in mean 24 h ambulatory blood pressure in the comprehensive intervention group. These studies confirm current guidelines and the value of comprehensive therapeutic lifestyle interventions for the prevention and management of hypertension.[1,79]

PHARMACOLOGICAL MANAGEMENT OF HYPERTENSION

JNC-7 recommends that all patients with Stage 2 hypertension initiate pharmacological treatment in conjunction with lifestyle change whereas those with uncomplicated Stage 1 hypertension should initiate lifestyle change for a trial of 6–12 months prior to initiation of pharmacotherapy.[1] Numerous different types of antihypertensive drugs are available including thiazide and potassium-sparing diuretics, β-adrenergic blockers, α-adrenergic blockers, ACE inhibitors, AR blockers, calcium channel inhibitors, centrally acting drugs, and direct acting vasodilators.[1] A thiazide diuretic is usually prescribed as the initial drug choice for patients with Stage 1 hypertension, whereas a two-drug combination is usually the initial prescription for patients with Stage 2 hypertension (e.g., a thiazide diuretic along with an ACE inhibitor or AR blocker, or β-adrenergic blocking agent, or calcium channel inhibitor).[1] Generally, multiple antihypertensive drugs are required to achieve the therapeutic target level; it is therefore imperative that the prescribing clinician pay particular attention to contraindications, drug interactions, and comorbidities when selecting antihypertensive drug therapy. The reader is referred to the JNC-7 report[1] for a more complete discussion of pharmacological therapy. To potentiate the efficacy of pharmacotherapy, initiation of the previously described lifestyle modifications is strongly recommended.[1]

TABLE 6.3
Lifestyle Modifications for Management of Hypertension

Modification	Recommendation	Blood Pressure Reduction
Weight reduction	Maintain a BMI between 18.5 and 24.9	5–20 mm Hg per 10 kg weight loss
DASH diet pattern	Consume a diet rich in fruit and vegetables Moderate in fat-free or low-fat dairy products Reduce saturated fat and cholesterol	8–14 mm Hg
Exercise	Regular aerobic exercise >150 min/week Or 60–90 min daily for weight reduction and maintenance	4–9 mm Hg
Reduced sodium/ salt intake	Lower salt intake as much as possible (1.5 g/day of sodium or 3.8 g/day of sodium chloride)	2–8 mm Hg
Limit alcohol consumption	No more than two drinks per day for men No more than one drink per day for women	2–4 mm Hg
Increase potassium	Increase intake to 4.7 g/day (level of DASH diet) Content from fruit, vegetables, and low-fat dairy products	2–4 mm Hg

Sources: Adapted from Chobanian, A.V. et al., *JAMA*, 289, 2560, 2003; Appel, L.J. et al., *Hypertension*, 47, 296, 2006.

SUMMARY OF CONCLUSIONS

The available evidence is robust in supporting TLC for the prevention and management, and as an adjunct to pharmacotherapy, of hypertension as is summarized in Table 6.3.

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7 Community Approaches to Reduce the Risks of Cardiovascular Disease

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CONTENTS

Introduction 83
Addressing CVD with Community-Based Approaches: Principles and Guiding Frameworks 85
Guiding Frameworks for Community-Based Approaches 85
Effective Community-Based Interventions to Address CVD 87
The Diabetes Prevention Program (1996–2001) 93
The Rockford Coronary Health Improvement Project (2000–2002) 94
Romsås in Motion Study (2000–2003) 95
Conclusions and Recommended Future Directions 95
Summary 96
References 97

INTRODUCTION

Up to 70% of deaths in the United States are due to chronic diseases, with heart disease, cancer, and stroke making up over half of all annual deaths [1]. Health care advances and public health efforts at local, state, and federal levels have contributed to marked decreases in death rates among 10 of the 15 leading causes of death [2]. While rates of heart disease and/or cardiovascular disease (CVD) have decreased by 3.7% since 2009 [2], they remain leading causes of death nationally and worldwide. It is estimated that one in three adults in the United States has at least one type of CVD [3]. The term "cardiovascular disease," or CVD, encompasses an array of syndromes that affect cardiovascular function, the most prevalent forms being coronary heart disease (CHD), cerebrovascular disease (i.e., stroke), hypertension, and heart failure [4]. The burden of CVD is substantial, resulting in diminished quality of life [5], disability [6], losses in productivity [6,7], and health care costs adding up to more than $400 billion dollars annually [7]. The burden is also impacted by health disparities that exist not only for overall CVD incidence and mortality, but also for the majority of CVD risk factors. CVD burden is even more remarkable given that the major CVD risk factors are preventable and modifiable [8].

Notably, the risk factors associated with the different types of CVD are fairly consistent and have a multifactorial etiology [9]. Contributing risk factors include nonmodifiable factors (age, gender, heredity/genetics), modifiable factors which include both sociodemographic characteristics (e.g., education or income) and behavioral or lifestyle factors (e.g., smoking, poor diet, physical inactivity, and obesity) [4,10,11], and physiological factors or conditions such as hypertension, hypercholesterolemia, or diabetes that impact CVD risk [12]. It is likely that nonmodifiable and modifiable factors are interrelated and function synergistically to impact CVD [9]. For example, a nonmodifiable risk factor (age) is one of the most important risk factors for CVD. What is modifiable, however, are the lifestyle risk factors associated with the aging process, such as physical inactivity or excess weight gain. Most interventions that target CVD attempt to intervene on one or more lifestyle risk factors (e.g., physical activity, diet, or weight) or risk conditions (e.g., hypertension, hypercholesterolemia, or diabetes) while acknowledging the biosociodemographic characteristics (e.g., race and age) that may be directly or indirectly related to CVD incidence and mortality.

Behavioral modifications to decrease or eliminate smoking, physical inactivity, unhealthy dietary patterns, excess weight/obesity, and stress management have demonstrated significant reductions in CVD risk [8,13,14]. For example, cigarette smoking, which is considered to be the most preventable risk factor for CVD, is associated with a two- to fourfold increase in CHD risk [15]. Smoking cessation interventions have demonstrated a reduction in risk from acute coronary syndrome by 61% [16] and a 35%–40% risk reduction in acute coronary syndrome among smokers with a previous CVD diagnosis [17]. Nevertheless, 17.2% of U.S. adults continue to report using tobacco products [18] including 44 million reported smokers. An estimated 443,000 smokers suffer premature smoking-attributable deaths each year [19]. As with other CVD risk factors, disparities in smoking rates exist. For example, American Indian and Alaskan Natives have the highest smoking rates in the country [19], and blue

collar workers have a smoking prevalence nearly twice that of white collar workers [20].

Interventions addressing physical activity, another behavior affecting CVD risk, have been effective at decreasing inactivity and CVD risk [13,21–25]. Regular moderate physical activity has been shown to decrease CVD incidence and mortality in a dose–response relationship with CHD risk reductions between 30% and 50% [23,24,26]. Additionally, moderate physical activity is linked to decreases in other CVD risk factors including obesity, hypertension, and hypercholesterolemia [27,28]. According to the 2008 National Health Interview Survey, however, only 18% of U.S. adults are currently meeting the national recommendations of getting at least 150 min of moderate physical activity on a weekly basis [18].

High levels of dietary cholesterol and saturated fat intake in the diet have also been linked to CVD [29]. Interventions to promote healthy diets have been shown to substantially decrease CVD risk, through modifications in glycemic load (e.g., how foods affect blood sugar and insulin levels) and through various dietary changes including increasing daily consumption of dietary fiber [30], decreasing total and saturated fats [30], and increasing omega-3 fatty acids [31]. Additionally, because of the association between hypertension and CVD, diets lower in sodium content are believed to decrease CVD risk [32,33].

Obesity is at epidemic proportions in the United States. Over 36% of adults are overweight (BMI = 25.0–29.9) and 27.6% are obese (BMI = 30.0+) and both increase risk of CVD [13]. Disparities exist in obesity rates such that compared to Caucasians, African Americans have a 51% higher obesity prevalence and Hispanics have a 21% higher prevalence [34]. Across racial groups, one theory explaining the biological link between high body mass index (BMI) and CVD risk is the "metabolic syndrome," which refers to a cluster of symptoms linked to excess weight, measured by waist circumference, fasting triglycerides, cholesterol, blood pressure, and plasma glucose levels [29]. Importantly, interventions to decrease body weight among adults have produced decreases in overall CVD incidence [35,36].

Psychological stress is defined as the response to perceived or actual environmental demands that burden or exceed one's ability to adapt [37]. Acute and chronic psychological stress has been linked to all types of CVD [38] and CVD risk [39], as well as CVD-attributable morbidity and mortality [40]. There is also research on the association between CVD and depression (e.g., Type D personality) [41] and measures of hostility [42], which are examples of psychological stress responses. Psychological/social stressors can include financial hardship, relationship and family problems, and work stress, and the subsequent psychological stress can manifest as mood and cognitive changes, as well as impact behaviors like smoking and alcohol consumption [40,43]. Stress reduction interventions have been effective in reducing CVD risk [40] through various pathways, including decreased activation of the "fight or flight" stress response [37].

Several conditions increase CVD risk, especially high blood pressure, high blood cholesterol, and high blood glucose levels. Hypertension, or high blood pressure (HBP), is a unique risk factor because it is simultaneously a chronic form of CVD and a risk factor for other types of CVD (e.g., stroke). Even after controlling for race, age, or gender, hypertension has been linked to CVD risk and increased mortality [44–47]. Interventions to reduce HBP have been effective in decreasing overall CVD risk [48–50]. High blood cholesterol, or hypercholesterolemia, is also a common risk factor for CVD [51]. CVD risk decreases 2%–3% for every 1 mg/dL incremental increase in high-density lipoprotein cholesterol (HDLC) [51,52]; additionally CVD risk can be decreased by treating hypercholesterolemia, with pharmacotherapy and behavioral interventions focused on diet and physical activity [53,54].

Diabetes mellitus (Type 1 and Type 2) is another CVD risk factor. Individuals with diabetes do not properly convert glucose (sugar) into energy. More than 18.8 million individuals are diagnosed with diabetes mellitus and it is estimated that another 7 million remain undiagnosed [55]. Ninety percent of individuals with diabetes have Type 2 diabetes [56], and Type 2 diabetes itself is the seventh leading cause of death in the United States [55,57]. Between 60% and 75% of individuals with Type 2 diabetes will die of a CVD [58]. African Americans, Hispanics, Native Americans, and Asian Americans have increased prevalence of Type 2 diabetes compared to Caucasians [57–59]. Type 2 diabetes risk is increased with obesity and physical inactivity. Interventions to decrease diabetes have also been shown to reduce CVD risk [60,61]. For example, the Diabetes Prevention Program (DPP) lifestyle intervention, which will be described in greater detail later in this chapter, was able to decrease the incidence of diabetes by 58% as compared with a diabetes medication placebo group [62]. The DPP has successfully been adapted for use in multiple community settings [63,64].

CVD-related disparities in risk, incidence, and mortality are a serious public health concern [65]. Health disparities are broadly defined as the difference in disease incidence, prevalence, mortality, burden, access to care, and care quality linked to demographic characteristics (e.g., age, race, ethnicity, gender, and sexual identity) and socioeconomic factors (e.g., income, education, and geographic location) [65–68]. For over 20 years, national initiatives have targeted disparities and these efforts continue, as evidenced by the Healthy People 2020 goals to "achieve health equity, eliminate disparities, and improve health for all groups" [69]. Despite the evidence that interventions to reduce HBP, HBC, tobacco use, stress, and increase physical activity can be effective in reducing both CVD risk factors and CVD incidence/mortality, and despite the 3.7% overall drop in CVD rates since 2009, there are certain population groups that consistently suffer CVD-related disparities and are not experiencing these positive outcomes.

Gender-, race-, and income-based differences in CVD prevalence and mortality are among the most prominent health disparities. CHD rates per 1000 males are 81.1 and nearly

double those of females whose CHD rates are 49.6/1000 [70]. Similarly, for all CVD types except stroke, males have higher CVD mortality rates than females. Racial/ethnic disparities related to CVD risk exist well. CVD incidence and mortality are higher among African Americans, American Indians, and Asian or Pacific Islander groups compared with Caucasians [7,65,66]. In 2009, although Caucasian males had the highest prevalence of CHD (67.2/1000 vs. 59.8/1000 among African American males), African Americans were significantly more likely to die from the condition (403.5/1000 vs. 292.7/1000) [70]. Individuals with low education and income levels suffer increased incidence and mortality across most types of CVD [7,65,66]. Income-related disparities are often linked with income inequality (i.e., large inequality between groups of individuals in income distribution often measured using the Gini coefficient or the Robin Hood index) [71]. Even after controlling for race, income-related disparities are associated nationally and globally with obesity and sedentary lifestyle [72], as well as overall CVD incidence and mortality [73,74].

To continue to make progress in reducing CVD incidence and mortality among U.S. adults, health professionals must find ways to reach and intervene with subgroups who suffer disparities in health. We advocate for community-based participatory research and practice to work collaboratively with those intended to benefit from the interventions. By engaging those who suffer disparities in health to participate in formative research, implementation, and evaluation, we are better able to reach these populations in settings where they live, work, play, pray, and socialize. Moreover, with community-based approaches we build relationships and trust with groups who are at highest risk of CVD when we enlist them to be active partners in eliminating health disparities. In addition to improving engagement and reach within these high-risk communities, we also need to identify effective interventions that can be adapted in culturally and contextually appropriate ways if we are to eliminate these disparities in health.

ADDRESSING CVD WITH COMMUNITY-BASED APPROACHES: PRINCIPLES AND GUIDING FRAMEWORKS

An effective community-based approach to addressing CVD disparities engages the community and also ensures that the interventions/programs are adapted to fit the needs and characteristics of the target community [75]. Ensuring that a program or intervention is culturally relevant—that is, it takes into account social and cultural aspects of health behavior, including family history and relationships, traditions, cultural norms, spending priorities, living arrangements, and support systems [76]—is a major strength of the participatory nature of most community-based approaches. Community representatives and leaders are knowledgeable about the needs and interests of their members, as well as barriers or challenges in a community that will affect program adoption and implementation. Community-based approaches establish connections with these local leaders, engaging them as equal partners in identifying and clarifying the health problem, deciding how to best reach the intended population, developing workable solutions, and tailoring interventions for the unique needs and interests of the community [75].

Community-based approaches begin with community-organizing and community-building activities [77]. Empowering community members to take ownership of their health promotes and facilitates the social change process needed for health promotion programs to be considered, adopted, implemented, and able to produce the desired behavioral and health outcomes [77]. Community growth, group identification, and working toward a collective health goal are believed to foster group cohesion and community pride [75]. The collective social support is believed to promote long-term behavioral changes [25]. Community-based approaches also draw attention to important health factors, available resources, and assets within communities, and work toward changing the health-related norms and culture of a given community [75,78,79].

In the previous edition of this book, Dr. Thompson gave a thorough account of the history of chronic diseases, the role of lifestyle behavior change in CVD, the use of experimental designs to modify these behaviors, and the role of community approaches to decrease risk by challenging/altering the health culture of a community. After highlighting several key studies, including the Community, Hypertension, Atherosclerosis, and Diabetes (CHAD) program, the Stanford Three-Community Study, the North Karelia Study, the Switzerland National Research Program, the Coronary Risk Factor Study (CORIS), the Stanford Five-City Project, the Minnesota Heart Health Program (MHHP), the Pawtucket Heart Health Program (PHHP), The Australian Studies, and the Community Intervention Trial for Smoking Cessation (COMMIT), Dr. Thompson recommended that health care providers become more engaged in community-based approaches as health advocates for their patients by participating in media advocacy efforts or collaborating with voluntary health groups. Here, we conduct a review of selected literature on more recent CVD intervention efforts, document advances in community-based approaches to reducing CVD, and emphasize the importance of ecological approaches and robust evaluation efforts that will help prioritize interventions to address and eliminate CVD disparities.

Guiding Frameworks for Community-Based Approaches

Social ecological models are fundamental guiding frameworks for a wide range of community-based health behavior change efforts. Social ecological models emphasize the importance of multiple factors and influences on health, including environmental, cultural, social, and psychological factors [80]. The core of an ecological model is that it serves as a useful heuristic for planning a comprehensive intervention that targets multiple levels and targets of influences on health behavior [81]. There are four key assumptions of

ecological models: (1) factors at multiple levels of influence impact behavior; (2) factors interact within and between levels of influence; (3) multilevel interventions (vs. single level) should be most effective in producing effective behavioral outcomes; and (4) multilevel interventions will be most effective when they are behaviorally specific. Multilevel interventions are a cornerstone of community-based approaches [82]. By nature, communities are complex, multidimensional, multilayered entities composed of interconnections of individuals, social networks, organizations, and are governed by social policies. The social ecological framework allows one to articulate these relationships and provides a useful guide for developing interventions that address the complexity of community-based approaches to decreasing CVD incidence and mortality.

According to Stokols [82] and McLeroy et al. [81], health behavior outcomes will be optimized when there are interventions at the intrapersonal, interpersonal, organizational, community, and/or social policy levels of influence [80,81]. Figure 7.1 depicts these multiple levels of influence within the social ecological framework. The intrapersonal level includes interventions to address the knowledge, attitudes, beliefs, intentions, and other characteristics within an individual that influence his/her health behavior choices and chances. These are often traditional educational efforts aimed at the individual. Interpersonal-level interventions target individuals as they interact with others (e.g., peers, parents, spouses, supervisors, health care providers). These interventions may include efforts to increase social support, improve communications between parents-kids, spouses, or patient providers. Organizational-level interventions target the places where individuals congregate such as worksites, health care settings, churches, beauty salons, libraries, and many other locations. Organizational-level interventions seek to influence the social and physical environment, and policies within selected institutions to support the health of those who are members of the organization. Community-level interventions target entire towns, cities, or regions with interventions that influence social and physical environment of these larger units where multiple organizations may be influenced via media efforts, community-organizing efforts, new walking trails, or other community-based strategies. Social policy influences all members of a larger community or society with broad social, political, or economic interventions such as national policies to promote healthy school lunches, tax credits for small businesses that offer health promotion programs for their employees, and national food labeling requirements. If interventions are simultaneously mounted at all levels of the SEF, then we assume that the likelihood of desired health behavior changes would be increased.



FIGURE 7.1 The social ecological framework, illustrating multiple levels of influence that affect health behavior.

The story of tobacco use in the United States offers a brilliant example of how interventions designed and delivered at multiple levels of the SEF have conspired to reduce tobacco use among adults from 25.5% to 17.2% over the past two decades [83,84]. Initially, all intervention strategies were aimed at individual smokers to get them to quit—this strategy worked for some, but not all smokers. Individual strategies were not as effective for smokers who were highly addicted to nicotine, for those who worked in blue collar or other smoke-filled work settings, or for smokers who lived with other smokers. And, it was realized that nonsmokers who were exposed to smoke were at increased risk of CVD and cancer. As a result, interventions moved beyond individually focused approaches at the intrapersonal or interpersonal level of the SEF, to more "upstream" intervention approaches that would restrict access to tobacco among youth; restrict tobacco use (and exposure to smoke) at schools, workplaces, and other public places; and limit tobacco advertising. Over time, interventions utilized media campaigns and "Quit and Win" contests at the community level, utilized free or low-cost quitline services, and offered access to effective pharmacologic treatments that would help smokers quit with higher success rates. And, policy and regulatory-level interventions utilized cigarette sales taxes, and other social policies to further prohibit smoking that completed a set of multilevel interventions running simultaneously at each level of the SEF. With this concerted effort, decreasing tobacco use and the resulting premature death and disability attributable to tobacco use and exposure to smoke have been a true public health success story. Now, similar multilevel intervention efforts are being applied to the problem of obesity.

Just as the social ecological framework is useful in the development of community-based approaches, RE-AIM is an effective framework for evaluating and prioritizing among community-based intervention approaches. RE-AIM, developed by Glasgow et al., evaluates the impact of health promotion programs using measures of "*R*each, *E*ffectiveness, *A*doption, *I*mplementation, and *M*aintenance" [85]. *Reach* is an individual-level construct and is defined as the proportion of the population that participates in a given program. *Effectiveness* refers to the success rate of the program; *adoption* measures the uptake of the program by organizations. Representativeness is a crucial consideration for assessing both *reach* and *adoption* because it relates to the type of individuals and organizations that participate in these

programs with an understanding that one seeks to attract a representative group of individuals/organizations versus a select, nonrepresentative group that may already be "healthy." *Implementation* assesses the extent to which a health program is implemented as designed and *maintenance* measures the sustainability of the program over time with individuals and organizations [85]. Community-based approaches benefit from applying the RE-AIM evaluative process because it reveals that interventions which reach the greatest numbers of individuals (i.e., high "reach"), with highly effective programs (i.e., high "effectiveness"), and are adopted by the greatest number and most representative organizations (i.e., high "adoption"), with the best or greatest fidelity to the implementation success (i.e., high "implementation"), and can be sustained over time within individuals/organizations (i.e., high "maintenance") are those that will be most effective and desirable to support. When interventions are evaluated using RE-AIM constructs, we can assess, identify, and prioritize among many competing strategies using a data-driven approach. In resource-limited times, RE-AIM allows practitioners and policy makers to invest wisely and provides crucial information for resource allocation. Moreover, for researchers, RE-AIM provides essential information that steers recruitment strategies at the individual and organizational levels, helps clarify fidelity and implementation challenges, and offers guidance on planning for sustainability of interventions once funding is done. Additionally, it provides critically important information to aid in the adaptation of effective interventions for diverse populations and communities. Using the RE-AIM framework, programs can be evaluated in ways that will assist with program improvements, translation, adaptation, and long-term sustainability within individuals, organizations, and communities.

EFFECTIVE COMMUNITY-BASED INTERVENTIONS TO ADDRESS CVD

We conducted a limited review of community-based approaches to decreasing CVD risk factors, incidence, and mortality. A PubMed search was conducted using each of the targeted risk factors (smoking, physical activity, diet, weight, and stress), and the key words "cardiovascular disease," "community-based," and "community programs CVD prevention," yielding 668 results. After excluding papers published after 1999 (to avoid redundancy with those reviewed by Thompson in the previous edition [86]), those focusing on non-adult populations, papers written in languages other than English, papers describing baseline or one-time data collection efforts, and those that described interventions based on DPP, CHIP, or MoRo (which we will describe in greater detail in the next section), 14 studies met our inclusion criteria. In Table 7.1, we organize study information by identifying the target population or community, the targeted risk factors, theories (if any) upon which the intervention was based, intervention components, level of SEF, settings, study design(s), and available results. While this table does not represent a comprehensive inventory of all multilevel community-based approaches to CVD prevention (due to exclusionary criteria and/or inadequate information of program components), it does provide a useful summary of some community-based efforts.

As previously mentioned and evidenced in Table 7.1, the term "community" refers to a population within a defined place or location or context [77]. Thus, "community" can describe individuals located within many settings, including worksites, faith-based organizations, individuals located within a specific geographic area, or individuals who identify with a specific cultural/ethnic or age group, or any number of defining characteristics. In the studies reviewed, we identified interventions that took place in a variety of community settings.

A myriad of intervention strategies were used in these studies to decrease CVD risk factors, or CVD incidence/mortality. The community-based intervention methods used included improving access to health educational materials (e.g., through educational classes, media campaigns, or group cooking classes), improving access to resources (e.g., increasing access to healthy foods through farmers markets or fitness activities), altering the physical environment (e.g., neighborhood cleanup and beautification projects or installation of treadmills), intervening with community health workers (CHW), and policy changes (e.g., paid exercise time for employees). Additionally, all of the studies reviewed utilized multilevel intervention strategies, categorized according to the SEF. All of the programs reviewed included both intrapersonal (e.g., individual knowledge and skill development) and interpersonal components (e.g., group fitness and healthy eating classes). Half of the programs (7 of 14) had interventions at the organizational level including programs that attempted to influence health of individuals at worksites and faith-based organizations. Thirty-five percent of the programs (5 of 14) had community-level components that included collaborations between different organizations (e.g., community organizations and primary care facilities). However, only two of the programs reviewed implemented a policy change; one implemented a provision for healthy food at meetings and in another, employees received paid time for exercise (see Table 7.1). The following descriptive data describe outcomes based on the type of community-based method implemented (e.g., educational interventions were associated with increased physical activity).

Each of the projects had an educational component to either increase awareness about CVD risks or intervene on a CVD risk factor or factors. Several of the studies were successful in improving CVD awareness [87–89], implementing environmental change [87,90], improving CVD screening [88], improving physical activity and diet [91], decreasing BMI and weight [92–94], improving self-reported health and mood [94], decreasing blood pressure [89,95,96], improving cholesterol levels [93], improving blood glucose levels [92,93], and decreasing smoking [95].

Policy changes can expedite transformations in the physical and social environment, as well as the health culture of

TABLE 7.1
Effective Community-Based Interventions to Address CVD

Project/Author	Target Population/ Community	CVD Risk Factor	Theory Used	Intervention Components	SEF	Settings	Methods	Results
Kansas City—Chronic Disease Condition (KC-CDC) / Collie-Akers et al. [87,126]	African Americans and Hispanics in Kansas City, MO	• Diabetes • Other CVD risk factors selected by participating collaborators, primarily diet and physical inactivity	Not reported	• Community organizing and coalition building • Educational literature • Group education sessions (including cooking demonstrations) • Group fitness activities • Provision of healthy food at meetings	1, 2, 3, 5	• Community organizations • Faith-based organizations	• Case study and time-series design • Time-series design for community change outcomes	• 321 documented community changes from October 2001 through December 2004. 75% of these were designed to reduce risk for both CVD and diabetes; 56% targeted primarily • Most community changes represent ongoing efforts, rather than one-time events (64.8% among neighborhood associations and 60% among faith organizations)
Union Town Community Health Project/ Cornell et al. [99]	African American women in Union Town, AL	• Smoking • Diet • Physical inactivity	Community empowerment, diffusion of innovation, and social cognitive theory	• CHW delivered • Community-wide screening and educational events • Group fitness activities • Group cooking classes • Neighborhood cleanup and beautification projects • Educational literature added to public library collection • Increased availability of ingredients and implements needed for healthy cooking in local stores	1, 2, 3, 4	• Community	• Pre–post community inventories	• CHWs reached 574 individuals through structured community-wide events, in addition to those reached in informal education and awareness raising activities • CHWs taught a total of 108 aerobics classes during the 12-month intervention period, attended by a total of 107 people, 74.7% of whom attended four or more classes per month • Monthly group cooking classes were attended by 76 community residents most of whom were regular attendees • Six community members attended two multi-session smoking cessation courses

Charlotte REACH 2010/DeBate et al. [90]	Northwest Corridor of Charlotte, NC, predominantly African American population	• Smoking • Diet • Physical inactivity • Diabetes	Not reported	• Group fitness activities • Farmers markets • Door-to-door visits from CHWs • Cue-to-action prescription pads for physicians to provide referrals to REACH programming and secondary prevention activities • Diabetes support groups • Grocery store tours	1, 2, 3, 4	• Community • Health care providers	• Focus groups	• Changes within and between ecological levels of change were observed • REACH participants reported an increase in knowledge of preventative health behaviors, the development of health-related skills, and the diffusion of knowledge to family • CHWs reported changes in individual health perceptions from disease- to prevention-oriented, and positive community changes
Farag et al. [21]	Employees of rural public school system in Southwestern Oklahoma	• Physical inactivity	Not reported	• CVD risk factor screening • Installation of treadmills at worksites • Educational literature on walking • Paid time for exercise	1, 2, 3, 5	• Worksite	• Pre/post-screening	• Pre/post-significant differences in: • Lower total ($p < 0.0001$), low- ($p = 0.01$), and high-density lipoprotein cholesterol ($p < 0.0001$) • Lower systolic blood pressure ($t = 2.9$, $p = 0.004$) • Trend toward higher self-reported physical activity levels ($p = 0.06$)
Goldhaber-Fiebert et al. [92]	Adults in rural Costa Rica	• Diabetes • Physical inactivity	Not reported	• Group fitness activities with family participation, facilitated by local community leaders • Group nutrition classes	1, 2	Community	• RCT	• Intervention group lost 1.0 ± 2.2 kg compared to 0.4 ± 2.3 weight gain in the control group ($p = 0.028$) • Fasting glucose decreased 19 ± 55 mg/dL in the intervention group and increased 16 ± 78 mg/dL in the control group ($p = 0.048$) • Glycosylated hemoglobin decreased 1.8% ± 2.3% in the intervention group and 0.4% ± 2.3% in the control group ($p = 0.028$)

(*continued*)

TABLE 7.1 (continued)
Effective Community-Based Interventions to Address CVD

Project/Author	Target Population/ Community	CVD Risk Factor	Theory Used	Intervention Components	SEF	Settings	Methods	Results
• Graffagnino et al. [93]	Overweight and obese adults	• Overweight • Obesity	Not reported	• Individualized nutrition counseling based on the Therapeutic Lifestyle Diet • Individualized physical activity regimen • Group classes on stress management, lifestyle change, healthy eating, physical activity • Optional behavioral health assistance	1, 2	• Community	• Retrospective analysis of 6-month intervention	• Weight loss of 7.3% in men and 4.7% in women • Significant improvement were noted in body weight ($p < 0.0001$), total cholesterol ($p < 0.0001$), LDL cholesterol ($p < 0.0001$), HDL cholesterol ($p < 0.005$), triglycerides ($p < 0.0001$), and fasting glucose ($p < 0.02$)
Un Corazón Saludable/ Harralson et al. [94]	Low-income urban Latinas	• Diet • Physical inactivity • Depression	Not reported	• Group fitness classes • Group educational classes (recognizing CVD risk factors and heart attack symptoms, communication with health care providers, healthy eating and recipe modification, depression and health, and physical activity)	1, 2	• Community	• Pre–post	• Statistically significant improvements • BMI ($p = 0.001$) • Abdominal obesity ($p < 0.001$) • Waist-to-hip ratio ($p = 0.04$) • Self-rated health ($p < 0.001$) • CES-D scores ($p < 0.001$)
Healthy Connections Project/Harvey et al. [88]	Latina and African American women at high risk for diabetes and/or hypertension in Detroit, MI	• Diabetes • High blood pressure	Not reported	• Screenings • Awareness raising and educational activities in a social, group setting, delivered by CHWs	1, 2, 3, 4	• Community	• Training program evaluation using observation, document review, group interviews, process surveys, and CHW knowledge tests	• Increased awareness and number of individuals screened • Eight CHWs conducted 124 house parties, conducted 1428 blood pressure screenings, and provided health education to 1646 individuals

Cardiovascular Health Awareness Program (CHAP)/ Kaczorowski et al. [98]	Older adults	• High blood pressure	Not reported	• CVD risk assessment and blood pressure screenings; results shared with family physicians • Peer education about blood pressure monitoring	1, 2, 3, 4	• Community pharmacies	• Cluster randomized trial	• Intervention communities experienced a significant reduction in admissions for acute MI (rate ratio 0.87, 0.79 to 0.97; $p = 0.008$) and congestive heart failure (rate ratio 0.90, 0.81 to 0.99; $p = 0.029$) but no significant decrease in hospital admissions for stroke
Finnmark Intervention Study/Lupton et al. [127]	Adults in Arctic coastal communities	• Physical inactivity • High blood pressure	Not reported	• Community empowerment • Cooperation between different organizations and the primary health care system • Mass media communications • Smoke-free policies at health centers and schools • Fitness class offerings at voluntary organizations • Group cooking classes	1, 2, 3, 4	• Community	• Quasi-experimental	• Males in the intervention community experienced an 8.6% ($p = 0.047$) increase in physical activity as compared to the control community, a 0.01 mm Hg ($p = 0.002$) reduction in systolic blood pressure and a 0.1 mm Hg ($p < 0.001$) decrease in diastolic blood pressure • Females in the intervention cohort experienced an 11.2% increase in use of low-fat milk ($p = 0.046$) as compared to the control community, an increase in systolic blood pressure by 2.1 mm Hg ($p = 0.024$), and a reduction in diastolic blood pressure by 2.1 mm Hg ($p < 0.001$)
The Ostego-Schoharie; Healthy Heart Program/Nafziger et al. [95]	Rural adults living in New York State	• Overweight • Smoking • Diet • Physical inactivity	Not reported	• Community organizing • Mass media communications • Screenings • Posting of fact sheets in workplaces and locations throughout the community • Supermarket tours, recipe contests • Walking groups • Smoking cessation referrals and education • Professional education • School classroom demonstrations	1, 2, 3, 4	• Community	• Pre–post	• Smoking prevalence declined (from 27.9% to 17.6%) • Systolic blood pressure was decreased • No change in diastolic blood pressure • Body mass index increased significantly

(*continued*)

TABLE 7.1 (continued)
Effective Community-Based Interventions to Address CVD

Project/Author	Target Population/ Community	CVD Risk Factor	Theory Used	Intervention Components	SEF	Settings	Methods	Results

Pasos Adelante/ Staten et al. [91]	Adults living in United States–Mexico border counties in AZ	• Smoking
		• Diet
		• Physical inactivity
		• Diabetes
		• High blood pressure
			Not reported	• Group educational classes
				• Group fitness activities
				• All intervention components delivered by CHWs
					1, 2	• Community	• Pre–post	• Increased mean number of minutes/week spent on moderate-to-vigorous walking ($p < 0.001$)
								• Reductions in weekly consumption of sweetened soda ($p < 0.001$)
								• Increases in weekly consumption of:
								  • Salads pre to post ($p < 0.001$)
								  • Vegetables ($p < 0.001$)
								  • Fruits ($p < 0.001$)

The Barber-Assisted Reduction in Blood Pressure in Ethnic Residents (Barber-1) Study/ Victor et al. [96,120]	African American men	• High blood pressure	Not reported	• Screening • Educational posters and literature • Peer education	1, 2	• Community barbershops	• Cluster randomized trial	• Greater improvement in hypertension control rate than the comparison treatment ($p = 0.04$)
Villablanca et al. [89]	Women, primarily African American	• Overweight • Physical inactivity	Not reported	• Risk-specific counseling • Heart and stroke education • Medical screenings	1, 2	• Community organizations • Faith-based organizations	• Longitudinal cohort • 32 sites • Pre–post-educational intervention	• Improved awareness of health disease, calling 911, and risk factors ($p < 0.05$) • Improved control of hypertension ($p < 0.05$) • Improvement of stage of change ($p < 0.05$)

Note: Levels of the Socioecological Framework: Key: Interpersonal = 1, Intrapersonal = 2, Organizational = 3, Community = 4, Policy = 5.

a community. For example, Collie-Akers et al. demonstrated that policy change (i.e., provision for healthy foods at meetings) was successful in facilitating broad-level environmental change in African American and Hispanic community and faith-based organizations [87]. Additionally, a worksite-based study adopted a policy of paid exercise time [21].

Increasing access to services (e.g., fitness activities and healthier foods) is another community-based intervention strategy. Efforts to increase access to fitness activities to decrease CVD risks within their community samples were successful in improving CVD awareness [87], promoting environmental change [87,90], improving physical activity [21,91] and diet [91], decreasing BMI and weight [92–94], increasing self-reported health and mood [94], improving blood pressure [21], improving cholesterol levels [21,93], and improving blood glucose levels [92,93]. Efforts to increase access to healthier foods were also successful in improving CVD awareness [87] and facilitating environmental change [90] within several community-based programs.

Other community-based intervention methods include using CHWs, individual and group counseling, and screening campaigns. CHWs serve as a bridge between health care organizations/providers and the intended beneficiaries of their programs/services [97] and because CHWs live in the communities where they work, they understand the needs and barriers of a community. In the studies reviewed, interventions using CHWs were effective in implementing environmental change [90], and improving physical activity and diet [91]. Individual and group counseling improved overall CVD risk [89], decreased BMI and weight [93], improved blood pressure [89], improved cholesterol levels [93], and improved blood glucose levels [93]. Lastly, the interventions that were designed to increase screening rates improved CVD awareness [88], improved screening rates [88], improved CVD-related hospital admittances [98], and improved blood pressure [96].

This review of community-based studies designed to decrease CVD risk using community-based approaches revealed that numerous intervention strategies were applied at multiple levels of the SEF to increase physical activity, decrease weight, increase healthy eating, decrease blood pressure, smoking rates, blood cholesterol, and blood glucose. And 4 of the 14 studies reviewed targeted a single-risk factor, while the remaining 10 used a multiple-risk factor design. Unfortunately, almost no studies reported that theory guided their intervention efforts. However, the influence of the SEF can be seen in many of the projects that used multilevel interventions targeting not only individual-level behavior but also community-wide environmental change. Notably, many targeted a population suffering CVD health disparities, specifically low-income populations [88,91,94], rural populations [21,92,95], older populations [98], and minority populations [87–91,96,99]. Study designs were varied and included randomized controlled trials (RCTs), longitudinal cohort studies, pre- and posttest designs, and mixed method designs. In some cases, the measures used to assess outcomes were not necessarily valid or reliable, or were complicated (e.g., reach of a screening awareness media campaign). This type of challenge can be exacerbated by multilevel interventions which also produce multilevel outcomes that may have synergistic outcomes. Less focus overall was attached to process measures that reveal important reasons why an intervention may prove effective, or not.

Since publication of the previous edition of this book, which highlighted a number of sentinel community-based CVD risk reduction programs such as the Stanford Five-City Project, the North Karelia Study, and the Minnesota and PHHP, several recent studies have attempted to build on the successes of these previous trials and have produced effective CVD outcomes and/or improvements in CVD risk factors. Here we select three community-based approaches: the DPP, the Coronary Health Improvement Program (CHIP), and the Romsås in Motion (MoRo) studies as examples of more recent community-based interventions that produced effective outcomes. Additionally, each of these studies has operated on at least two levels of the social ecological framework.

The Diabetes Prevention Program (1996–2001)

Diabetes is an important risk condition for CVD, and both of them share several common risk factors, including obesity and overweight, physical inactivity, and hypertension. Effective community interventions that address risk factors for diabetes, therefore, can provide useful lessons for preventing or reducing CVD. The DPP was a multicenter clinical trial involving 3324 adults with prediabetes who were randomized to one of three study arms: placebo, medication (metformin), or a lifestyle modification program [60,62]. In order to be eligible for the program, adults needed to have a BMI of 24 or higher (22 or higher in Asians), fasting glucose concentration of 95–125 mg/dL, and 140–199 mg/dL 2 h after 75 g oral glucose [62]. The lifestyle modification arm focused on achieving and maintaining a weight reduction of at least 7% through dietary changes and engaging in moderate physical activity for at least 150 min/week. The intervention's core education curriculum targeted the intrapersonal level of the social ecological framework and consisted of 16 educational modules delivered over a 24-week period by lifestyle coaches using motivational interviewing techniques. The educational modules covered basic information about balancing nutritional input with energy output, but also covered potential barriers to lifestyle change, including motivational and social challenges [60]. Participants were taught self-monitoring techniques and recorded physical activity and fat and calorie intake for at least 1 week/month [60]. To address the interpersonal level of the social ecological framework, participants learned strategies to leverage social relationships to help, rather than hinder, achievement of their behavior change goals by finding physical activity partners and using social cues to promote healthy behavior [60]. Finally, participants attended group education classes on topics such as healthy cooking and resistance training [60]. After 3 years of follow-up, the incidence of diabetes in the lifestyle intervention was reduced by 58% (95% CI = 48%, 66%) and 31%

(95% CI = 17%, 43%) in the metformin group as compared to the placebo group [62]. With regard to weight, participants in the lifestyle intervention lost a mean of 5.6 kg, whereas the mean weight loss for the metformin and placebo groups was 2.1 and 0.1, respectively ($p < 0.001$) [62]. Particularly relevant to the goal of eliminating health disparities, minority groups that suffer disproportionately from Type 2 diabetes (African Americans, Hispanic Americans, Asian Americans and Pacific Islanders, and Native Americans) comprised 45% of the participants enrolled in the original DPP study [100]. Results in the DPP lifestyle intervention were similar across gender and racial/ethnic groups [62].

Since its original success, the DPP lifestyle intervention has been adapted for use in many new community settings and for diverse populations. In her review of seven studies of community-based translations of the DPP, Jackson summarized characteristics and results for these translation efforts [101]. One such effort was a modified DPP lifestyle intervention in a semi-urban YMCA that demonstrated a significant difference ($p < 0.001$) in 6-month weight reduction between intervention (6.0% of body weight; 95% CI = 4.7, 7.3) and control groups (2.0% of body weight; 95% CI = 0.6, 3.3) and in total cholesterol (−22 vs. +6 mg/dL) [63]. The DPP educational modules were also used in rural African American churches, integrating prayer with church leadership and peer support into DPP-based group activities [102]. Following the 4-month intervention, participants had significant ($p < 0.05$) decreases in weight (7.5 lb [3.6%]), systolic (16 mm Hg [11.7%]) and diastolic (12 mm Hg [14.0%]) blood pressure, and fasting glucose (5 mg/dL [4.8%]) [102]. Cramer et al. adapted the DPP to implement a less costly and more sustainable intervention in a low-resource urban environment with a primarily African American population [103]. The intervention arm of the 9-month RCT delivered an adapted DPP curriculum and also integrated case management program with a family medicine clinical care services. This adapted DPP program resulted in greater reductions in the intervention group compared to the usual care group in HbA1c levels (−1.87 vs. −0.54) and weight (−2.47 vs. +0.88 kg) ($p = 0.011$) [103]. In addition to these three examples of the extension of the DPP into the organizational level (i.e., YMCAs, churches, and community clinics) of the social ecological framework, the DPP has also been applied to worksites [104]. For example, Aldana et al. reported that 2 years after a 12-month DPP-based worksite intervention, participants maintained significant improvements as compared to baseline in oral glucose tolerance (26.59 mg/dL decline; $p < 0.05$) and aerobic fitness (18.65 mL/kg/min; $p < 0.05$) [104]. Additional DPP translation efforts using a CBPR approach have been undertaken with underserved Latino populations in Chicago [105] using a CHW model to deliver intervention components. These efforts resulted in participants' forward movement along the stages of change model for the behaviors of increasing fruit and vegetable intake, increasing physical activity, and reducing fat intake. Additional translations of the DPP are being implemented with Native American youth in Montana (results not yet available) [106] and with low-income African American women and Latinas (results not yet available) [107].

The Rockford Coronary Health Improvement Project (2000–2002)

The CHIP was initially designed as a 30-day, 40 h outpatient hospital-based education program in Kalamazoo, MI, that aimed to reduce blood lipid levels, blood pressures, and blood sugar levels, decrease excess weight, eliminate smoking, enhance daily exercise, adopt better stress coping strategies, and decrease medication for hypertension, diabetes, and heart disease for high-risk adults [73]. The original CHIP study enrolled 304 adults over age of 40 years all of whom were designated "at risk" for developing coronary artery and related diseases based on body weight, diagnosis of diabetes or hypertension, and/or a history of coronary artery disease [73]. Participants were encouraged to exercise for 30 min daily and to adhere to "The Optimal Diet," a plant-centered, high-fiber, low-fat, low-sugar, low-salt diet. The Kalamazoo feasibility study yielded statistically significant ($p < 0.001$) improvements between baseline and 4-week follow-up in blood pressure, weight, BMI, and decreases in triglyceride levels [73].

CHIP was subsequently implemented in five Rockford, IL communities through the Center for Complementary Medicine of Swedish American Health System in Rockford, IL. The "Consolidation Phase" of this 7-year project, for which results are available, enrolled 1517 self-selected adults from the general population through presentations at service clubs, churches, and corporations and through exposure to billboards, brochures, and health care providers [108]. Pooled results from the five Rockford community programs showed a significant ($p < 0.001$) reduction in the mean number of coronary risk factors for men and women from 3.4 to 2.3 [108]. Individuals with the greatest number of coronary risk factors (≥3 risk factors) showed clinically significant improvements in total cholesterol, LDL, weight, systolic and diastolic blood pressure, and glucose levels [108]. In addition to these individual outcomes, researchers reported community-level changes due to consumer demand for healthier foods, resulting in changes in nutritional offerings in several major grocery stores, 25 restaurants, and a fast food chain [108]. Englert et al. acknowledge the need for RCTs to evaluate CHIP; however, the program shows potential in creating a "critical mass" to effect change at the community level of the social ecological framework [108].

CHIP has also been adapted for use in six workplaces in Rockford, IL [109]. The modified 32 h program consisted of 15 educational models, delivered over 8 weeks via twice-a-week videos and facilitated group discussions. After the 8-week intervention, employees in all participating worksites demonstrated significant improvement in weight, BMI (−1.3 and −1.6 for overweight and obese

participants, respectively), total cholesterol (–28.8 and –47.3 mg/dL for participants with borderline and high total cholesterol, respectively), and LDL cholesterol (–35.4 and –61.7 mg/dL for participants with high and very high LDL, respectively) [109]. The CHIP video-based intervention has subsequently been implemented in community- and faith-based organizations in addition to workplace and outpatient clinical settings [110]. These video-based interventions focus on the intrapersonal level, interpersonal level (through social support and encouragement of family participation), and organizational level (when implemented at worksites, community- and faith-based organizations) of the social ecological framework.

Romsås in Motion Study (2000–2003)

The MoRo study was a quasi-experimental test of the effectiveness of a 3-year community-based intervention to reduce risk factors for diabetes and CVD among adults in a multiethnic, low-income district of Oslo, Norway, with a large non-Western immigrant population. The intervention was designed using a CBPR approach that established a local resource group consisting of lay members of the community and solicited input from local politicians, lay leaders, and health and welfare workers to assist in planning and implementation [22]. The program design drew upon aspects of expectancy-value theories, Social Cognitive Theory (SCT), and the stages of change model to specifically target physically inactive individuals with low psychosocial readiness for change [22]. Intervention components included strategies to increase awareness, improve knowledge, and change attitudes about physical activity using brochures, individual counseling, group fitness activities involving participants' friends and family members, and a mass media campaign [22]. BMI, cholesterol, blood pressure, blood glucose, and self-reported physical activity and smoking status were measured at baseline and at the end of the 3-year intervention period. Significant differences between individuals from the intervention district and individuals from a matched comparison district of Oslo were found in smoking status (net proportion of quitting was 2.1% in favor of the intervention community; $p = 0.043$), higher self-reported physical activity (9.5% net increase in favor of the intervention; $p = 0.008$), resting heart rate for men (–1.70 beats/min; 95% CI = –3.31,–0.10; $p = 0.038$), systolic blood pressure for men and women (–3.79 mm Hg; 95% CI = –5.74, –1.84; $p \leq 0.001$ and –3.52 mm Hg; 95% CI = –5.17, –1.86; $p < 0.001$, respectively), and body weight and BMI change for men (–1.24 kg; 95% CI = –1.88, –0.60; $p < 0.001$ and –0.42 kg/m^2; 95% CI = –0.63, –0.21, respectively) [22]. Body mass increased in both districts, but 50% less so in the intervention district as compared to the control. The net proportion that increased body mass was significantly lower overall 14.2% ($p < 0.001$) and even lower among non-Western immigrants in the intervention with a 27.5% lower proportion of increased body mass as compared to the comparison district [111]. MoRo was able to successfully leverage community- and intrapersonal-level influences to encourage behavior change among physically inactive individuals.

CONCLUSIONS AND RECOMMENDED FUTURE DIRECTIONS

While impressive progress has been made in reducing CVD mortality by nearly 4% over the past 15 years, significant and alarming disparities in CVD risk behaviors, incidence, and mortality persist, particularly among low-income and ethnic minorities. Moreover, because of the aging baby boomer generation and longer life span, the population over 65 years will double over the next 15 years [112], dramatically increasing chronic disease burden and rates. Therefore, identifying effective interventions that will reach large numbers of individuals who suffer disparities (e.g., race-, age-, and income-based) in CVD disease risk and incidence/mortality are increasingly important. Moreover, multilevel interventions that are adoptable by large numbers of organizations and communities, plus "upstream" intervention approaches that embrace social, political, and economic intervention strategies, are needed. Like the successes we have experienced in tobacco, the new twenty-first-century public health challenges that will need to be surmounted in a resource diminished environment demand that they are effective, adaptable, and sustainable over time. Applying evaluation constructs like RE-AIM to these multilevel intervention strategies will allow us to prioritize among and between different strategies that can help maximize the use of resources at any given time point to address disparities in CVD incidence and mortality.

The results of our selected review of community-based approaches to address CVD provided a number of important insights. First, 100% of these programs used multilevel interventions and 10 of 14 targeted multiple risk factors. The community-based projects we identified were effective in decreasing targeted CVD risk factors using a myriad of intervention strategies such as education materials, mass media campaigns, environmental and policy changes, and improving access to health care services via CHW. Programs were successful in modifying most of the targeted risk factors for CVD, including physical activity, decreasing weight, increasing healthy eating, and decreasing blood pressure, smoking rates, cholesterol, and blood glucose. In particular, we singled out three community intervention strategies for special consideration. Of these, the DPP is a unique and important success story because this clinically based intervention has been adapted now for a wide range of community settings and diverse populations. The intervention has been modified for easier implementation while maintaining its effectiveness—a crucially important outcome. The story associated with the DPP and the ongoing evolution of this program will be important to chart so that all key lessons can be learned from this effort.

This review also demonstrated that many programs focused on target communities who suffer a disproportionate

CVD burden including low-income communities [88,91,94], rural communities [21,92,95], older populations [98], and minority groups [87–91,96,99]. However, very few reported use of theory to guide the interventions and many did not adopt community-based participatory research principles that might have enhanced program recruitment, acceptance, outcomes, and long-term sustainability. We remain advocates for CBPR approaches when addressing populations who suffer disparities in health.

Despite the effectiveness of these community-based approaches, several important challenges were identified. One of the challenges of community-based approaches efforts is matching the agenda of researchers and health professionals with the needs and expectations of community who suffer disparities in health [78]. Adopting a co-learning process that embraces and values both community and academic methods is an inherently valuable aspect of community-based participatory research principles [78]. Researchers may be challenged to reconcile the strict application of community-based approaches with funding constraints; however, such challenges can be met when researchers, health professionals, and community partners are respectful about community collaborations and the development or implementation of evidence-based programs with community partners. Academic and community partnerships take time to develop and may operate differently depending upon project-specific and community contexts; however, many have found a balance for optimizing resources with community needs and expectations [75,77,78].

Another challenge is that community-based intervention studies often have limited power to detect statistically significant changes [113]. New analytic strategies provide some opportunity for overcoming this challenge; however, this concern remains. Measurement efforts that are reliable and valid, as well as allow us to detect small improvements in CVD risk factors, have proven that they can have long-term clinical effects. For example, a 1% drop in blood cholesterol levels led to a 2%–3% drop in CVD mortality [113]. On a population basis, these small effects can produce large changes in CVD incidence and mortality [113]. New study designs that move beyond the limits of RCTs are gaining favor [114]. Optimizing designs [115,116] and interrupted time series [117] maximize power, preserve the opportunity to study "natural experiments" involving policy changes, and give researchers new opportunities to study the influence of multilevel interventions. Pennant et al. observe that preventing contamination between intervention and comparison groups in multilevel, community-based interventions is challenging [113]. Community-wide interventions and mass media campaigns will reach all members of a community. Using matched community comparison designs, like the one adopted for the MoRo evaluations, is one way to address this issue, which also ameliorates the threat of differential attrition. Cheadle et al. note that rigorous evaluations, especially those that measure health outcomes of individual health behavior, are costly and can even exceed implementation costs of community-based studies [118]. For this reason, they advocate for the use of community-level indicators (CLIs) to monitor and demonstrate changes over time in important intervention outcomes, such as changes in store inventories to support healthy eating [118]. Such indicators offer an opportunity to measure change in multiple levels of the social ecological framework to supplement findings at the individual level. Cost analyses, cost-effectiveness, and return on investment analyses are growing in importance and popularity.

We also believe that the mechanisms of behavior change, and certain key influences on behavior, have not been adequately addressed in community-based interventions to date. For example, very few of the projects we reviewed account for psychosocial factors like mood (e.g., depression and anxiety) and stress. It is possible that psychosocial factors are a barrier that may play more of a role in behavior change in some populations (e.g., those with high stress or depression rates) than currently hypothesized. Few community-based interventions have been developed to address stress or other mental health issues in healthy communities. There is much room for new thinking and new intervention approaches to address this important area of influence on CVD.

Very few studies clarified the frameworks or theories used to guide interventions they were testing. The field will advance when we can learn from each other and build on intervention successes and failures. To do this well, we need to understand the basis upon which interventions are developed and tested. To improve upon and maximize the benefits of community-based approaches, the development of new theories, research questions, designs, and methods is essential to ensure that this field of research continues to expand. For example, there are potentially unlimited possibilities in emerging technology. The use of social media and other tools (e.g., texting) to recruit, unite, remind, or educate is an intriguing and growing trend.

Nontraditional community settings are another way to advance community-based approaches and improve reach. For example, barbershops and beauty salons are located in all communities and are unique, historical places which may be particularly well suited for reaching African Americans [119]. One of the community-based interventions we reviewed [120] was effective in increasing blood pressure screening among African American men who visit barbershops. Other barbershop interventions have improved hypertension [96,121–123], smoking rates [124], diabetes [122,123], and stroke awareness [125].

SUMMARY

To deal with the complexity and burden associated with CVD, health professionals must be creative and strategic with community-based approaches to decrease CVD risk factors, incidence, and mortality. Many CVD risk factors overlap with risk factors associated with other chronic diseases, such as cancer, diabetes, and arthritis. Thus, what is learned with interventions applied to these chronic diseases can and should be considered in the development of CVD-related interventions. Evidence-based interventions that engage the

community and address multiple levels of the social ecological framework have universal appeal. Evaluating the impact of community-based interventions can be facilitated via rigorous research designs with measures taken from the RE-AIM framework. Strategies to maximize reach, adoption, and effectiveness, while attempting to ensure representativeness and sustainability, mindful of costs, are critically important. Full engagement of community members and community organizations in these efforts leverages the strengths of a community and fosters the type of mutual respect and trust that can lead to long-term, sustainable changes that have the potential for reducing or eliminating disparities in health.

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Part II

Nutritional Aspects of Lifestyle Medicine

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8 Nutrition 101

The Concept of Nutritional Status and Guides for Nutrient Intakes, Eating Patterns, and Nutrition

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CONTENTS

Introduction 103
Concept of Nutritional Status and Its Measurement 103
Dietary Status 105
Biomarkers 106
Dietary Reference Intakes 107
- Overview of the DRI 107
- Criteria on Which Nutrient Recommendations Are Based 107
- RDA 107
- EAR 108
- AI 108
- UL 108

AMDR 109
- Current Status of the DRI 109
- Individuals versus Populations 109
- Uses outside the United States: Are the DRI Exportable? 110
- Revising the DRI 110
- Next Steps for the DRI 110

Uses of the DRI 110
Dietary Guidelines for Americans 111
USDA's Food Guide Pyramid, MyPyramid, and ChooseMyPlate 111
Healthy Eating Index 112
Nutrient Labeling 113
Healthy People 113
Conclusions 115
Acknowledgments 115
References 115

INTRODUCTION

This chapter provides an overview of the tools that are available for evaluating dietary intakes of individuals. It describes the concepts of dietary status, nutritional status, and some simple tools for measuring them. The dietary reference intakes (DRI), which are the standards for nutrient intakes that are used in the United States and Canada, are described and their uses are discussed. The latest Dietary Guidelines for Americans, recommendations to help guide Americans in altering their current intakes in more healthful directions, are summarized. MyPlate (formerly MyPyramid and the Food Guide Pyramid), a guide that provides food-based recommendations based on the Dietary Guidelines for Americans and the DRI, is described. The Healthy Eating Index (HEI), a simple means of evaluating the balance, variety, and adequacy of intakes based on these standards, is also discussed. Finally, Healthy People 2020, a set of national goals for promoting health and preventing disease that involve nutrition, is briefly mentioned.

CONCEPT OF NUTRITIONAL STATUS AND ITS MEASUREMENT

Nutritional status is a component of health status that represents the bodily state resulting from the intake, absorption, utilization, and metabolism of food. It also reflects growth, development, and infectious, traumatic, or other factors that affect health.

TABLE 8.1
Forms of Malnutrition and Clinical Terms Used to Describe Them

Form and Cause of Malnutrition	Clinical Terms to Describe It	Comments
Dehydration: Inadequate fluid intake to meet bodily needs	Dehydration	Often occurs secondary to fever, exertion, very warm dry climate, or because of diets with high solute loads or drugs that have diuretic effects.
Starvation: Virtually totally inadequate intakes of all nutrients	Marasmus, emaciation, cachexia	Occurs with prolonged fasting; withholding of fluids worsens its effects.
Protein–calorie malnutrition	Kwashiorkor, protein–calorie malnutrition	Often occurs secondary to disease and infection, probably via cytokine-mediated responses to acute infection or trauma, e.g., HIV/AIDS. Sarcopenia due to inadequate intake of protein and/or cytokine-mediated responses to insult.
Vitamin, mineral, or other specific nutrient deficiencies	Pellagra (niacin/tryptophan), scurvy (ascorbic acid deficiency), rickets and osteomalacia (vitamin D deficiency in children and adults, respectively), iron deficiency anemia (iron deficiency), nutritional anemia (iron, vitamin B6, folic acid or vitamin B12 deficiency), essential fatty acid deficiency	Often occur secondarily to inadequate food intake or inadequate dietary quality. May also occur as conditioned deficiencies secondary to disease.
Increased diet-related chronic disease risk factors due to imbalances of nutrients	Excess of saturated fat, cholesterol, and other atherogenic and thrombogenic dietary lipids (hyperlipidemias and perhaps altered clotting factors), excess of salt and/or sodium (blood pressure risk factors)	Imbalance or excess of energy-yielding nutrients or related substances may give rise to metabolic aberrations and increase risk of ill health, especially in those with certain genetic patterns.
Obesity: Excess food energy intake and/or insufficient energy output	Excess food energy regardless of source gives rise to obesity and overweight	Physical inactivity may increase likelihood of excess energy intakes.
Alcohol excess	Alcoholism, problem drinking	At very high levels of alcohol intake, all persons develop physical signs of chronic disease; at lower levels of intake some individuals are particularly susceptible.
Excess of other specific nutritionist (vitamins, minerals, others)	Specific toxicities vary: hypervitaminosis A (vitamin A), hypervitaminosis D (vitamin D), fluorosis (fluoride), etc.	Intakes that exceed the upper level of the Dietary Reference Intakes generally increase risk of compromising one or more functions. The possible functions vary from nutrient to nutrient.
Toxicity: Excess of other constituents in food, drink, or supplements	Names vary depending on substance; lead poisoning, lathyrism, etc.	Many substances other than nutrients in food and supplements may cause illness.
Foodborne disease	Food poisoning or food intoxication: salmonellosis, botulism, staphylococcal food poisoning, others. Parasites such as beef tapeworm may cause problems. Prions or viruses as in bovine spongiform encephalopathy	Food is the carrier for a microorganism, virus, or parasite.

Table 8.1 summarizes the reasons why several measures of malnutrition are necessary to assess nutritional status. Because each method has its limitations, several different measures that tap many characteristics and different levels of effects are usually employed. Nutritional status assessment usually includes anthropometric, biochemical, clinical, and dietary measures as well as food-related quality of life. It also considers the individual's eating habits and metabolically relevant health characteristics.

Table 8.2 shows the various forms of malnutrition, which include deficiencies, excesses, and imbalances of nutrients. Nutritional assessment describes the specific form of malnutrition present, the stage in the development of malnutrition, and the severity of the problem.

The clinical signs of malnutrition, their effects on weight, on functions such as the activities of daily living and quality of life, are the end result of a pathological process of malnutrition that starts much earlier. This preclinical phase of malnutrition can often be identified by the use of dietary measures, biochemical, hematological, or other biomarkers in blood, urine, or other bodily secretions, as well as individual cells, tissues, and organ systems. If diet is the cause of the malnutrition, food intake alterations are usually apparent for days, weeks, or months before metabolism is altered and changes in biochemical measurements are present. Therefore, if the goal is to prevent malnutrition and to do it as early as possible, dietary assessment is worthwhile.

TABLE 8.2
Why Multiple Indicators of Nutritional Status Are Needed to Diagnose Malnutrition

Multiple forms of malnutrition exist.
See Table 8.1 for some examples

The causes of malnutrition vary.
Some are due to deficient quality or quantity of diet alone (primary malnutrition) but most are secondary to disease, social or psychological problems, and may occur even in the face of adequate and appropriate food in the environment. Many different pieces of information are necessary to arrive at an understanding of how these causes interact.

No single indicator for all the forms of malnutrition exists.
The most sensitive, least costly and most specific indicators of malnutrition vary from nutrient to nutrient.
Even for a specific form of malnutrition, indicators vary with respect to how sensitive, specific, valid, and reliable they are.

Severity of malnutrition varies.
Milder forms require different and more sensitive indicators (e.g., measures of tissue or blood stores) than the more severe (which may be evident with anthropometric or clinical measures alone).

DIETARY STATUS

This chapter focuses on only one aspect of nutritional status: dietary status. It involves the assessment of an individual's consumption of foods, food groups, or food patterns. Dietary status and nutritional status are not always similar, because food consumption is not the only factor involved in determining if dietary intakes are sufficient to maintain health.

The rationale for measuring dietary intake and status is that intake is a factor affecting nutritional status that can be altered. The most important aspects of dietary intake are the amount of food, the forms in which the nutrients are present in the diet (e.g., food, beverages, supplements, or nutrient containing medications, because they may affect absorption), and the presence of other bioactives in food that may have beneficial or harmful effects.

The usual goal of assessing diet is to obtain an estimate of habitual or usual intake, either by measuring diet directly by observation or indirectly by report. Because most health effects depend on usual or habitual intake, it is important that the report includes a sufficiently long period of time (e.g., many days or weeks) to be representative of usual intake. Only representative intakes over relatively long periods are meaningful for assessing the effects of diet on nutritional status or the associations between diet, health, and disease. The one exception is the type of very recent intake information that is usually collected when incidents of foodborne illness are being traced. Then, foods eaten in the hours or days before the poisoning accident, details on food preparation, and other factors that may have caused the contamination are also investigated.

The many methods for assessing dietary intake are reviewed in detail elsewhere [1]. Although the methods all have their limitations, they do provide a picture of food and nutrient consumption that may be useful for purposes of planning intakes or assessing what has been eaten.

The major shortcoming of most dietary assessment methods is that while they furnish a general profile of nutrient intakes, they are less accurate in providing information on the absolute amounts of nutrients or bioactives that are consumed. Most dietary assessment methods depend heavily on the eater's report of what was eaten, because it is very difficult for an outsider to collect duplicates or observe everything a person eats. But eaters' reports may be inaccurate and biased. People may forget what they ate, have difficulty judging the amounts they have eaten, report inaccurately because they want to appear to conform to what the questioner wants to hear, or they may unconsciously change what they eat when they are asked to record it. Therefore, information on dietary intakes is never perfectly accurate. These errors are usually quite large, perhaps 20% or more, and even higher among certain groups such as the very obese, or those with impaired memories, such as children, the very old, or individuals with mental health problems. A common error is failure to mention dietary supplements, which, in countries such as the United States, often contribute substantially to dietary intakes [2]. Forgetting what has been eaten is a particular problem when people are asked to remember what they have consumed over long periods, such as during the past year, especially if they are to provide estimates of the frequency and amounts they have eaten. Such estimates probably reflect more recent intake (e.g., a few weeks), and they are probably most accurate when individuals have fairly fixed intake patterns. When people are given lists of foods and asked to record their frequency of eating these foods, they often overestimate how much they ate, and results are usually adjusted to provide estimates that are more in line with plausible energy intakes. Also when people are asked to keep food records or diaries, often they unconsciously change what they eat to make the recording task simpler, or because they are surprised at how much they eat and decide to eat less to make their intakes appear more "balanced."

Dietary intake assessment is used as a proxy for nutritional status because it is less expensive and easier to obtain than a full-fledged nutritional status assessment, and can often provide enough useful information to remedy problems. For example, it can identify those who are very undernourished because they are eating too little, too much, or imbalanced amounts of foods and nutrients. Dietary assessment also helps to clarify and strengthen assumptions about the presumed causes of changes in nutritional status when it is synchronized with information derived from anthropometric, biochemical, clinical, and other measures. Questioning can also reveal many environmental factors that influence dietary intakes and nutritional status that may need to be changed, such as climate, living conditions, exposure to pathogens, and socioeconomic conditions.

However, dietary status assessment only measures what an individual eats, and not what is actually metabolized;

so, it may miss other causes of poor nutritional status, such as malabsorption. Although dietary assessment theoretically is an extremely sensitive indicator of malnutrition, since it reflects a very early stage in the development of the pathology, in practice it is often not useful by itself. Dietary data are less precise and reliable than biochemical and anthropometric indices. Because they are usually obtained by report from the patient or respondent, they are usually more subject dependent and vary more in validity and reliability from one person to the next. They often fail to reflect usual intakes and instead reflect only the prior few days. Intakes of nutrients from dietary supplements and oral nutritional supplements may be disregarded, causing more underestimation errors. Thus, it is difficult to determine whether suspected deficits in dietary intake are actually due to diet or to errors in reporting. Therefore, in order to fully assess nutritional status, dietary information must be combined with the other types of data.

BIOMARKERS

Because there are many problems involved in obtaining accurate information on food intakes, if precise estimates of intakes are necessary, as is the case in research studies, surrogate markers of intake such as biomarkers are often used. Biomarkers are reliable and accurate biochemical or other measurements that can be objectively measured and evaluated. They can be indicators of intake, normal biological processes, and nutritional status, pathological processes, pharmacological responses to an intervention, or health outcomes.

In order to be useful, biomarkers must be analytically valid, useful, clearly show associations between the biomarker and disease, and reflect interventions with changes in both the biomarkers and clinical outcomes.

The most common sources of biomarkers are indices in blood, urine, and other body fluids such as saliva. There are also functional biomarkers that measure processes such as immune function or cognitive function, and more nonspecific biomarkers, such as grip strength.

Some biomarkers reflect intake, others nutritional status, risk, or health outcomes. The biochemical biomarkers in blood or urine that reflect nutrient intakes or nutritional status are used most commonly. Some intake biomarkers are listed in Table 8.3. However, biomarkers also have their limitations. They reflect different things; some reflect dietary intake, others nutritional status, and still others risk or outcome of disease.

Among the biomarkers reflecting *intake* are ascorbic acid and serum folic acid; they are specific but often only reflect intake over a short time (e.g., hours or days) rather than a longer time. Most of the biochemical or other biomarkers of intake are very specific and only reflect intakes of a single nutrient rather than the overall diet. For some nutrients, there are no acceptable biomarkers that reflect long-term intake, and other biomarkers are available but very expensive and

TABLE 8.3
Some Biochemical Biomarkers of Intake (Exposure) and/or Nutritional Status

Nutrient	Biomarker	Comments
Iron	Hemoglobin	Low specificity (many different causes of anemia decrease hemoglobin, not just iron). Cutoffs vary by age, sex, and ethnicity. This is a good indicator for monitoring improvement in iron status if individual is iron deficient.
	Serum plasma ferritin	This is an acute phase protein, but it is nonspecific; it increases independently due to acute or chronic inflammation, infection, malignancy, hyperthyroidism, liver disease, heavy alcohol use.
	Serum transferrin receptor	A specific indicator of iron-deficient erythropoiesis that is not affected by inflammation.
	TIBC	Nonspecific and varies over the day.
	ZnPP erythrocyte zinc protoporphyrin	A sensitive indicator for diagnosis of the deficiency. However, the specificity is limited since it is affected by lead poisoning, the anemia of chronic disease, chronic infection and inflammation, hemoglobinopathy, and hemolytic anemias.
Zinc	Serum plasma zinc	Responds to zinc supplementation, but easily affected by contamination, and is also affected by inflammation, fasting, estrogen use, hemolysis, and chronic illness.
B12	Serum/plasma total zinc	Measures total biologically active B12. Poor correlation with dietary zinc. Also cutoffs are uncertain and kits for the test vary.
	Serum/plasma methylmalonic acid	Cutoffs are uncertain. Test is sensitive.
	Serum/plasma holotranscobalamin HoloTC	
Folate	Serum/plasma folate	Varies with recent intake, and kits to test vary.
	Erythrocyte folate	Kits vary. Samples are difficult to prepare and cannot be stored.
	Serum/plasma total homocysteine	Depends on B2 status, B12 status, B6 status, and MTHR polymorphism state.
Vitamin A	Serum retinol	Sensitive to intake, but only if stores are low. Also not very sensitive because it is under homeostatic control.

difficult to use except in research studies. Therefore, biochemical and other measures of dietary intake also have their limitations in clinical practice.

Other biomarkers reflect *nutritional status*. One is serum 25OH vitamin D, which reflects both dietary intake and exposure to the sunlight's ultraviolet rays that activate the provitamin D in the skin. Some of the nutritional status biomarkers are too nonspecific to be useful. For example, serum albumin is a marker of dietary intake, but it reflects not only protein nutritional status but also inflammation and infection. Other status markers, such as serum thiamine, are specific, but they only reflect status over a short time (e.g., hours or days) rather than habitual intakes. Other status markers, such as red blood cell folate, reflect intake over a somewhat longer period of time (e.g., several weeks).

A third type of biomarkers reflects *outcomes*, such as coronary artery disease or stroke. Often, instead of outcomes themselves that take so long to develop, surrogate endpoints are used such as serum cholesterol or blood pressure. These so-called surrogate endpoints are substitutes for a clinical endpoint that predicts a clinical benefit or a harm based on good evidence. For example, high levels of low-density lipoprotein cholesterol (LDL-C) reflect risk of coronary heart disease, and hypertension is associated with risk of stroke. Biochemical indices such as LDL-C and high blood pressure are therefore considered good *biomarkers of risk or outcome*.

DIETARY REFERENCE INTAKES

The DRI are quantitative standards for nutrient reference intakes used for planning and assessing the diets of healthy people. Prior to the development of the DRI, the 1989 Recommended Dietary Allowances (RDA) served as the standards for nutrient intakes. The DRIs were developed conjointly by Health Canada and the Food and Nutrition Board, U.S. National Academy of Sciences in the 1990s. They are used as the basis for other materials, such as the Dietary Guidelines for Americans, that provide food-based dietary guidance [3,4].

Overview of the DRI

The DRI consist of multiple reference points that serve as dietary standards for various uses instead of the single reference values used in the past [5–12]. They were developed because of the availability of new data on many nutrients and potential candidate nutrients. Also, new concepts on assessing dietary deficiency and excess were available by the 1990s. It was also felt that if possible, dietary recommendations should be based on standards that would prevent obesity and reduce risks for chronic disease and excess. Finally, new-user needs, such as nutrient labeling, made a revision of existing recommendations imperative.

The DRIs include the estimated average requirement (EAR), the RDA, or, if the RDA cannot be calculated, an adequate intake (AI). An upper reference level (UL) is also set. And, acceptable macronutrient distribution ranges and energy needs are also provided [13]. The EAR, RDA, and AI are defined with specific criteria of nutrient adequacy. The UL, in contrast, is defined using specific indicators of excess. The reference weights and heights for the adults and children for whom the dietary recommendations are designed are based on recent population-based surveys of the United States.

Criteria on Which Nutrient Recommendations Are Based

The criteria for adequacy upon which nutrient needs are formulated are critical, and these vary from nutrient to nutrient. Each EAR, RDA, and AI is described in terms of a selected criterion or criteria of adequacy. These criteria include the best level to determine the risk of an individual's nutrient stores becoming deficient. For example, the criterion for folic acid among women in the childbearing years is based on a combination of biochemical indicators, primarily red blood cell folate, and secondarily plasma homocysteine and serum folate levels. Other criteria relate to reducing the risk of disease if they are available, although often they are not. For example, a separate recommendation for folic acid is made for women capable of becoming pregnant based on a criterion related to reducing the level of neural tube defects. Prevention of chronic degenerative disease is a focus of some other nutrient adequacy criteria. For example, the calcium criterion was selected to be a level of intake sufficient to provide retention of calcium during growth and minimizing bone loss during adulthood. In the case of fluoride, the amount of fluoride needed to decrease rates of dental caries was chosen. However, the evidence base for a level of other nutrients including phosphorus, magnesium, vitamin D, the B vitamins, and choline is insufficient to define a function such as preventing chronic disease, and must rely on other criteria, such as mineral balance.

RDA

The RDA is the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (e.g., 97%–98%) of healthy persons of a specific gender at a particular stage of life or physiological condition, such as pregnancy or lactation. The only use of the RDA is to serve as a goal for individuals, not for populations. These are available on the World Wide Web at http://www.iom.edu/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx

To establish an RDA, agreement on the criterion to be used is the first issue that must be solved. This criterion is used to assess adequacy. An appropriate cutoff must then be established for each criterion that is used to determine the

difference between what is considered an adequate and an inadequate level of nutritional status. In order to set this cutoff, there must be sufficient data on individuals who are consuming levels of intake at which some reach the suggested cutoff for the criterion and at which others do not. This permits the establishment of a dose–response relationship. It is also necessary to have an understanding of the distribution of requirements among individuals in the group from which the requirement is estimated. When nutrient requirements are skewed for a population, other approaches are used to find the 97th to 98th centile to set the RDA.

Recommendations are also available for water and electrolytes.

The RDA is the values that should be used for planning individual intakes. The RDA is not appropriate for assessing the diets of either individuals or groups, or for planning diets for groups. An interactive tool for calculating the appropriate RDA/AIs and energy needs from an individual's age, sex, physiological condition, weight, height, and physical activity level is available at the following website: http://fnic.nal.usda.gov/interactiveDRI/dri_results.php, and it can also be accessed at http://www.iom.edu/Activity/Nutrition/SummaryDRIs/DRI-Tables.aspx

EAR

The EAR is the amount of a nutrient that is estimated to meet the requirement of half of the healthy individuals in a specific life stage and gender group. The EAR is used to assess adequacy of intakes of population groups, and along with knowledge of the distribution of requirements, to develop RDA. The requirement is the lowest level of a nutrient eaten chronically that will maintain a defined level of nutriture in a person. Before setting an EAR, a specific criterion of adequacy must be chosen. This selection is based on a careful review of the literature. Among the criteria that may be used, reduction of disease risk may be considered, along with other health parameters. It is assumed that the distribution of requirements is normal. Ideally, the standard deviation (SD) of the requirement, that is, an estimate of its variability of requirement, is also available. If the SD is not available, then a coefficient of variation (CV) is used, usually of 10%. Under these circumstances, the RDA is assumed to be 1.2 × EAR. Conversely, if the CV is 15%, the RDA is 1.3 × EAR.

Recommendations for energy intake differ from those for vitamins, minerals, and protein because individuals of the same age, sex, reference weight, and physiological condition often differ markedly in their energy needs, and such factors as actual weight, height, and physical activity level are also needed to calculate it. Moreover, the standard to achieve is the EAR to maintain weight and health, not an RDA. Two SD above the EAR as a recommendation would cause individuals to consume excess food energy, which would be stored as body fat, with adverse effects upon health.

AI

The AI is a recommended daily intake level based on observed or experimentally determined estimates of nutrient intake in a group of healthy people. The main use of the AI is as a goal for the nutrient intake of individuals. It is used when an RDA cannot be determined. The AI is usually based on observed levels of intake that appear to maintain an acceptable level of health or growth. The presence of an AI is an indication that experts believe that sufficient data on requirements are not yet present for the functional criterion that has been chosen, and that more research needs to be done. The AI is set at a level that is expected to cover the needs of at least 98% of people, but it might cover far fewer, or far more, since the EAR cannot be estimated. Unfortunately, the degrees to which AIs exceed average requirements differ among nutrients and population groups. Therefore, it is meaningless to describe the proportion of the population below the AI; it is more useful to report the proportion of the population *above* the AI.

In the DRI reports, AIs rather than RDA are provided for all nutrients in infants up to a year of age, and fluoride, pantothenic acid, biotin, and choline for persons of all ages (see http://www.iom.edu/Activity/Nutrition/SummaryDRIs/DRI-Tables.aspx). Both the RDA and AI are appropriately used for setting goals for intakes of individuals. However, greater uncertainty surrounds the AI.

UL

Nutrients are essential for basic functions of human life and well-being. However, at excessive levels of intake they have possible adverse effects. Adverse effects include any significant alterations in the structure or function or any impairment of a physiologically important function in an individual. Also, since intakes of one nutrient may alter the health benefits conferred by another, detrimental nutrient–nutrient interactions are also considered to be adverse health effects. These values are also available at the Institute of Medicine website (http://www.iom.edu/Activity/Nutrition/SummaryDRIs/DRI-Tables.aspx).

It is important to remember that at the levels of nutrient intakes from diets of foods, human experience is considerable. It is only in the past few decades that single concentrated sources of nutrients have become available in the form of dietary supplements and highly fortified foods; so now, the possibility of higher intakes is more likely. At present, there is no evidence to suggest that nutrients consumed at current RDA and AI levels in enriched or fortified foods pose a risk of adverse effects to most persons [14]. However, with very high amounts of fortified foods, dietary supplements, and over-the-counter medications that contain nutrients all consumed together, total intakes may reach or exceed the safe levels.

The tolerable (or safe) upper intake level (UL) is the highest level of chronic and usual daily nutrient intake that is likely to

pose no risks of adverse health effects to almost all individuals in the general population. The more the intake is above the UL, the greater the risk of adverse effects. The intakes included in the UL for most nutrients are food, water, and nonfood sources such as nutrient supplements and pharmacological preparations. The word "tolerable" is used because most individuals should be able to tolerate this level of intake. However, it does not imply that this high a level of intake is desirable. The UL is *not* an intended level of a nutrient to be consumed. Moreover, the UL is not a level at which there is a beneficial effect. Rather, it describes the intake level at which there is a high probability that the dose of the nutrient can be tolerated biologically. When total intakes have been associated with toxicity, this fact is stated. In a few cases, it may be that toxicities are only associated with nutrients used in supplements or as drugs. For example, excessive β-carotene appears to be associated with adverse outcomes but only in supplements; and therefore, the UL for β-carotene is based only on supplements. Many individuals use large amounts of nutrients containing dietary supplements for preventive or curative purposes. Excessive intakes are a particular concern for nutrients that are not easily metabolized or disposed of by the body, such as fat-soluble vitamins.

Risk assessments describe the relationships between exposure to a nutrient and the likelihood that adverse health effects will occur in the exposed population. Risk assessment systematically evaluates the probability of adverse health events occurring in humans from excess exposure to an environmental agent such as a nutrient or food component.

Risk–risk assessments involve both the risks of taking too much of the nutrient versus the risk of not taking enough of the nutrient or supplement [15]. Such assessments are becoming increasingly common. A constant set of scientific principles involving risk assessment is used to set the UL. The process involves identifying hazards, assessing dose–responses, intake assessment, characterization, and evaluation of risk. All evaluations and judgments are explicit and evidence is provided to document the conclusions that are reached. Both qualitative and quantitative types of evidence are considered. ULs are set by first reviewing the literature to determine levels at which no observed adverse effects (NOAEL) are noted, or at the lowest level of intake associated with observed adverse effects. Then an uncertainty factor is applied to reduce the intake level from the lowest adverse effect level to insure that even the most sensitive persons would not be affected by the UL dose chosen. At present, for many nutrients there is simply not enough evidence to develop a UL. The risk is expressed as the fraction of the exposed population, if any, that has nutrient intakes in excess of the estimated ULs [6].

ULs are not always certain, fixed, and unvarying values. For many nutrients, ULs are not available because data are so sparse. Often, although intakes are available, there are no data on the adverse effects of taking large amounts of nutrients, or the data are only anecdotal in nature. In such cases, the UL cannot be established. This does not mean that there is no risk of adverse effects from high intake of the nutrient; in fact, when data about adverse effects are very limited, extra caution may be warranted. The data that exist are often scanty or drawn on studies to address other questions.

AMDR

The acceptable macronutrient distribution range (AMDR) for the energy-yielding nutrients provides a range of intakes that appear to be compatible with good health for them. The DRI and AI for water and macronutrients, and AMDR ranges for fat, carbohydrate, and protein, as well as recommended ranges for dietary cholesterol, trans fatty acids, saturated fatty acids, and added sugars are available at http://www.iom.edu/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx. Energy needs can also be calculated from tables given in the DRI report on macronutrients and energy.

Current Status of the DRI

The most recent report on DRIs was completed in 2010 on calcium and vitamin D because of the substantial amount of new information available on both nutrients [16]. Both were given new EARs and RDA on the basis of new data which were available, and the recommendations for each were raised slightly over the previous report issued in 1997 [5]. The values for other nutrients in the 1997 report (magnesium and phosphorus) were not revised and remain the same. The report on folic acid and other B vitamins was issued in 1998 [10]. The report on "antioxidant" nutrients (ascorbic acid, vitamin E, and possibly others) was issued shortly thereafter [20], and then the macronutrients and energy [17], and a volume on electrolytes and water [7]. Volumes on the uses of the DRI for assessment [18] and planning [19] were also developed by a panel on the uses of the DRI. A composite volume is available for practitioners [20]. DRIs for all nutrients, energy, and water are also available.

For individuals who are ill, the best recommendations for nutrient intakes depend on the disease itself and its effects on the absorption, metabolism, storage, and/or excretion of specific nutrients. In such cases, recommendations are best set by medical specialists for the diseases involved. Most nutrient needs are not usually affected, however, and the DRI for healthy individuals can be used for them.

Individuals versus Populations

The DRI Committee set recommendations that apply to intakes of nutrients of individuals, but not to total populations. Eventually, the thorny issue of population recommendations must be addressed, but at present population recommendations have not been set for the United States or Canada, but only for individuals. Population recommendations for nutrient intakes are much more environmentally influenced and culture bound than estimates of population requirements, and likely vary much more between countries. This is because average intakes of nutrients differ greatly

between populations of one country and another, as do nutrient intake distributions, which are very wide in some countries and very narrow in others. Recommended levels for population intakes must therefore take into account not only EARs but also these distributions of nutrient intakes within each population. Strategies such as fortification, supplementation, nutrition education, limitation of excessive intakes, and others that may be acceptable for bringing intakes into an optimal range in one country may not be so in another. Also, variations in resource and environmental constraints exist. The desired percent of the population having access to, or actually achieving, intakes that meet whatever criteria are chosen for the DRI also vary from one country to another. Economic realities, usual intakes, and historical precedents are best considered separately from biological requirements. Setting population recommendations for intakes involves scientific judgment, but also political will.

Uses Outside the United States: Are the DRI Exportable?

In the past decade, the DRI have been used in whole or in part by many other countries. While the DRI are an excellent set of standards, North America is not the world repository of all nutrition scientific wisdom and truth, and, as time goes on, they will no doubt be refined by experts in other countries as well as in the United States. It may be useful to consider which of the DRI are likely to be useful and which are not.

Many factors influencing DRI values are based primarily on biological rather than environmental influences, and these are largely the same from one country to another. Determinations of the EAR and UL, which are determined largely by human biology, should also be useful in other countries. The evidence-based reviews of the scientific literature on experimental studies of requirements for each nutrient focus on these biological factors. As new studies become available, other experts can review the evidence, add to it, and come to their own conclusions. Other factors are not as easily exportable from one country to another. For example, the functional criteria that could be used to set the U.S./Canadian requirements are many, and the most appropriate ones for another country may vary with the environment, expert judgment, and health realities. Other countries may have circumstances that make different functional criteria and endpoints more appropriate.

Exportability of the AMDR is also likely to be limited since they rely more on U.S. and Canadian intake levels and not on direct experiment. Food patterns, nutrient intakes, and environmental factors vary from country to country. In other countries, population profiles, resource constraints, and expert judgment may lead to the choice of different criteria for adequacy, with the result that AMDR, EAR, RDA, AI, and UL values chosen may differ from one country to the next.

Diversity in expert judgments often helps to drive science forward and seek firmer evidence. For other countries, the DRI recommendations, which are more evidence-based than ever before, deserve examination. The DRI may serve as useful compendia to review for efforts in other countries. Exportability/importability judgments of existing U.S./Canadian values must be considered on a case-by-case basis.

Revising the DRI

Science is constantly changing and growing; therefore, there is always a need for revision as new data become available. The DRI were conceived as the first attempt, and not as the last word, leaving room for them to change and diversify. Because all scientific conclusions are subject to revision as new evidence emerges, constant review is needed [9,10,21]. Similar efforts are now in progress in the European Union, led by the European Food Standard Agency (EFSA) and elsewhere. Expert groups in other countries and regions will no doubt have useful suggestions and improvements that the U.S./Canadian committees can learn from and incorporate into revisions. There is growing realization that systematic evidence-based reviews tailored to nutritional data are important in evaluating the evidence and that these MUST go hand in hand with expert judgment [22–26].

Next Steps for the DRI

Dietary reference standards must be revised periodically as new science become available. There is current interest in the nutrition community developing DRI for omega 3 fatty acids and several other bioactives, such as flavonoids, polyphenols, and isothiocyanates. Alcohol, while not an essential nutrient, also requires more detailed consideration than it has yet received, because it appears to have both beneficial and detrimental health effects.

Eventually, it is likely that many of the processes of evidence review and other technical aspects of data collections will be conducted in one country and then used as the basis of recommendations in other countries. The World Cancer Research Foundation has adopted a systematic process for ongoing evidence reviews for dietary recommendations on cancers that may also be adaptable to reviews of nutrient requirements [27]. To learn more about the Canadian/U.S. DRIs, the World Wide Web address is http://www2.nas.edu//fnb.

USES OF THE DRI

For assessing the adequacy of individual intakes, the best criterion is to compare intake to the EAR, although only a very rough estimate of adequacy can be made (for this reason other indices of nutritional status are also necessary). The RDA is a useful target for planning individual intakes. The most appropriate ways to evaluate the intakes of groups are to use the EARs when they are available. The proportion of individuals below the 50th centile (e.g., the EAR) is estimated. These are the individuals who are at greatest risk of dietary inadequacy. Note that the percent of the population below the RDA is *not* the population at risk of inadequacy; doing

so will overestimate the proportion truly at risk because of the very definition of the RDA. The AI is probably close to the group mean intake in some but not all instances. If the mean intake of a group is at or above the AI for a nutrient, there is unlikely to be a problem. However, it is not possible to assess risk of inadequacy quantitatively with AIs, although qualitative statements can be made. The AI is a good target for planning group intakes.

DIETARY GUIDELINES FOR AMERICANS

The Dietary Guidelines for Americans [4] are recommendations to help guide individuals to make healthy dietary choices. They are targeted to people over the age of 2 years; other recommendations are more appropriate for small infants and toddlers who are not yet consuming family fare. The guidelines emphasize healthy eating, which involves not only getting enough food but also balance, variety, and moderation in consumption patterns to decrease diet-related risks of chronic degenerative diseases.

The original Dietary Guidelines, first issued in 1980 and presented in Table 8.4, have stayed quite constant over the years [28]. However, the messages have evolved from proscriptive suggestions that centered on foods and dietary constituents to be minimized or avoided, to more prescriptive recommendations about positive dietary behaviors. Also, as scientific evidence supporting them has increased, the emphasis and content have changed somewhat based on new information [29].

Chapter 10 presents an excellent, detailed overview of the 2010 Dietary Guidelines. Updates and details on the Scientific Advisory Committee Report [30] are available at http://www.dietaryguidelines.gov. Current Dietary Guidelines for Americans recommend that to stay healthy, one should eat a variety of foods, maintain or improve one's weight by balancing food intake with physical activity, choose a diet that is plentiful in grain products, vegetables, and fruits, moderate in salt, sodium, and sugars, and low in fat, saturated fat, and cholesterol. For those who consume alcoholic beverages, they need to do so in moderation [4]. Note that the guidelines are qualitative for the most part, recommending patterns of foods and food groups, rather than very specific amounts of foods or nutrients. This qualitative emphasis reflects both scientific uncertainty about exactly how much of each nutrient should be eaten, and the Dietary Guidelines' educational purpose. Some of the guidelines are more quantitative. For example, the variety goal is defined more precisely in the text that accompanies the dietary guidelines. Also, specific goals are provided for dietary fatty acids, since the evidence base on intakes of these nutrients is now very well developed.

It goes without saying that providing guidelines is one thing, incorporating them into one's daily life is quite another and much more difficult task for experts as well as laypersons. Recommendations for putting Dietary Guidelines into action are available and downloadable in consumer-friendly format. They deserve careful reading by health professionals and consumers. Many other guidelines are also available, including many disease-specific guidelines, such as those issued by the American Heart Association, the American Cancer Society, and the American Association of Cancer Research [31]. In most respects, these other guidelines are similar to the Dietary Guidelines for Americans. There is no evidence that they promote better health or decreased risk of chronic disease than the Dietary Guidelines, although they may be helpful and reassuring to those who know they are at risk for particular health problems.

TABLE 8.4
Original Dietary Guidelines for Americans in 1980

Dietary Guidelines for Americans, 1980
Eat a variety of foods
Maintain desirable weight
Avoid too much fat, saturated fat, and cholesterol
Eat foods with adequate starch and fiber
Avoid too much sugar
Avoid too much sodium
Drink alcohol in moderation, if you drink
Calorie levels assuming choices are low fat, lean foods from the five major food groups, using foods from the fats, oils, and sweets group sparingly.
Women who are pregnant or breast-feeding, teenagers, and young adults age of 24 years need three servings.

USDA'S FOOD GUIDE PYRAMID, MYPYRAMID, AND CHOOSEMYPLATE

Over the years, there have been various efforts to develop graphics to accompany guides for healthy eating. Fifty years ago, the most popular guide was called the Four Food Groups. It focused only on intakes of foods that were necessary to assure AIs of protein, vitamins, and minerals and assumed that people would eat additional foods to meet their energy needs. Over time, the need for a graphic representation that included entire intakes including energy became evident. The U.S. Department of Agriculture introduced the Food Guide Pyramid in 1992 in response to these requests. Figure 8.1 presents this "first" pyramid. It provided a simple graphic tool that assisted people in choosing healthy dietary patterns that were varied, balanced, and moderate. The pyramid also suggested the number of recommended servings per day from each food group that people were likely need to eat to meet their nutrient needs from food alone. The reason for dividing foods into groups was that each of the food groups provided some, but not all, of the nutrients people need eat every day. The pyramid design emphasized the importance of consuming a menu that was based on plenty of breads, cereals, rice and pasta, vegetables and fruits, two

to three servings from the milk group, and two to three servings from the meat group, with an emphasis on minimizing foods high in fats, sugars, and alcohol, and avoiding excessive energy intakes.

The suggested serving sizes that were provided in the first pyramid were not necessarily those that people were accustomed to eating, and this led to confusion among consumers and health professionals. The amount people ate at a sitting would often be more than just one serving. For example, a usual dinner portion of spaghetti counted as two or three servings, and not a single serving of pasta. No serving sizes were given for fats, oils, and sweets, although it was noted that they should be limited if a person needed to lose weight. These calorie-dense foods, and alcohol, provide calories but relatively few vitamins or minerals.

The "second" pyramid, *MyPyramid*, was introduced in conjunction with the Dietary Guidelines of 2005. Figure 8.1 also provides an illustration of MyPyramid. Instead of an Egyptian style pyramid of bricks representing food groups, this pyramid appeared to many commentators to look more like a circus tent, with colored streamers representing each food group in tiers down the pyramid. The designers' hope was that the graphic better portrayed the desirability of eating nutrient-dense foods that were less calorically dense first (e.g., the base or bottom of each food group), and only later the more calorie-dense foods if energy needs had not been met (foods at the narrow top of the pyramid). However, the concept was difficult to grasp and the graphic was not successful in depicting the concept of "nutrient-dense foods first." Several other attempts to convey this concept have been made but none has gained traction with professionals or consumers [32,33]. Another web-based innovation in 2005 offered a calculator to tailor the pyramid to individual needs. It customized recommendations to the individual's age, sex, and weight and presented menus that were appropriate in calories and other nutrients. The MyPyramid Planner is still available on the World Wide Web and is useful for helping people tailor their intakes of specific foods. It is available at http://www.MyPlate.gov.

The third graphic, and the one that is now current, is the ChooseMyPlate icon, which consists of a plate (see Figure 8.1). A new interactive tool will soon be available at http://www.ChooseMyPlate.gov and will permit health professionals and consumers to develop their own personalized nutrition and physical activity plans and to track intakes and outputs. Other support on planning intakes and making healthier choices is also available there. Most of the information and educational materials that were developed for MyPyramid can also be used with ChooseMyPlate.

There are many other graphics, pyramids, and other shapes produced by other organizations and designed to help consumers. Oldways, an organization dedicated to changing the ways people eat and to featuring traditional cuisines, has produced Vegetarian, Asian, Latino, and Mediterranean diet pyramids. The pyramids are available on the World Wide Web at http://www.oldwayspt.org. Special Pyramids are also available for older Americans, children, and other groups. The extent to which these "other" pyramids meet the DRIs may vary however, and their construction needs to be reviewed before they are adopted for use in counseling.

HEALTHY EATING INDEX

The HEI is a summary measure of people's overall diet quality. In a sense, the score for the population as a whole provides a "report card" on how well Americans are eating [34,35]. The latest version, revised in 2005, consists of a score that is the sum of 20 components, each representing a different aspect of a healthful diet [36,37]. The first five components measure the degree to which a person's diet conforms to the USDA Food Guide Pyramid's recommendations for servings from the five major food groups: grains (bread, cereal, rice, and pasta), vegetables, fruits, milk (milk, yogurt, and cheese), and the meat group (meat, poultry, fish, dry beans, eggs, and nuts). The sixth component measures total fat consumption as a percentage of total food energy intakes (e.g., calories). The seventh component focuses on saturated fat consumption as a percentage of total food energy intakes. The eighth component measures total cholesterol intake, the ninth total sodium intake, and the tenth focuses on the variety in a person's diet. Each of these 10 components has a maximum score of 10 and a minimum score of zero.

The HEI score will probably be revised again to reflect the 2010 Dietary Guidelines for Americans. A high score on a component indicates that intakes are close to the recommended ranges or amounts, as stated in the USDA Food Guide Pyramid/ChooseMyPlate, the 2005 Dietary Guidelines for Americans, or some other similar authoritative food-based dietary guidance. Low scores indicate less adherence with recommended ranges or amounts of nutrients. Thus, the maximum overall score for the 20 components combined is 100.

A "report card" on the nation's eating habits was compiled using HEI data from the 1994–1996 Continuing Survey of Food Intakes by Individuals, a nationally representative food consumption survey. It was evident that most Americans could improve their intakes considerably. Approximately 12% of the population had a good diet, with an HEI over 80, and 18% had a poor diet, as signified by HEI scores of less than 51. Special areas needing improvement were consumption of fruit and milk and milk products. Males age 15–18 years, African Americans, people with low incomes, and those with a high school diploma or less education tended to have lower quality diets [38]. A recent study from England shows that a high HEI like score is positively associated with health literacy and sugar-sweetened beverage intake [39]. More recent assessments of HEI scores among Americans suggest that much remains to be done for eaters to bring their eating patterns more in line with recommendations [40]. The website which describes all of these and other studies is http://www.cnpp.usda.gov/HealthyEatingIndex.htm. Other recent studies reporting the

HEI scores for large groups in the population are available at these websites:

http://www.cnpp.usda.gov/Publications/NutritionInsights/Insight43.pdf
http://www.cnpp.usda.gov/Publications/NutritionInsights/Insight42.pdf
http://www.agingstats.gov/agingstatsdotnet/Main_Site/Data/2010_Documents/Docs/OA_2010.pdf
http://www.childstats.gov/americaschildren/health6.asp

Definitive, comprehensive reports on nutritional status were issued periodically by the Federal government for many years in a single document on national nutrition monitoring. Each report provided detailed discussions of dietary patterns and nutrient intakes, but the process of assembling them took many years [41] (Life Sciences Research Office 1989). Today, reports on specific issues are published periodically in a more timely manner by agencies in the relevant departments.

NUTRIENT LABELING

Another consumer education and awareness tool is the food label. Processed food products have had ingredient labeling for many years, with ingredients listed by weight and now many perishable foods and commodities are labeled as well. These ingredient lists are helpful for persons who want to include or avoid certain food ingredients in their diets for health or cultural reasons. New information is also available on labels now make it even easier for consumers. Nutrient labeling of processed foods was first made mandatory in 1993. The "Nutrition Facts" panel now provides information about the nutrient content of processed foods in standardized portion sizes. This label information can be used as a tool to help people select healthy diets. Today, the vast majority of processed foods and commodities, such as fresh fruits and vegetables, meats, poultry, and fish, have nutritional labels. The percentage of a standard population weighted value based on nutrient needs, called the USRDA, is used, which consists of the highest values for each adult age group by gender at the time when the label was promulgated. In addition to these labels, over-the-counter vitamin and mineral supplements have supplement facts that use a dietary standard known as the Daily Value (DV), which is also based on the RDA, to provide a comparison of the content with this nutrient standard.

Over the last two decades, nutrient content claims, health claims, and structure–function claims have also been permitted on foods. Nutrient content claims on food labels, such as "low in fat" or "good source of dietary fiber," are specified so that the same standard is used on all foods of the same type. Health claims describe the relationship between a nutrient or food and a disease. These provide additional information for consumers. Structure–function claims describe the association between a nutrient or other bioactive in food and a bodily function. Some permissible health claims for food packages are presented in Table 8.5. All health claims for foods that are currently allowed are found at the FDA website, and they are updated as new claims become available: http://www.fda.gov/Food/LabelingNutrition/LabelClaims/ucml11447.htm

HEALTHY PEOPLE

In the early 1970s, the need for explicit, measurable, prevention objectives for government, private, and voluntary groups became increasingly necessary. The Office of the Assistant Secretary for Health in the U.S. Department of Health, Education, and Welfare (now the U.S. Department of Health and Human Services) began the process of developing consensus on some national goals that could guide prevention efforts in the future. The first effort was a slim volume entitled Promoting Health, Preventing Disease: Objectives for the Nation [42]. It stated general goals and objectives in various areas of public health and preventive medicine and ways to measure progress in achieving them. In the late 1970s U.S. Surgeon General Julius Richmond, who was also Assistant Secretary for Health, commissioned a much larger effort, entitled Healthy People, that set forth an ambitious prevention plan [43]. Using a management by objectives planning process, the U.S. Public Health Service set out objectives focusing on improving health status, risk reduction, public and professional awareness of prevention, health services, and protective measures, surveillance, and evaluation. The objectives were organized in 15 priority areas under the general headings of preventive services, health protection, and health promotion. Targets for achieving the objectives were set, usually with a 10-year timeframe. It was recognized that in order to achieve the objectives, a health system reaching all Americans and integrating personal health care and public health measures focusing on the entire population (population-based measures) would be necessary. Moreover, it was clear that most prevention did not occur solely within the health system, but in community institutions as well, including schools, workplaces, families, and neighborhoods. Therefore, these environments as well as the traditional health care system were included as a focus for the preventive efforts.

Starting in 1980, and at the beginning of every decade thereafter, HHS has convened public, private, and voluntary groups to update the plan and assess progress toward achieving it. The resulting document is called Healthy People. It is now customary to issue a "mid-course review" halfway through the decade to make midterm corrections and redirect resources if this should prove to be necessary.

The current prevention plan is entitled "Healthy People 2020." The entire report is hundreds of pages long and accessible on the Internet at http://www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid = 29. The overall goals of Healthy People are simple: Increase the span of healthy life, reduce health disparities among Americans, and achieve access to preventive services for all Americans. For each life stage, there are specific objectives stated in terms of reducing mortality and in the various areas. Goals are also

TABLE 8.5
Permissible Health Claims for Food Packages*

Health Claim	Example of Some Statements
Osteoporosis	
Calcium, vitamin D, and osteoporosis	A calcium-rich diet is linked to a reduced risk of osteoporosis, a condition in which the bones become soft or brittle.
Heart disease	
Dietary saturated fat and cholesterol and risk of coronary heart disease	A diet low in saturated fat and cholesterol can help reduce the risk of heart disease.
Fiber containing grain products, fruits, and vegetables, and cancer	A diet rich in high fiber grain products, fruits, and vegetables can reduce the risk of some cancers.
Soluble fiber from certain foods and risk of coronary heart disease	
Soy protein and risk of coronary heart disease	
Soluble fiber from certain foods and risk of coronary heart disease	
Soy protein and risk of coronary heart disease	
Stanols/sterols and risk of coronary heart disease	
Substitution of saturated fat with unsaturated fatty acids and risk of heart disease	
Whole grain foods and risk of heart disease and certain cancers	
Nuts and heart disease*	
Walnuts and heart disease*	
Omega 3 fatty acids and coronary heart disease*	
Unsaturated fatty acids from canola oil and coronary heart disease*	
Corn oil and heart disease*	
B vitamins and vascular disease*	
Monounsaturated fatty acids from olive oil and coronary heart disease*	
Unsaturated fatty acids from canola oil and coronary heart disease	
Corn oil and heart disease	
Dental caries	
Fluoride and the risk of dental caries	
Dietary non-cariogenic carbohydrate sweeteners and dental caries	
High blood pressure	
Sodium and hypertension	
Potassium and the risk of high blood pressure and stroke	
Calcium and hypertension, pregnancy-induced hypertension, and preeclampsia*	
Cancer	
Dietary lipids (fat) and cancer	A diet low in total fat is linked to a reduced risk of some cancers.
Fruits and vegetables and cancer	A diet high in fruits and vegetables and foods that are low in fat and may contain dietary fiber, vitamin A, or vitamin C is linked to lower risk of some cancers.
Whole grain foods and risk of heart disease and certain cancers	
Tomatoes and/or tomato sauce and prostate, ovarian, gastric, and pancreatic cancers*	
Calcium and colon/rectal cancer and calcium and recurrent colon/rectal polyps*	

TABLE 8.5 (continued)
Permissible Health Claims for Food Packages*

Health Claim	Example of Some Statements
Green tea and cancer*	
Selenium and cancer*	
Antioxidant vitamins and cancer*	
Other	
Choline	
100% whey protein partially hydrolyzed infant formula and reduced risk of atopic dermatitis*	
Chromium picolinate and diabetes*	
Phosphatidylserine and cognitive* dysfunction and dementia*	
0.8 mg folic acid and neural tube birth defects*	

Claims with an asterisk * are qualified health claims subject to enforcement discretion. These refer to claims when there is emerging evidence for a relationship between a food, food component, or dietary supplement and reduced risk of a disease or health-related condition, but the evidence is not established well enough to meet significant scientific agreement standard, and so qualifying language is needed.

set for each priority area. Nutrition is considered as one of these areas. They deal with health status, risk reduction, and services-related issues and set measurable objectives in each area. The nutrition-related goals for Healthy People 2020 are discussed in detail in Chapter 9.

For some objectives, the 2010 nutrition targets have been met. But for other objectives, such as obesity, little progress has been made or progress has been in the wrong direction. The 2020 goals reflect these problems. These are the areas where the nation must concentrate efforts in the future.

CONCLUSIONS

Dietary intake is only one facet of nutritional status, but it is an important one. The Dietary Guidelines for Americans provide recommendations for altering current intakes in more healthful directions. The DRIs, such as the RDA and UL, provide useful guides for planning nutrient intakes for individuals. Other tools, such as MyPyramid and ChooseMyPlate, are helpful food-based recommendations that, if followed, ensure that the DRI are met. Food labels aid in making wise choices in line with dietary recommendations. The HEI provides a simple tool for evaluating the balance, variety, and adequacy of intakes based on the Food Guide and Dietary Guidelines for Americans. Health professionals can use these simple tools to plan and assess their own eating patterns and those of their clients. For many practical purposes, these tools will suffice. For more elaborate planning and assessment and for research, other tools may be necessary.

The Year 2020 nutritional goals for promoting health and preventing disease provide additional useful health targets to aim for as a nation.

ACKNOWLEDGMENTS

This project has been funded at least in part with Federal funds from the National Institutes of Health and the U.S. Department of Agriculture, Agricultural Research Service, under contract number 53/3-K06-5-10. The contents of this chapter do not necessarily reflect the views or policies of the U.S. Department of Agriculture, nor do they mention trade names, commercial products, or organizations that imply endorsement by the U.S. government.

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9 Healthy People 2020
Highlights in the Nutrition and Weight Status Focus Area

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CONTENTS

Background 119
Highlights 119
Health Promotion and Health Prevention 120
Impact of Determinants of Health on Nutrition and Weight Status (Focus of HP2020) 120
Social 120
Individual Behavior 120
Biology 121
Health Disparities 121
Emerging Trends in Nutrition and Weight Maintenance 121
Dietary Intake Trends 121
Healthy People 2020 Goals for Nutrition and Weight Status Topic Area 121
Healthy People 2020 Objectives for the Nutrition and Weight Status Topic Area 121
References 128

BACKGROUND

In 1979, Dr. Julius Richmond released *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention* [1], which launched the Healthy People (HP) initiative that defined a national agenda to enhance the health of the U.S. population in five major life stages (infants, children, adolescence, adults, and older adults). Initially, 15 priority areas were identified with 226 targeted measurable health objectives for improving the health of the nation were set for HP1990. The initiative has continued with HP2000, 2010, and most recently 2020, which was launched in December 2010. The goals of HP1990 were to decrease mortality in infants through adults and increase independence among older adults. HP2000 focused on increasing the span of healthy life, reducing disparities, and achieving access to preventative services for all. HP2010 targeted increasing the quality and years of healthy life and eliminating health disparities. The newly launched HP2020 aims to attain high-quality longer lives free of preventable disease, achieve healthy equity, eliminate disparities, create social and physical environments that promote good health and promote quality of life, healthy development, and healthy behaviors across life stages with 42 focus areas and over 600 objectives. Nutrition has been a vital focus area in HP initiative, evolving from the Nutrition and Overweight chapter to the current Nutrition and Weight Status (NWS) Focus Area.

HIGHLIGHTS

Although *HP2020* incorporates several elements of HP2010, it expands the goals, topic areas, objectives, and outreach and is more action oriented than previous years. Promoting quality of life, healthy development, and healthy behaviors across life stages and creating social and physical environments that promote good health are included among the overarching goals of HP2020. These goals reinforce the importance of healthy lifestyles throughout the life span and introduce the social determinants of health, which is a major focus and new topic area of HP2020. There are a total of 13 new topic areas that are geared toward specific populations, diseases, and prevention-based strategies to improve health (Table 9.1).

Nearly 600 objectives were developed by federal experts from various topic areas and reflect input from the general public through public comment. It is important to note that objectives must have a reliable data source, baseline data, and an achievable target. Securing nationally representative data in order to ensure valid monitoring can be particularly problematic and has prevented several objectives from going forth to become a part of HP2020.

Communication and outreach efforts of HP2020 have significantly improved and facilitated accessibility to a broader group of users. HP2020 utilizes new media strategies and allows users to receive updates through social networking sites such

TABLE 9.1
List of New Topic Areas Added to Healthy People 2020

Adolescent health
Blood disorders and blood safety
Dementias, including Alzheimer's disease
Early and middle childhood
Genomics
Global health
Health care–associated infections
Health-related quality of life and well-being
Lesbian, gay, bisexual, and transgender health
Older adults
Preparedness
Sleep health
Social determinants of health

as Twitter, and LinkedIn. Additionally, the recent unveiling of the redesigned HP website, a relational database of HP2020 objectives and implementation strategies, will make it possible for HP2020 to be more of a "living," action-oriented document compared to previous textbook versions. This interactive database will be updated regularly to reflect new data and changes to evidence-based resources. This website will be continuously evolving throughout the decade to include ongoing implementation strategies, collaborative efforts, data integration, and personalized information based on the specific needs of the user.

While HP2020 comprises 42 topic areas, this chapter will specifically highlight the NWS Focus Area of HP2020. It will focus on NWS as a public health concern, new developments impacting this topic area, and changes made to objectives since HP2010.

HEALTH PROMOTION AND HEALTH PREVENTION

Historically, HP has been a 10 year plan focused on improving health status and reducing disease risk for Americans. Similar to previous versions, many of the health promotion and disease prevention goals outlined in HP2020 can be helpful in preventing and managing chronic diseases. Many of the chronic diseases plaguing the United States are preventable and could be significantly reduced by diet and weight management. Increased portion sizes, high-calorie foods and beverages, and sedentary lifestyles have contributed to the obesity epidemic, which has been linked to an increased risk of heart disease, stroke, diabetes, arthritis, and some types of cancers. Therefore, it can be deduced that the prevention of some chronic diseases can be impacted by NWS.

HP2020 emphasizes a life stage approach. It focuses on promoting healthy behaviors throughout the life span, which can be helpful in preventing risk associated with age-specific developmental stages. For example, recent data suggest that poor nutrition in the early stages of life may be a predictor of chronic disease in adulthood [2]. Similarly, childhood obesity has been linked with cardiovascular risk factors later in life [3]. This knowledge suggests that health promotion and preventative actions should be geared toward early childhood to increase the benefit and the likelihood of sustainability.

IMPACT OF DETERMINANTS OF HEALTH ON NUTRITION AND WEIGHT STATUS (FOCUS OF HP2020)

HP2020 discusses how determinants of health can influence disease. It was developed to focus on societal determinants because they are linked to the root cause of disease, have the potential to aid in controlling disease, and must be addressed in order to achieve health equity. Social, behavioral, and biological factors have all been associated with health outcomes. These factors can also be linked to dietary and obesity patterns seen in individuals and certain populations.

Social

Social determinants of health refer to environments in which people are born, live, learn, play, work, and age. These determinants of health encompass economic and environmental conditions, and may be the contributors of obesity and poor dietary choices. The National Center for Health Statistics Data Brief on Obesity and Socioeconomic Status in Children and Adolescence concluded that low-income children were more likely to be obese than their higher-income counterparts, although this trend was not consistent across race and ethnicity groups [3]. However, it is important to note that between 1988–1994 and 2007–2008, the prevalence of childhood obesity increased at all income and education levels [3]. In regard to environment, availability and affordability to nutritious foods may be challenging in low-income neighborhoods. In studies performed in Baltimore, Atlanta, and New York, supermarkets were significantly more common in white and higher-income areas than in predominantly black and lower-income neighborhoods [4–6].

Individual Behavior

An individual's behavior is shaped by his or her beliefs, perceptions, values, and social environment. Recognition of specific behaviors has been attributed to increased risk of disease. For example, the consumption of *trans* fat and sedentary behaviors are associated with an increased risk of cardiovascular disease [7]. Likewise, the Centers for Disease Control and Prevention (CDC) identified tobacco, poor diet, and inactivity as the leading contributors of death—all of which are linked to behavioral choices [8]. The relationship between health and behavior is an enormously complex one and is controlled by multiple environmental factors (physical, biological, social, political, and economical), which makes promoting sustainable behavior change difficult. Yet the recent advances in evidence-based research, medical innovations, surveillance monitoring, and understanding of the many aspects of behavior have led to the development of multifaceted public health strategies and interventions aimed at behavior change.

Biology

Biological determinants of health refer to genetic factors that are attributed to the likelihood of disease. It is important to point out, genes can be considered only as contributors to a greater or lesser risk of health outcomes; they are not predictors. Several studies have suggested that obesity is heavily influenced by genetics and linked to causal genes [9,10] and attributed appetitive traits to genetically determined phenotypes [11,12]. Even with this knowledge, the interplay of behavior, lifestyle, and social influence cannot be removed from the equation. Obesity is a multiple causation disease that will require a multifactorial approach to reduce its prevalence.

Health Disparities

As previously mentioned, one of the overarching goals of HP2020 focuses on achieving health equity and eliminating health disparities. The elimination of health disparities remained in HP2020 because the gaps between ethnic and racial minorities and their white counterparts still exist in terms of incidence of chronic disease and obesity. HP2020 defined health equity as achieving the highest level of health for all people. Health equity entails focused societal efforts to address avoidable inequalities by equalizing the conditions for health for all groups, especially for those who have experienced socioeconomic disadvantage or historical injustices [13]. By definition, the pursuit of healthy equity promotes the elimination of health disparities. For this reason, the inclusion of health equity in HP2020 is progressive and prevention oriented.

EMERGING TRENDS IN NUTRITION AND WEIGHT MAINTENANCE

The increased rate of obesity has given rise to increased use of treatment, and prevention options in science, medicine, and government aimed at reducing and controlling the obesity epidemic.

Dietary Intake Trends

Before exploring emerging nutritional trends, it is important to establish the dietary intake patterns of Americans to help understand why some of the options outlined in this section are being pursued. The overall food supply has significantly increased. Yet Americans are still failing to meet the minimum requirements of MyPyramid's (now MyPlate's) nutrient-rich food groups like vegetables, whole grains, fruits, and milk products. On the other hand, many American diets include an overconsumption of solid fat and added sugars. In an article on dietary sources of energy [14], grain desserts (cakes, cookies, doughnuts, etc.), pizza, and soda were found to be the top three contributors of energy for 2–18 year olds. Many of these food selections contain "empty" calories with very little nutritional value. Americans are also consuming an increased amount of food outside of the home and eating more frequently at fast-food restaurants. This trend has significantly affected America's youth, among whom fast-food consumption was associated with higher intake of total energy, fat, saturated fat, carbohydrates, sugar, and carbonated soft drinks and lower intake of micronutrients, fruits and vegetables, and milk [15,16].

HEALTHY PEOPLE 2020 GOALS FOR NUTRITION AND WEIGHT STATUS TOPIC AREA

The name of the topic area "Nutrition and Overweight" used in HP2010 was changed to "Nutrition and Weight Status" in HP2020. "Weight status" was used because it can refer to healthy weight, overweight, and obesity—all of which are used in this topic area. There are 18 objectives found in the NWS topic area of HP2020. These objectives reflect both health promotion and prevention through consumption of a healthful diet and weight reduction or maintenance. They are geared around healthier food access, health care and worksite settings, weight status, food insecurity, food and nutrient consumption, and iron deficiency. Since no targets were met in HP2010, many of the objectives in HP2010 have been carried forward to HP2020 in an identical or somewhat modified manner. As of the latest HP2010 progress review, eight objectives moved away from its target, seven showed little or no progress, and two were moving toward its target. There were three objectives that were not carried forward to HP2020 (growth retardation among low-income children, consumption of calories from total fat, and anemia among low-income children [Table 9.2]).

HEALTHY PEOPLE 2020 OBJECTIVES FOR THE NUTRITION AND WEIGHT STATUS TOPIC AREA

The following section contains the objectives for the NWS. Each objective, some with sub-objectives, is listed with the rationale for choosing them within the focus group. The baseline, target, and data source for all objectives can be found in Table 9.3.

NWS-1: Increase the number of states with nutrition standards for foods and beverages provided to preschool-aged children in childcare.

Approximately one of every four children aged 2–5 years in the United States is either overweight or obese (at or above the 85th percentile on the 2000 CDC growth curves) [19]. About 75% of preschool children aged 3–5 years participate in child care at least once per week; 41% of preschool children are in child care for 35 h or more per week. Thus, young children have the potential to consume a large portion of their caloric intake in childcare settings [20]. Most states' childcare licensing regulations lack specific nutrition standards for child care sites aimed at improving dietary quality and preventing childhood obesity within those facilities [20–22]. Enhancing state regulations for nutrition could help address poor diet quality and the obesity epidemic in young children in the United States.

TABLE 9.2
Justification for the Removal of Objectives from the Healthy People 2020 Nutrition and Weight Status Topic Area

Objective	Justification
Reduce anemia among low-income pregnant females in their third trimester	• The data used for measuring this objective are not nationally representative • The objective ascertains anemia and not iron deficiency or iron-deficiency anemia, which is the outcome of interest under this nutrition section • Efforts to address iron-deficiency anemia are needed for both lower- and higher-income pregnant women. This objective focuses on only low-income women • The measurement of iron-deficiency anemia in a nationally representative sample of pregnant women will be captured in the retention of NWS-22 (reduce iron deficiency among pregnant females). As such, this objective does not add a sufficient amount of new information to guide public health interventions
Reduce growth retardation among low-income children under the age of 5 years	• The prevalence of growth retardation at the 1997 baseline (6%) and at the 2008 progress review (6%) was relatively low. In addition, this prevalence is very close to the prevalence that would be expected due to normal biological variation (5%) • The 2010 target (based on better than the best objective setting criteria) is 4%. There is a relatively small difference between the 2008 progress review level and the target • Public health interventions that address this issue such as WIC are already in place. It is unclear what addition public health efforts would be undertaken to continue to lower this prevalence
Increase the proportion of persons aged 2 years and older who consume no more than 30% of calories from total fat	• This objective was primarily based on the *2000 Dietary Guidelines for Americans* recommendation that Americans consume a diet moderate in fat—aiming for a total fat intake of no more than 30% of calories [17] • We propose to remove this objective because the emphasis on promoting heart health in the *2005 Dietary Guidelines for Americans* is more on types of fat than on total amount of fat consumed [18]

NWS-2: Increase the percentage of schools that offer nutritious foods and beverages outside of school meals.

There are two sub-objectives under this objective: *NWS-2.1 Increase the proportion of schools that do not sell or offer calorically sweetened beverages to students*; and *NWS-2.2 Increase the proportion of school districts that require schools to make fruits or vegetables whenever other food is offered or sold*.

The need to promote healthy eating among youth has intensified as a result of the growing national epidemic of obesity. Their failure to meet fruit and vegetable guidelines and the obesity prevalence highlight the need for school-based nutrition education, and supportive school environments encourage youth to eat more healthfully [23]. Schools are in a unique position to influence and promote healthy dietary behaviors and help ensure appropriate nutrient intake. Research has shown a relationship between the availability of high-calorie, low-nutrient snacks and drinks sold in schools and students' high intakes of total calories, soft drinks, total fat, and saturated fat, and lower intake of fruits and vegetables [24]. Conversely, students in schools with restricted snack availability had higher intakes of fruits and vegetables than students in schools without restricted snack availability [25]. System-level interventions, policy, and environmental approaches have the potential to influence individual dietary behavior through improvements to the food environment [20,26]. Tracking this objective as part of HP2020 will promote a food environment for children that more closely aligns with current dietary guidance.

NWS-3: Increase the number of states that have state-level policies that incentivize food retail outlets to provide foods that are encouraged by the *Dietary Guidelines*.

Poor dietary patterns and obesity, established as risk factors for chronic disease, have been linked to neighborhood deprivation, neighborhood minority composition, and low area population density [27]. Research suggests that neighborhood residents with better access to supermarkets and other retail stores that provide healthful foods and limited access to convenience stores tend to have healthier diets, including higher intakes of fruits and vegetables [27–31].

Evaluation of a food retail provision intervention in a low-income deprived area of England showed a modest, positive impact of the retail intervention on fruit and vegetable consumption [32]. The intervention consisted of provision of a major food supermarket to an area considered a "food desert" because access to healthy affordable food was poor. Among respondents who consumed ≤2 servings of fruits and vegetables in the pre-intervention period, 60% increased their fruit and vegetable consumption in the post-intervention [32]. An evaluation of the Apache Healthy Stores Program, a multicomponent intervention that included stocking healthier food items, found an increase in the purchase of healthy food,

TABLE 9.3
NWS Focus Area Objectives: Status, Baseline, Target, and Data Source

2020 Objective	Status	Baseline	Target	Data Source
NWS-1	New	24 States had nutrition standards for foods and beverages provided to preschool-aged children in child care in 2006	34 States with standards	National Resource Center for Health and Safety in Child Care and Early Education, and child care licensing websites from each State government and the District of Columbia
NWS-2	New	9.3% of schools did not sell or offer calorically sweetened beverages to students in 2006	21.3%	Health Policies and Programs Study, CDC
NWS-2.2	New	6.6% of school districts that require schools to make fruits or vegetables whenever other food is offered or sold to students in 2006	18.6%	School Health Policies and Programs Study, CDC
NWS-3	New	Eight states (including the District of Columbia) had state-level policies that incentivized food retail *outlets* to provide foods that are encouraged by the *Dietary Guidelines* in 2009	18 States	CDC State Indicator Report on Fruit and Vegetables. The Report gathers data sources: (1) CDC Nutrition, Physical Activity, and Obesity Legislative Database, (2) National Conference of State Legislatures Health Community Design and Access to Healthy Food Legislative Database, (3) The Food Trust
NWS-4	New	Developmental	Developmental	Developmental
NWS-5.1	New	48.7% of primary care physicians regularly assessed body mass index (BMI) in their adult patients in 2008	53.6%	National Survey on Energy Balance-Related Care among Primary Care Physicians
NWS 5.2	New	49.7% of primary care physicians regularly assessed body mass index (BMI) for age and sex in their child or adolescent patients in 2008	54.7%	National Survey on Energy Balance-Related Care among Primary Care Physicians
NWS-6.1	Retained/ modified from HP2010	20.8% of physician office visits made by patients with a diagnosis of cardiovascular disease, diabetes, or hyperlipidemia that include counseling or education related to diet and nutrition in 2001 (age adjusted to the year 2000 standard population)	22.9%	National Ambulatory medical Care Survey, CDC, NCHS
NWS-6.2	Retained/ modified from HP2010	28.9% of physician office visits made by adult patients who are obese that include counseling or education related to weight reduction, nutrition, or physical activity in 2007 (age adjusted to the year 2000 standard population)	31.8%	National Ambulatory medical Care Survey, CDC, NCHS
NWS-6.3	Retained/ modified from HP2010	12.2% of physician visits made by all children or adult patients that include counseling about nutrition or diet in 2007 (age adjusted to the year 2000 standard population)	15.2%	National Ambulatory medical Care Survey, CDC, NCHS
NWS-7	New	Developmental	Developmental	Developmental
NWS-8	Retained/ modified from HP2010	30.8% of persons aged 20 years and over were at a healthy weight in 2005–2008 (age adjusted to the year 2000 standard population)	33.9%	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-9	Retained/ modified from HP2010	34.0% of persons aged 20 years and over were obese in 2005–2008 (age adjusted to the year 2000 standard population)	30.6%	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-10.1	Retained/ modified from HP2010	10.7% of children aged 2–5 years were considered obese in 2005–2008	9.6%	National Ambulatory medical Care Survey, CDC, NCHS
NWS-10.2	Retained/ modified from HP2010	17.4% of children aged 6–11 years were considered obese in 2005–2008	15.7%	National Ambulatory medical Care Survey, CDC, NCHS

(*continued*)

TABLE 9.3 (continued)
NWS Focus Area Objectives: Status, Baseline, Target, and Data Source

2020 Objective	Status	Baseline	Target	Data Source
NWS-10.3	Retained/ Modified from HP2010	16.2% of children aged 6–11 years were considered obese in 2005–2008	14.6%	National Ambulatory medical Care Survey, CDC, NCHS
NWS-11.1–5	New	Developmental	Developmental	Developmental
NWS-12	Retained/ modified for HP2010	1.3% of households with children had very low food security among children in 2008	0.2%	Food Security Supplement to the Current Population Survey, U.S. Department of Commerce, Bureau of the Census
NWS-13	Retained/ modified from HP2010	14.46% of households were food insecure in 2008	6.0%	Food Security Supplement to the Current Population Survey, U.S. Department of Commerce, Bureau of the Census
NWS-14	Retained/ modified from HP2010	0.5 of cup equivalents of fruits per 1000 calories was the mean daily intake by persons aged 2 years and older in 2001–2004	0.9 cup equivalents per 1000 calories	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-15.1	Retained/ modified from HP2010	0.8 cup equivalents of total vegetables per 1000 calories was the mean daily intake by persons aged 2 years and older in 2001–2004 (age adjusted to the year 2000 standard population)	1.1 cup equivalents per 1000 calories	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-15.2	Retained/ modified from HP2010	0.1 cup equivalents of dark green or orange vegetables or legumes per 1000 calories was the mean daily intake by persons aged 2 years and older in 2001–2004 (age adjusted to the year 2000 standard population)	0.3 cup equivalents per 1000 calories	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-16	Retained/ modified from HP2010	0.3 of cup equivalents of whole grains per 1000 calories was the mean daily intake by persons aged 2 years and older in 2001–2004 (age adjusted to the year 2000 standard population)	0.6 cup equivalents per 1000 calories	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-17.1	New	18.9% was the mean percentage of total daily calorie intake provided by solid fats for the population aged 2 years and older in 2001–2004 (age adjusted to the year 2000 standard population)	16.7%	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-17.2	New	15.7% was the mean percentage of total daily calorie intake provided by added sugars for the population aged 2 years and older in 2001–2004 (age adjusted to the year 2000 standard population)	10.8%	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-17.3	New	34.6% was the mean percentage of total daily calorie intake provided by solid fats and added sugars for the population aged 2 years and older in 2001–2004 (age adjusted to the year 2000 standard population)	29.8%	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-18	Retained/ modified from HP2010	11.3% was the mean percentage of total daily calorie intake provided by saturated fat for the population aged 2 years and older in 2003–2006 (age adjusted to the year 2000 standard population)	9.5%	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-19	Retained/ modified from HP2010	36,418 mg of sodium from foods, dietary supplements, antacids, drinking water, and salt use at the table was the mean total daily calorie intake by persons aged 2 years and older in 2003–2006 (age-adjusted to the year 2000 standard population)	2300 mg	National health and Nutrition Examination Survey (NHANES), CDC, NCHS

TABLE 9.3 (continued)
NWS Focus Area Objectives: Status, Baseline, Target, and Data Source

2020 Objective	Status	Baseline	Target	Data Source
NWS-20	Retained/ modified from HP2010	1118 mg of calcium from foods, dietary supplements, antacids, and drinking water was the mean total daily calorie intake by persons aged 2 years and older in 2003–2006 (age adjusted to the year 2000 standard population)	1300 mg	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-21.1	New	15.9% of children aged 1–2 years were iron deficient in 2005–2008	14.3%	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-21.2	New	5.3% of children aged 3–4 years were iron deficient in 2005–2008	4.3%	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-21.3	New	16.1% of pregnant females aged 12–49 years were iron deficient in 2005–2008	14.5%	National health and Nutrition Examination Survey (NHANES), CDC, NCHS
NWS-22	Retained/ modified from Hp 2010	16.1% of pregnant females with iron deficient in 2003–2006	14.5%	National health and Nutrition Examination Survey (NHANES), CDC, NCHS

including fruits and vegetables, by households located near the program stores [33]. Therefore, policy and infrastructure that support introducing supermarkets to underserved areas and improving the quality of foods sold at supermarkets and other retail venues may provide an opportunity to increase access to and availability of healthy food options for Americans.

NWS-4: Increase the proportion of Americans who have access to a food retail outlet that sells a variety of foods that are encouraged by the *Dietary Guidelines.*

Research in the United States suggests that neighborhood residents with better access to supermarkets and other retail stores that provide healthful foods tend to have healthier diets, including higher intakes of fruits and vegetables [27–31].

While supermarkets generally offer a wider variety of foods at affordable prices, some have limited shelf space devoted to fresh fruits and vegetables, and other encouraged foods. Moreover, in some neighborhoods, supermarkets do not exist [34] and residents may be unable to travel to areas where they do exist due to a lack of reliable transportation [28,35]. In rural and lower-income neighborhoods, convenience stores and other small grocery or "corner" stores may be more prevalent than supermarkets [36,37]. These stores generally stock little or no encouraged foods such as fruits and vegetables due to limited space or lack of refrigerators or storage equipment, and they may charge more for what is sold [36,38]. Low-income communities and areas with limited access to public and private transportation often rely on these stores as their primary venues for groceries. Thus, research suggests that characteristics of local food environments can play a role in both healthy diet and the prevention of overweight and obesity [39].

NWS-5: Increase the proportion of primary care physicians who regularly measure the body mass index (BMI) of their patients.

There are two sub-objectives under NWS-5: *NWS-5.1 Increase the proportion of primary care physicians who regularly assess body mass index (BMI) in their adult patients*; and *NWS-5.2 Increase the proportion of primary care physicians who regularly assess body mass index (BMI) for age and sex in their child or adolescent patients.*

Obesity is a significant health problem for both children and adults. Within the medical care setting, screening can identify persons whose weight increases their risk for other chronic conditions. For adults, the U.S. Preventive Services Task Force (USPSTF) recommends that clinicians screen all patients for obesity and offer intensive counseling and behavioral interventions to promote sustained weight loss for obese adults [40]; body mass index is the recommended measure for screening. However, other clinical organizations recommend routine screening. The American Academy of Pediatrics recommends that that body mass index be calculated and plotted once a year in all children and adolescents [41]. An expert committee convened by the American Medical Association (AMA) recommends that physicians and allied health care providers perform, at minimum, a yearly assessment of weight status for all children and that this assessment include calculation of height, weight, and BMI for age and that these measures are plotted on standard growth charts. In addition to recommendations from these clinical organizations, the routine assessment of body mass index for adults and body mass index percentile for children is also a Health Effectiveness Data and Information Set measure of the National Committee for Quality Assurance.

NWS-6: Increase the proportion of physician office visits that include counseling or education related to nutrition or weight.

This objective has three sub-objectives: *NWS-6.1 Increase the proportion of physician office visits made by patients with a diagnosis of cardiovascular disease, diabetes, or hyperlipidemia that include counseling or education related*

to diet and nutrition; *NWS-6.2 Increase the proportion of physician office visits made by adult patients who are obese that include counseling or education related to weight reduction, nutrition, or physical activity*; and *NWS-6.3 Increase the proportion of physician visits made by all child or adult patients that include counseling about nutrition or diet*.

Primary care providers are well positioned in the health care system to provide preventive services including nutrition screening and assessment, referral, and counseling. For persons with chronic conditions, the USPSTF found sufficient evidence to recommend counseling for two groups of adult patients—those with cardiovascular and diet-related chronic disease and those with obesity. Specifically, the USPSTF recommends intensive behavioral dietary counseling for adult patients with hyperlipidemia and other known risk factors for cardiovascular and diet-related chronic disease and that clinicians screen all patients for obesity and offer intensive counseling and behavioral interventions to promote sustained weight loss for obese adults [40,42].

The USPSTF [42] concluded that the evidence was insufficient to recommend for or against routine behavioral counseling to promote a healthy diet in unselected patients in primary care settings. However, both the AMA Guidelines for Adolescent Preventive Services [43] and the Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents include recommendations [41] to provide guidance about nutrition during health visits.

NWS-7: (Developmental) Increase the proportion of worksites that offer nutrition or weight management classes or counseling.

The recommendation to retain this intervention is based on potential research, evidence that worksite health programs can alter health outcomes. However, we recommend that making this a developmental objective as the data source for this objective is not currently funded. Other groups within the federal government have expressed interest in potentially fielding a study in this area.

Approximately two-thirds of the U.S. civilian population aged 16 and older is employed [44]. As such, worksites provide a channel to reach significant numbers of adults and older adolescents. Research supports the use of worksite interventions to change health behaviors or outcomes. For example, the Task Force on Community Preventive Services recommended worksite programs to improve diet and/or physical activity behaviors based on strong evidence of their effectiveness for reducing weight among employees [45]. In 1988–1999, only 54% of worksites offered nutrition or weight management classes or counseling. This is 30% lower than the 2010 target [46].

NWS-8: Increase the proportion of adults who are at a healthy weight.

Maintaining a healthy weight can be a key factor in helping to reduce the burden of many illnesses and chronic diseases. Based on the ongoing National Health and Nutrition Examination Survey (NHANES) data sets, collected throughout the decade from 1999 to the present, the proportion of population within the healthy weight BMI range (18.5 to <25) continued to decrease. For this reason, this objective remains and is part of HP2020.

NWS-9: Reduce the proportion of adults who are obese.

The rates of obesity in the United States among adults remain high. Obesity is a major public health concern and is associated with chronic diseases such as type 2 diabetes, stroke, cardiovascular diseases, and some types of cancer that have significant morbidity and mortality.

NWS-10: Reduce the proportion of children and adolescents who are considered obese.

This objective has four sub-objectives: *NWS-10.1 Children aged 2–5 years*; *NWS-10.2 Children aged 6–11 years*; *NWS-10.3 Children aged 12–19 years*; and *NWS-10.4 Children aged 2–19 years*.

On January 28, 2010, Health and Human Services (HHS) released *The Surgeon General's Vision for a Healthy and Fit Nation* [47], in which it is stated "Children and adolescents with a BMI at or above the sex-and age-specific 95th percentile of this reference population [the data set used to derive the 2000 CDC BMI Growth Curve] are often considered obese…" The publication states that these cutoff points are not diagnostic criteria, although elevated BMI among children most often indicates increased risk for future adverse health outcomes. In order to provide consistency between the definition that has been proposed for this objective and the terminology most recently adopted in the HHS publication, the wording of the objective was changed to use the term "considered obese" rather than "overweight and obese." A sub-objective to monitor youth ages 2–5 years was added due to the observed increase in the prevalence of obesity in this age group.

NWS-11: (Developmental) Prevent inappropriate weight gain in youth and adults.

There are five sub-objectives under this objective: *NWS-11.1 Children aged 2–5 years*; *NWS-11.2 Children aged 6–11 years*; *NWS-11.3 Children aged 12–19 years*; *NWS-11.4 Children aged 2–19 years*; and *NWS-11.5 Adults aged 20 years and older*.

Gradual inappropriate weight gain with age has been the primary contributor to the obesity epidemic. Multiple factors have contributed to this gradual upward shift in weight. This trend suggests that for both youth and adults, many Americans are not engaging in or sustaining the healthful behaviors needed to prevent inappropriate weight gain. This objective provides a major emphasis on the prevention of inappropriate weight gain (maintaining energy balance) in youth and adults in order to prompt actions that will be more effective and realistically achievable than weight reduction.

NWS-12: Eliminate very low food security among children.

Although most Americans are food secure (with access to enough food for an active, healthy life for all household members throughout the year), many are not. Over 6 million households with children were food insecure in 2007. Even when resources are inadequate to provide food for the entire

family, children are usually shielded from the disrupted eating patterns and reduced food intake that characterize very low food security. However, children as well as adults experienced instances of very low food security in 323,000 households in 2007. Although the number of children that experience the most severe form of food insecurity is small, no child should go hungry when the nation has the agricultural abundance, economic means, and resources to ensure an adequate diet for all. As a result, President Obama's administration has committed to end childhood hunger.

NWS-14: Increase the contribution of fruits to the diet of the population aged 2 years and older.

The *Dietary Guidelines for Americans (DGA), 2005* [18], recommends that individuals consume a sufficient amount of fruits daily. Reduced risk of chronic diseases (stroke and perhaps other cardiovascular diseases, type-2 diabetes, and cancers in certain sites) is associated with increased intake of fruits and vegetables as part of a healthful diet.

NWS-15: Increases the variety and contribution of vegetables to the diets of the population aged 2 years and older.

There are two sub-objectives within this objective: *NWS-15.1 Increase the contribution of vegetables to the diets of the population aged 2 years and older*; and *NWS-15.2 Increase the contribution of dark green vegetables, orange vegetables, and legumes to the diets of the population aged 2 years and older.*

The *DGA, 2005* [18], recommends that individuals consume a sufficient amount of vegetables daily. Reduced risk of chronic diseases (stroke and perhaps other cardiovascular diseases, type-2 diabetes, and cancers in certain sites) is associated with increased intake of fruits and vegetables as part of a healthful diet. Instead of combining the measures into one objective, the HP2020 sub-objectives address (1) quantity and (2) variety. It has been modified to take into account the recommendations in the 2005 DGAs for vegetable consumption—which are linked to calorie levels and expressed in cups.

One sub-objective assesses the contribution of vegetables to the diets of the population aged 2 years and older rather than the proportion of the population that met a single recommendation for consumption of total vegetables (i.e., at least three daily servings). This change was made since recommendations are linked to calorie levels and estimated calorie requirements vary substantially for the population by age and gender and physical activity level.

The DGAs recommend that Americans consume a variety of vegetables daily and select from all five vegetable groups (dark green, orange, legumes, starchy vegetables, and other vegetables) several times a week. Many Americans fall short of these recommendations (see the data presentation for April 2008 progress review in the above link).

NWS-16: Increase the contribution of whole grains to the diets of the population aged 2 years and older.

A key recommendation in the *DGA, 2005* [16], was for Americans to consume sufficient amounts of whole grain products daily. Whole grains are an important source of fiber and other nutrients. Diets rich in foods containing fiber, such as fruits, vegetables, and whole grains, may reduce the risk of heart disease.

The HP2010 objective was based on the recommendation in the 1995/2000 DGAs for Americans aged 2 years and older to consume at least six daily servings, with several from whole grain foods. The most recent assessment of progress on this HP2010 objective showed little change from baseline (i.e., 4% in 1994–1996 compared to 3% in 2003–2004) [48] with a much greater proportion of the population meeting the 2000 DGA recommendation for consumption of total grain products (i.e., 54%) than for whole grains (3%).

The HP2020 objective has incorporated a modification to be in line with the recommendations of the 2005 DGAs, which emphasize consumption of sufficient amounts of whole grains and identify grain recommendations in ounce-equivalents for different calorie levels. The modified wording and operational definition for this objective would allow progress to be assessed in meeting DGA recommendations, without the need to change the operational definition for recommendations (and consequently baseline estimates) as these guidelines are updated in 2010, 2015, and beyond.

NWS-17: Reduce consumption of calories from solid fats and added sugars in the population aged 2 years and older.

NWS-17 contains three sub-objectives: *NWS-17.1 Reduce the consumption of calories from solid fats*; *NWS-17.2 Reduce the consumption of calories from solid fats and added sugars*; and *NWS-17.3 Reduce the consumption of calories from solid fats and added sugars.*

Americans frequently consume diets that provide an excess of energy and that are also inadequate in meeting nutrient needs [49–51]. An examination of usual dietary intakes of Americans aged 1 year and older found that mean energy consumption from solid fats and added sugars was 780 kcal/day (425 kcal from solid fats and 355 kcal from added sugars). Clearly, consumption of solid fats and added sugars is contributing significant amounts of excess energy to the diets of Americans and is a public health concern because of the alarming prevalence of overweight and obesity in the United States. Additionally, there is evidence that the amount of energy provided by energy-dense, nutrient-poor foods in the diets of Americans is increasing [52–55].

Tracking consumption of solid fats and added sugars in adults and children 2 years of age and older will enable health and nutrition professionals and policy makers to evaluate success of nutrition education programs and policies designed to persuade Americans to increase the nutrient density of their diets and to balance energy intake with energy expenditure.

NWS-18: Reduce the consumption of saturated fat in the population aged 2 years and older.

A key recommendation in the *DGA, 2005* [18], is for Americans to consume less than 10% of calories from saturated fats, less than 300 mg/day of cholesterol, and to keep *trans* fat consumption as low as possible. High intake of saturated fats, *trans* fats, and cholesterol increases the risk of

unhealthy blood lipid levels, which, in turn, may increase the risk of coronary heart disease.

The most recent assessment of progress on the 2010 saturated fat objective showed little change from baseline (i.e., 36% in 1994–1996 compared to 34% in 2003–2004) [56].

NWS-19: Reduce consumption of sodium in the population aged 2 years and older.

A key recommendation in the *DGA, 2005* (2005 DGAs), is for Americans to consume less than 2300 mg (about 1 teaspoon of salt) of sodium daily. Decreasing salt intake is advisable to reduce the risk of elevated blood pressure. Keeping blood pressure in the normal range reduces an individual's risk of coronary heart disease, stroke, congestive heart failure, and kidney disease.

The most recent report of progress on the 2010 sodium intake objective, which assessed the proportion of the population that consumed less than 2400 mg daily, showed little change from baseline [56]. In 2003–2004, only an estimated 11% of Americans aged 2 years and older consumed less than 2300 mg of sodium daily. The median total usual daily intake of sodium was an estimated 3556 mg/day for the population aged 2 years and older, with males 19–50 years having an estimated median total daily intake of more than 4590 mg [56]. The mean total daily sodium intake for the population aged 2 years and older was an estimated 3627 mg.

NWS-20: Increase consumption of calcium in the population aged 2 years and older.

Calcium intake is of continued public health importance. Calcium plays a key role in bone health, and adequate intake may reduce the risk of osteoporosis. The most recent assessment of the 2010 objective suggests some improvement in increasing total calcium intakes (from foods, dietary supplements, and antacids). That is, the proportion of persons aged 2 years and older who had total usual calcium intakes at or above 100% of the Institute of Medicine Adequate Intake values increased from 1988–1994 to 2003–2004 [56].

NWS-21: Reduce iron deficiency among young children and females of childbearing age.

There are three sub-objectives under NWS-21: *NWS-21.1 Children aged 1–2 years*; *NWS-21.2 Children aged 3–4 years*; and *NWS-21.3 Females aged 12–49 years.*

This objective was recommended based on the adverse health effects of iron deficiency, the availability of potential interventions, and the finding that iron deficiency is still a prevalent condition. Iron deficiency is associated with poorer cognitive performance, lower work performance and endurance, anemia, and, in more severe cases of anemia, increased maternal and child mortality [57]. Young children, because of their transition in feeding practices, and women of reproductive age, because of the loss iron with menstruation, are at risk for iron deficiency [57]. Obesity may represent an additional risk factor for iron deficiency [58]. For both young children and women of reproductive age, public health strategies to address iron deficiency exist. These include education on appropriate dietary practices, and screening and/or supplementation for high-risk individuals [59]. Public health nutrition programs such as Women, Infants and Children can also support high-risk women and children in improving their iron status.

For two of these subgroups, iron deficiency is relatively high and does not appear to be declining [60]. Data from NHANES 2003–2006 indicate that the prevalence of iron deficiency among nonpregnant women has not declined [61].

NWS-22: Reduce iron deficiency among pregnant females.

This objective was retained based on the health effects associated with iron deficiency in pregnant women, the potential for intervention, and the prevalence of the condition. Iron deficiency is associated with poorer cognitive performance, lower work performance and endurance, anemia, and, in more severe cases of anemia, increased maternal and child mortality [57]. For pregnant women, iron deficiency with anemia is associated with birth outcomes such as premature birth and low birth weight [57]. Pregnant women are at risk for iron deficiency because of the iron requirements of pregnancy. Screening, supplementation, and education about appropriate dietary practices are strategies to improve the iron status of pregnant individuals [62].

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10 Dietary Guidelines for Americans, 2010
National Nutrition Policy

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CONTENTS

Introduction 132
Background 132
Overview of the Dietary Guidelines for Americans, 2010 133
Balancing Calories to Manage Weight 133
  Key Recommendations 133
An Obesogenic Environment 134
  Calorie Balance: Calories from Foods and Beverages 134
    Calorie Sources: Carbohydrate, Protein, Fat, and Alcohol 135
    Individual Foods and Beverages and Body Weight 135
    Placing Individual Food Choices into an Overall Eating Pattern 135
  Calorie Balance: Physical Activity 135
  Principles for Promoting Calorie Balance and Weight Management 136
Foods and Food Components to Reduce 136
  Key Recommendations 137
  Sodium 137
  Fats 137
  Added Sugars 138
  Refined Grains 138
  Alcohol 138
Foods and Nutrients to Increase 138
  Key Recommendations 139
  Recommendations for Specific Population Groups 139
  Vegetables and Fruits 139
  Grains 139
  Milk and Milk Products 140
  Protein Foods 140
  Oils 140
  Nutrients of Concern 140
    Additional Nutrients of Concern for Specific Groups 141
Building Healthy Eating Patterns 142
  Key Recommendations 142
  Common Elements of Healthy Eating Patterns 142
  Principles for Achieving a Healthy Eating Pattern 143
  Putting the Principles for a Healthy Eating Pattern into Action 143
    USDA Food Patterns 143
    Vegetarian Adaptations of the USDA Food Patterns 144
    DASH Eating Plan 145
Helping Americans Make Healthy Choices 145
Additional Resources 146
Implementation by Health Professionals 146
References 147

INTRODUCTION

Nutrition and physical activity are vital components of a healthy lifestyle; poor nutrition and physical activity choices over time are associated with an array of chronic diseases and conditions. The purpose of the *Dietary Guidelines for Americans* (Dietary Guidelines) is to help Americans navigate their food, beverage, and activity choices to optimize long-term health and prevent chronic disease. Health care professionals are uniquely positioned to disseminate Dietary Guidelines' messages among the American public, in an effort to reduce chronic disease risk and burden at the individual and population levels.

The *Dietary Guidelines for Americans, 2010* (2010 Dietary Guidelines) [1] was developed during a particularly challenging era of modern public health: the epidemic of overweight/obesity in the United States. Approximately two-thirds of adults [2] and one-third of children and adolescents [3] are overweight or obese. Poor diet and physical inactivity are the most significant factors contributing to this public health crisis.

Even in the absence of overweight, poor diet and physical inactivity are associated with major causes of morbidity and mortality, including cardiovascular disease, hypertension, type 2 diabetes, osteoporosis, and some types of cancer. Poor diet and physical inactivity are second to tobacco as the leading cause of death in the United States [4]. Some racial and ethnic population groups are disproportionately affected by the high rates of overweight, obesity, and associated chronic diseases. In addition, risk factors for adult chronic diseases are increasingly found in children and adolescents.

The recommendations contained in the Dietary Guidelines traditionally have been intended for healthy Americans ages 2 years and older. However, since the 2010 Dietary Guidelines was released at a time of rising concern about the health of the American population, its recommendations accommodate the reality that the majority of Americans are overweight or obese and/or at risk of various chronic diseases. Therefore, the recommendations in the 2010 Dietary Guidelines are intended for Americans ages 2 years and older, including those who are at increased risk of chronic disease. Despite this expansion, the Guidelines are not appropriate as a therapeutic tool; the focus of the Guidelines remains on prevention.

The Dietary Guidelines serve as the cornerstone for nutrition policy and education efforts in the United States. They are the basis for the nutrition standards of many federally funded nutrition programs such as the National School Lunch Program and the Home Delivered Nutrition Services program for older Americans; they are also at the core of national nutrition education campaigns and resources. The Dietary Guidelines are considered the authoritative resource for nutrition guidance for the general population, and go hand-in-hand with the *Physical Activity Guidelines for Americans*, which provide more detailed physical activity recommendations.

This chapter will provide a brief background on the development and major themes of the 2010 Dietary Guidelines, as well as a more detailed examination of the key recommendations and resources within. Also, this chapter will conclude with some ideas on how physicians and other health professionals could implement the Guidelines in both clinical and nonclinical settings.

BACKGROUND

The Dietary Guidelines are congressionally mandated under the 1990 National Nutrition Monitoring and Related Research Act (Public Law 101-445, Section 301 [7 U.S.C. 5341], Title III), which requires the Dietary Guidelines to be based on the preponderance of current scientific and medical knowledge. The Dietary Guidelines have been jointly released by the U.S. Department of Agriculture (USDA) and the U.S. Department of Health and Human Services (HHS) every 5 years since 1980.

Over time, Federal dietary guidance has expanded from a traditional focus on nutrient adequacy to also address the impact of diet on chronic disease. The Dietary Guidelines have generally been consistent in their recommendations about the components of a health-promoting diet, but they have also evolved to reflect the emerging body of scientific evidence on nutrition, the food and physical activity environment, and health.

The development of the 2010 Dietary Guidelines occurred in two stages. In the first stage, an external scientific advisory committee, the Dietary Guidelines Advisory Committee (DGAC), was appointed to provide recommendations to the Federal government for updating the 2005 Dietary Guidelines. The DGAC was charged to conduct an analysis of new scientific information on diet and health and to prepare a report summarizing its findings. The 2010 DGAC considered approximately 180 questions pertinent to the Dietary Guidelines that covered a broad range of topics, such as calorie balance, nutrient adequacy, dietary patterns, food groups, beverages, behaviors, and food safety. The 2010 DGAC worked with the newly established USDA Nutrition Evidence Library (NEL) to conduct evidence-based systematic reviews to answer the majority of their questions. The NEL uses a systematic process to objectively review, evaluate, and synthesize scientific research to answer specific diet-related questions. The DGAC graded the strength of the evidence supporting their conclusions and provided recommendations based on the strongest available scientific evidence. The methodology used by the NEL [5] ensures government compliance with the Data Quality Act, which mandates that Federal agencies ensure the quality, objectivity, utility, and integrity of the information used to form Federal guidance. The evidence relevant to each review is publicly available at www.NEL.gov. The remaining questions were addressed using analyses of dietary intake data,* food pattern modeling

* Usual nutrient, food group, and selected dietary component intakes by Americans in the 2010 Dietary Guidelines and 2010 DGAC Report were drawn from analyses conducted by the National Cancer Institute, a component of HHS's National Institutes of Health, and by USDA's Agricultural Research Service, using data from the National Health and Nutrition Examination Survey (NHANES). Updated data are available at http://riskfactor.cancer.gov/diet/usualintakes/ and http://www.ars.usda.gov/ba/bhnrc/fsrg

analyses, and existing authoritative reviews and reports. The DGAC summarized their findings in a 445-page report, *Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010* [6].

During the second stage, USDA and HHS developed the policy document, *Dietary Guidelines for Americans, 2010.* The policy document writing group consisted of nutritionists who assisted the DGAC as they reviewed the evidence and prepared the resulting conclusions. The policy document's organization and recommendations are based on the DGAC's report, with consideration of public and Federal agency comments received throughout the process. More information about the development of the 2010 Dietary Guidelines is available at www.dietaryguidelines.gov

OVERVIEW OF THE DIETARY GUIDELINES FOR AMERICANS, 2010

The Dietary Guidelines represent the body of current knowledge about individual nutrients and food components, summarized and synthesized into an interrelated set of recommendations for healthy eating that can be adopted by the public. Taken together, the 2010 Dietary Guidelines recommendations encompass two overarching concepts:

- *Maintain calorie balance over time to achieve and sustain a healthy weight.* People who are most successful at achieving and maintaining a healthy weight do so through continued attention to consuming only enough calories from foods and beverages to meet their needs and by being physically active. To curb the obesity epidemic and improve their health, many Americans must decrease the calories they consume from foods and beverages and increase the calories they expend through physical activity.
- *Focus on consuming nutrient-dense* foods and beverages.* Americans currently consume too much sodium and too many calories from solid fats (i.e., saturated fatty acids and *trans*-fatty acids), added sugars, and refined grains, making it difficult to achieve recommended nutrient intake while controlling calorie and sodium intake. A healthy eating pattern limits intake of sodium, solid fats, added sugars, and refined grains and emphasizes nutrient-dense (i.e., high nutrient-to-calorie ratio) foods and beverages—vegetables, fruits, whole grains, fat-free or low-fat milk and milk products, seafood, lean meats and poultry, eggs, beans and peas, and nuts and seeds.

* Nutrient-dense foods and beverages provide vitamins, minerals, and other substances that may have positive health effects, with relatively few calories. They are lean or low in solid fats, and minimize or exclude added fats, sugars, starches, and sodium. All vegetables, fruits, whole grains, seafood, eggs, beans and peas, unsalted nuts and seeds, fat-free and low fat milk and milk products, and lean meats and poultry—when prepared without solid fats or added sugars—are nutrient-dense foods.

The organization of the 2010 Dietary Guidelines corresponds to major themes that emerged from the DGAC's review of the evidence, and the previously mentioned overarching concepts are woven throughout. The recommendations that are provided are based on the preponderance of scientific evidence for nutritional factors that are important for promoting health and lowering risk of diet-related chronic disease.

The 2010 Dietary Guidelines are divided into sections that focus on particular aspects of eating patterns:

- Balancing Calories to Manage Weight
- Foods and Food Components to Reduce
- Foods and Nutrients to Increase
- Building Healthy Eating Patterns
- Helping Americans Make Healthy Choices

Although divided into these sections, the Dietary Guidelines are intended to be integrated recommendations for health. To get the full benefit, individuals should carry out the recommendations in their entirety as part of an overall healthy eating pattern. The key recommendations and strategies identified in the 2010 Dietary Guidelines are highlighted in the following pages.

BALANCING CALORIES TO MANAGE WEIGHT

Achieving and sustaining appropriate body weight across the lifespan is vital to maintaining good health and quality of life. Because of the high prevalence of overweight and obesity in the United States, the 2010 Dietary Guidelines provide recommendations and strategies to help Americans balance calories to manage body weight. Calorie balance refers to the relationship between calories consumed from foods and beverages and calories expended in normal body functions and through physical activity. The current high rates of overweight and obesity among virtually all subgroups of the population demonstrate that many Americans are in calorie imbalance—that is, they consume more calories than they expend. All Americans—children, adolescents, adults, and older adults—are encouraged to achieve and maintain a healthy body weight.

Key Recommendations

- Prevent and/or reduce overweight and obesity through improved eating and physical activity behaviors.
- Control total calorie intake to manage body weight. For people who are overweight or obese, this will mean consuming fewer calories from foods and beverages.
- Increase physical activity and reduce time spent in sedentary behaviors.
- Maintain appropriate calorie balance during each stage of life—childhood, adolescence, adulthood, pregnancy and breastfeeding, and older age.

AN OBESOGENIC ENVIRONMENT

The overall environment in which many Americans now live, work, learn, and play has contributed to the obesity epidemic. Environment affects both sides of the calorie balance equation; many environments currently promote the overconsumption of calories and discourage physical activity and calorie expenditure. For example, many portion sizes offered for sale have increased in recent decades, and research has shown that when larger portion sizes are served, people tend to consume more calories. Also, since the 1970s, the number of fast food restaurants has more than doubled. Evidence shows that children, adolescents, and adults who eat out, particularly at fast food restaurants, are at an increased risk of weight gain, overweight, and obesity. As a result of the changing food environment, individuals need to deliberately make food choices, both at home and away from home, that are nutrient-dense, lower in calories, and appropriate in portion size. Similarly, many home, school, work, and community environments do not facilitate a physically active lifestyle; thus, many people today need to make a special effort to be physically active to meet physical activity needs.

Calorie Balance: Calories from Foods and Beverages

Controlling calorie intake from foods and beverages is fundamental to achieving and attaining calorie balance. The total number of calories consumed is the essential dietary factor relevant to body weight. The number of calories a person needs each day varies and depends on a number of factors, including the person's age, gender, height, weight, and level of physical activity. In addition, a desire to lose, maintain, or gain weight affects how many calories should be consumed. Estimated calorie needs (see Table 10.1) range from 1600 to 2400 cal/day for adult women and 2000 to 3000 cal/day for adult men. Calorie needs are lower for sedentary individuals than active individuals of the same age and gender. Also, due to reductions in basal metabolic rate that occurs with aging, calorie needs generally decrease for adults as they age. Estimated needs for young children range from 1000 to 2000 cal/day, and the range for older children and adolescents varies substantially from 1400 to 3200 cal/day, with boys generally having higher calorie needs than girls. These are only estimates, and the best way for people to assess whether they are eating the appropriate number of calories is to monitor body weight

TABLE 10.1
Estimated Calorie Needs per Day by Age, Gender, and Physical Activity Level[a]

		Physical Activity Level[b]		
Gender	**Age (Years)**	**Sedentary**	**Moderately Active**	**Active**
Child (female and male)	2–3	1000–1200[c]	1000–1400[c]	1000–1400[c]
Female[d]	4–8	1200–1400	1400–1600	1400–1800
	9–13	1400–1600	1600–2000	1800–2200
	14–18	1800	2000	2400
	19–30	1800–2000	2000–2200	2400
	31–50	1800	2000	2200
	51+	1600	1800	2000–2200
Male	4–8	1200–1400	1400–1600	1600–2000
	9–13	1600–2000	1800–2200	2000–2600
	14–18	2000–2400	2400–2800	2800–3200
	19–30	2400–2600	2600–2800	3000
	31–50	2200–2400	2400–2600	2800–3000
	51+	2000–2200	2200–2400	2400–2800

Notes: Estimated amounts of calories needed to maintain calorie balance for various gender and age groups at three different levels of physical activity. An individual's calorie needs may be higher or lower than these average estimates.

[a] Based on Estimated Energy Requirements (EER) equations, using reference heights (average) and reference weights (healthy) for each age/gender group. For children and adolescents, reference height and weight vary. For adults, the reference man is 5 ft 10 in. tall and weighs 154 lb. The reference woman is 5 ft 4 in. tall and weighs 126 lb. EER equations are from the Institute of Medicine (2002).

[b] Sedentary means a lifestyle that includes only the light physical activity associated with typical day-to-day life. Moderately active means a lifestyle that includes physical activity equivalent to walking about 1.5–3 miles/day at 3–4 miles/h, in addition to the light physical activity associated with typical day-to-day life. Active means a lifestyle that includes physical activity equivalent to walking more than 3 miles/day at 3–4 miles/h, in addition to the light physical activity associated with typical day-to-day life.

[c] The calorie ranges shown are to accommodate needs of different ages within the group. For children and adolescents, more calories are needed at older ages. For adults, fewer calories are needed at older ages.

[d] Estimates for females do not include women who are pregnant or breastfeeding.

and adjust calorie intake and participation in physical activity based on changes in weight over time. A calorie deficit of ≥500 cal/day is a common initial goal for adult weight loss. However, maintaining a smaller deficit can have a meaningful influence on body weight over time. The effect of a calorie deficit on weight does not depend on how the deficit is produced—by reducing calorie intake, increasing expenditure, or both.

Calorie Sources: Carbohydrate, Protein, Fat, and Alcohol

Carbohydrate, protein, and fat are the main sources of calories in the diet. Most foods and beverages contain combinations of these macronutrients in varying amounts. The Institute of Medicine (IOM) has established ranges for the *percentage of calories* in the diet that should come from carbohydrate, protein, and fat [7]:

- Young children (1–3 years): 45%–65% carbohydrate, 5%–20% protein, 30%–40% fat
- Older children (4–18 years): 45%–65% carbohydrate, 10%–30% protein, 25%–35% fat
- Adults (19 years and older): 45%–65% carbohydrate, 10%–35% protein, 20%–35% fat

These recommendations take into account both chronic disease risk reduction and intake of essential nutrients. Strong evidence shows that there is no optimal proportion of macronutrients that can facilitate weight loss or assist with maintaining weight loss; the critical issue is whether or not the eating pattern is reduced in calories and the individual is able to maintain this reduced calorie intake over time.

Alcohol is also a source of calories. Moderate evidence suggests that moderate drinking of alcoholic beverages* is not associated with weight gain. However, heavier than moderate consumption of alcohol over time is associated with weight gain. Reducing alcohol intake is a strategy that can be used by adults to consume fewer calories.

Individual Foods and Beverages and Body Weight

When total calorie intake is held constant, there is little evidence that any individual food groups or beverages have a unique impact on body weight. However, intake of some foods and beverages that are widely over- or underconsumed has been associated with effects on body weight. For example, strong evidence shows that children and adolescents who consume more sugar-sweetened beverages have higher body weight compared to those who drink less, and moderate evidence supports this relationship in adults. Also, moderate evidence among adults shows that increasing intake of whole grains, vegetables, and fruits may protect against weight gain. As individuals vary a great deal in their dietary intake, the best advice is to monitor dietary intake and replace foods higher in calories with nutrient-dense foods and beverages relatively lower in calories. Since body weight is not the only important factor to consider when making food and beverage choices, additional guidance on these foods and beverages is provided throughout the 2010 Dietary Guidelines.

Placing Individual Food Choices into an Overall Eating Pattern

Because people consume a variety of foods and beverages throughout the day as meals and snacks, a growing body of research has begun to describe overall eating patterns that promote calorie balance and weight management. The concept of eating patterns is the primary focus of the section entitled "Building Healthy Eating Patterns". One aspect of these patterns that has been researched in relation to body weight is the concept of calorie density, or the amount of calories provided per unit of food weight. Strong evidence shows that eating patterns that are low in calorie density improve weight loss and weight maintenance. Foods high in water and/or dietary fiber typically have fewer calories per gram and are lower in calorie density, while foods higher in fat are generally more calorie-dense. A dietary pattern low in calorie density is characterized by a relatively high intake of vegetables, fruit, and dietary fiber and a relatively low intake of total fat, saturated fat, and added sugars. Consuming an eating pattern low in calorie density may help to reduce calorie intake and improve body weight outcomes and overall health.

Calorie Balance: Physical Activity

Physical activity is the other side of the calorie balance equation and should be considered when addressing weight management. Additionally, participating in adequate amounts of physical activity conveys many health benefits independent of body weight. In 2008, HHS released the *2008 Physical Activity Guidelines for Americans* (Physical Activity Guidelines) [8], a comprehensive set of physical activity recommendations for Americans ages 6 years and older. The Physical Activity Guidelines include specific recommendations for various types of activity, including aerobic, muscle-strengthening, and bone-strengthening activities. Weight management, along with other outcomes, including premature death, diseases (such as coronary heart disease, type 2 diabetes, and osteoporosis), and risk factors for disease (such as high blood pressure and high blood cholesterol), were considered in developing the Physical Activity Guidelines.

The amount of physical activity necessary to successfully maintain a healthy body weight depends on calorie intake and varies considerably among adults, including older adults. To achieve and maintain a healthy body weight, adults should do at least the equivalent of 150 min of moderate-intensity aerobic activity[†] each week. If necessary, adults should

* Moderate alcohol consumption is the consumption of up to one drink per day for women and up to two drinks per day for men.

[†] Moderate-intensity physical activity is aerobic activity that increases a person's heart rate and breathing to some extent, while vigorous-intensity physical activity greatly increases a person's heart rate and breathing. One minute of vigorous-intensity physical activity counts as 2 min of moderate-intensity physical activity toward meeting the recommendations.

increase their weekly minutes of aerobic physical activity gradually over time and decrease calorie intake to a point where they can achieve calorie balance and a healthy weight. Some adults may need to participate in more than the equivalent of 300 min/week of moderate-intensity activity to meet weight control goals.

For children and adolescents ages 6 years and older, 60 min or more of physical activity per day is recommended. Although the Physical Activity Guidelines do not include a specific quantitative recommendation for children ages 2–5 years, young children should play actively several times each day. Children and adolescents are often active in short bursts of time rather than for sustained periods of time, and these short bursts can add up to meet physical activity needs. Physical activities for children and adolescents of all ages should be developmentally appropriate and enjoyable, and should offer variety. Additional information on the Physical Activity Guidelines, including materials for consumers, is available at www.health.gov/paguidelines

Principles for Promoting Calorie Balance and Weight Management

To address the current calorie imbalance in the United States, individuals are encouraged to become more conscious of what they eat and what they do. This means increasing awareness of what, when, why, and how much they eat, deliberately making better choices regarding what and how much they consume, and seeking ways to be more physically active. Several behaviors and practices have been shown to help people manage their food, beverage intake, and calorie expenditure and ultimately manage body weight. The behaviors with the strongest evidence related to body weight include

- *Monitor food intake*. Monitoring intake has been shown to help individuals become more aware of what and how much they eat and drink. The Nutrition Facts label found on food packaging provides calorie information for each serving of food or beverage and can assist consumers in monitoring their intake. Also, monitoring body weight and physical activity can help prevent weight gain and improve outcomes when actively losing weight or maintaining body weight following weight loss.
- *When eating out, choose smaller portions or lower calorie options.* When possible, individuals are encouraged to order a small-sized option, share a meal, or take home part of the meal. By reviewing the calorie content of foods and beverages offered, individuals can choose lower calorie options. Calorie information may be available on menus, in a pamphlet, on food wrappers, or online. Or, instead of eating out, individuals can cook and eat more meals at home, where they can control what and how foods are prepared.
- *Prepare, serve, and consume smaller portions of foods and beverages, especially those high in calories.* Individuals eat and drink more when provided larger portions. Serving and consuming smaller portions is associated with weight loss and weight maintenance over time.
- *Eat a nutrient-dense breakfast*. Not eating breakfast has been associated with excess body weight. Consuming breakfast also has been associated with weight loss and weight loss maintenance, as well as improved nutrient intake.
- *Limit screen time*. In children, adolescents, and adults, screen time, especially television viewing, is directly associated with increased overweight and obesity. Children and adolescents are encouraged to spend no more than 1–2 h each day watching television, playing electronic games, or using the computer (other than for homework). Also, eating while watching television can result in overeating.

Although obesity is related to many chronic health conditions, it is not the only lifestyle-related public health problem confronting the nation. Eating patterns that are high in calories, but low in nutrients can leave a person overweight but malnourished. Nutritionally unbalanced diets and a sedentary lifestyle can negatively affect a person's health regardless of weight status. Improved eating patterns and increased physical activity have numerous health benefits beyond maintaining a healthy weight.

FOODS AND FOOD COMPONENTS TO REDUCE

Recommendations to reduce intake of certain foods and food components were developed after consideration of the current dietary intake of Americans in relation to research on chronic disease risk associated with overconsumption of these foods and food components. As such, this section of the 2010 Dietary Guidelines focuses on particular foods and food components that are currently consumed by Americans in excessive amounts and may increase the risk of certain chronic diseases. Many children, adolescents, adults, and older adults currently overconsume sodium, solid fats (major sources of saturated and *trans*-fatty acids), added sugars, and refined grains. In addition, the diets of most men exceed the recommendation for cholesterol, and some people consume too much alcohol.

This excessive intake replaces nutrient-dense forms of food in the diet, making it difficult for people to achieve recommended nutrient intake and control calorie intake. Many Americans are overweight or obese and are at a higher risk of chronic diseases such as cardiovascular disease, diabetes, and certain types of cancer. Even in the absence of overweight or obesity, consuming too much of the previously mentioned foods and food components increases the risk of some of the most common chronic diseases in the United States. The recommendations in this section are based on evidence that eating less of these foods and food components

can help Americans reduce their chronic disease risk, while meeting their nutritional needs and staying within appropriate calorie ranges.

Key Recommendations

- Reduce daily sodium intake to less than 2300 mg and further reduce intake to 1500 mg among persons who are 51 and older and those of any age who are African American or have hypertension, diabetes, or chronic kidney disease. The 1500 mg recommendation applies to about half of the U.S. population, including children and the majority of adults.
- Consume less than 10% of calories from saturated fatty acids by replacing them with monounsaturated and polyunsaturated fatty acids.
- Consume less than 300 mg/day of dietary cholesterol.
- Keep *trans*-fatty acid consumption as low as possible, especially by limiting foods that contain synthetic sources of *trans*-fats, such as partially hydrogenated oils, and by limiting other solid fats.
- Reduce the intake of calories from solid fats and added sugars.
- Limit the consumption of foods that contain refined grains, especially refined grain foods that contain solid fats, added sugars, and sodium.
- If alcohol is consumed, it should be consumed in moderation—up to one drink per day for women and two drinks per day for men—and only by adults of legal drinking age.

Sodium

Sodium is an essential nutrient and is needed by the body in relatively small quantities. On average, the higher an individual's sodium intake, the higher the individual's blood pressure. A strong body of evidence in adults documents that as sodium intake decreases, so does blood pressure. Moderate evidence in children also has documented that as sodium intake decreases, so does blood pressure. Since keeping blood pressure in the normal range reduces an individual's risk of cardiovascular disease, congestive heart failure, and kidney disease, adults and children should limit their intake of sodium. However, virtually all Americans consume far too much sodium. While the IOM has defined the tolerable upper intake level (UL) for sodium to be 2300 mg/day [9], the estimated average intake for all Americans ages 2 years and older is closer to 3400 mg/day. Most of this sodium comes from salt added during food processing.

The 2010 Dietary Guidelines emphasize the importance of sodium reduction, in light of emerging evidence on sodium and blood pressure in children as well as updated data on the percentage of the population at high risk for sodium-related health consequences. Americans should reduce their sodium intake to less than 2300 or to 1500 mg/day, depending on age and other characteristics. African Americans; individuals with hypertension, diabetes, or chronic kidney disease; and individuals ages 51 years and older comprise about half of the U.S. population ages 2 years and older. While nearly everyone benefits from reducing their sodium intake, the blood pressure of these individuals tends to be particularly responsive to the hypertensive effects of sodium; therefore, these groups should reduce their intake to 1500 mg/day.

Fats

Fats supply calories and essential fatty acids and help in the absorption of the fat-soluble vitamins A, D, E, and K. The IOM established acceptable ranges for total fat intake, as a percentage of calories, among children and adults (ages 1–3 years: 30%–40%; ages 4–18 years: 25%–35%; ages 19 and older: 20%–35%), which provide adequate intake of essential nutrients while not elevating risk of cardiovascular disease [7]. The most recent data indicate that total fat intake contributes an average of 34% of calories in Americans' diets. Fatty acids are categorized as being saturated, monounsaturated, or polyunsaturated; *trans*-fatty acids and cholesterol are particular types of fat commonly targeted in disease-prevention efforts. The types of fatty acids consumed are more important in influencing the risk of cardiovascular disease than is the total amount of fat in the diet.

Saturated fatty acids. A strong body of evidence indicates that higher intake of most dietary saturated fatty acids is associated with higher levels of blood total cholesterol and low-density lipoprotein (LDL) cholesterol. Consuming less than 10% of calories from saturated fatty acids *and* replacing them with monounsaturated and/or polyunsaturated fatty acids is associated with low blood cholesterol levels and lower risk of cardiovascular disease. Lowering the percentage even more, to 7% of calories, can further reduce risk. Americans currently consume an average of 11% of their calories from saturated fatty acids.

trans-fatty acids. trans-fatty acids can be either naturally occurring ("natural" or "ruminant") or formed during food processing ("synthetic" or "industrial") by the process of hydrogenation. *trans*-fatty acids have been associated with increased risk of cardiovascular disease, due in part to an LDL-cholesterol raising effect. There is limited evidence to conclude whether synthetic and natural *trans*-fatty acids differ in their metabolic effects and health outcomes. Americans are advised to keep their intake of *trans*-fats as low as possible; however, the complete elimination of natural *trans*-fatty acids (e.g., in low-fat milk and lean meats) is not recommended because of the potential implications for nutrient adequacy. Levels of synthetic *trans*-fats in the food supply have been significantly reduced due to public health measures in recent years.

Cholesterol. Cholesterol is produced by the body in quantities sufficient for necessary structural and physiological functions; therefore, dietary cholesterol is unnecessary. Cholesterol from

food sources has been shown to raise blood LDL-cholesterol levels in some individuals, and moderate evidence shows a relationship between higher intake of cholesterol and increased risk of cardiovascular disease. However, the potential negative effects of dietary cholesterol are relatively small compared to those of saturated and *trans*-fatty acids. Consuming less than 300 mg/day of dietary cholesterol can help maintain normal blood cholesterol levels; consuming less than 200 mg/day can further help individuals already at high risk of cardiovascular disease. Currently, cholesterol intake among American men exceeds these recommendations, averaging 350 mg/day; average intake among women is 240 mg/day.

Added Sugars

Fructose and lactose are examples of naturally occurring sugars that are found in foods such as fruits and milk; however, the majority of sugars in the typical American diet are sugars that are added to foods during processing, preparation, or at the table. Unlike most foods that contain naturally occurring sugars, often, foods that contain *added* sugars supply calories but few or no essential nutrients. Currently, added sugars contribute an average of 16% of the total calories in American diets; the predominant source is sugar-sweetened beverages (e.g., soda, energy drinks, sports drinks). Reducing the consumption of added sugars will lower the calorie content of the diet without compromising its nutrient adequacy; this is an important measure in terms of achieving and maintaining a healthy weight.

[SIDEBAR:] Interestingly, solid fats and added sugars together comprise a substantial portion of the calories regularly consumed by Americans—nearly 800 cal/day—without a marked contribution to the overall nutrient adequacy of the diet. Foods containing solid fats and added sugars are no more likely to contribute to weight gain than any other sources of calories; however, as the amount of solid fats and/or added sugars increases in the diet, it becomes more difficult to attain sufficient dietary fiber and essential vitamins and minerals while staying within calorie limits. Of course, solid fats and added sugars also push many Americans' diets above required caloric levels.

Refined Grains

Grains are consumed either as whole grains or as refined grains. The refining of whole grains involves a process that results in the loss of vitamins, minerals, and dietary fiber. Most refined grains are enriched with iron, thiamin, riboflavin, niacin, and folic acid before entering the marketplace; however, this enrichment does not return all naturally occurring nutrients and fiber to the grains. Unlike solid fats and added sugars, enriched refined grain products have a positive role in providing some vitamins and minerals. When consumed beyond recommended levels, though, they commonly provide excess calories in the typical American diet. Although Americans generally eat enough total grains, most of the grains consumed are refined grains rather than whole grains. Refined grains should be replaced with whole grains, such that at least half of all grains consumed are whole grains. In particular, consumption of refined grain products that are also high in solid fats and/or added sugars (e.g., cakes, cookies, donuts) should be targeted for reduction.

Alcohol

The consumption of alcohol can have beneficial or harmful effects, depending on the amount consumed, age, and other characteristics of the person consuming the alcohol. Strong evidence from observational studies has shown that moderate alcohol consumption is associated with a lower risk of cardiovascular disease. Moderate consumption is defined as up to one drink per day for women and up to two drinks per day for men. Moderate alcohol consumption is also associated with reduced risk of all-cause mortality among middle-aged and older adults and may help to keep cognitive functioning intact with age. However, it is not recommended that anyone begin drinking or drink more frequently on the basis of potential health benefits because moderate alcohol intake is also associated with increased risk of breast cancer, violence, drowning, and injuries from falls and motor vehicle crashes.

Excessive (i.e., heavy, high-risk, or binge) drinking has no benefits but increases the risk of cirrhosis of the liver, hypertension, stroke, type 2 diabetes, cancer of the upper gastrointestinal track and colon, injury, auto-accidents, and violence. Further, excessive drinking over time is associated with increased body weight and can impair short- and long-term cognitive function. The 2010 Dietary Guidelines recommend that adults of legal drinking age not exceed moderate intake levels.

For the first time, the 2010 Dietary Guidelines provide information on alcohol consumption among lactating women. Evidence suggests that breastfeeding mothers may consume a single alcoholic beverage if she then waits at least 4 h before breastfeeding, provided that the infant's breastfeeding behavior is well established, consistent, and predictable (no earlier than 3 months of age). This information was included because of the substantial evidence clearly demonstrating the health benefits of breastfeeding and the concern that women may stop breastfeeding in order to occasionally consume an alcoholic beverage.

FOODS AND NUTRIENTS TO INCREASE

This section of the 2010 Dietary Guidelines describes food choices that should be emphasized to help Americans close nutrient gaps and move toward healthful eating patterns. Recommendations related to foods and nutrients to increase were made after examination of the current dietary intake of Americans in relation to nutrient needs as well as research on the particular foods or nutrients (i.e., the health benefits of consumption or the public health concern related to inadequate intake). Many Americans do not eat the array of foods that will provide all needed nutrients while staying within calorie needs.

This section highlights general recommendations to increase intake of certain food groups by replacing foods and

beverages currently consumed with more nutritious choices. More specific quantitative guidance is discussed in the section titled "Building Healthy Eating Patterns."

Key Recommendations

Individuals should meet the following recommendations as part of a healthy eating pattern and while staying within their calorie needs:

- Increase vegetable and fruit intake.
- Eat a variety of vegetables, especially dark-green and red and orange vegetables and beans and peas.
- Consume at least half of all grains as whole grains. Increase whole-grain intake by replacing refined grains with whole grains.
- Increase intake of fat-free or low-fat milk and milk products, such as milk, yogurt, cheese, or fortified soy beverages.
- Choose a variety of protein foods, which include seafood, lean meat and poultry, eggs, beans and peas, soy products, and unsalted nuts and seeds.
- Increase the amount and variety of seafood consumed by choosing seafood in place of some meat and poultry.
- Replace protein foods that are higher in solid fats with choices that are lower in solid fats and calories and/or are sources of oils.
- Use oils to replace solid fats where possible.
- Choose foods that provide more potassium, dietary fiber, calcium, and vitamin D, which are nutrients of concern in American diets. These foods include vegetables, fruits, whole grains, and milk and milk products.

Recommendations for Specific Population Groups

Women capable of becoming pregnant:

- Choose foods (such as meats) that supply heme iron, which is more readily absorbed by the body than nonheme iron, additional iron sources, and enhancers of iron absorption such as vitamin C-rich foods.
- Consume 400 mcg/day of synthetic folic acid (from fortified foods and/or supplements) in addition to food forms of folate from a varied diet.

Women who are pregnant or breastfeeding:

- Consume 8–12 oz of seafood per week from a variety of seafood types.
- Due to their methyl mercury content, limit white (albacore) tuna to 6 oz/week and do not eat the following four types of fish: tilefish, shark, swordfish, and king mackerel.
- If pregnant, take an iron supplement as recommended by an obstetrician or other health care provider.

Individuals ages 50 years and older:

- Consume foods fortified with vitamin B_{12}, such as fortified cereals, or dietary supplements.

Vegetables and Fruits

The recommendation for Americans to eat more vegetables and fruits is supported by three main facts. First, most vegetables and fruits are major contributors of a number of nutrients that are underconsumed in the United States, including folate, magnesium, potassium, dietary fiber, and vitamins A, C, and K. Second, consumption of vegetables and fruits is associated with reduced risk of many chronic diseases. Specifically, moderate evidence indicates that intake of at least 2½ cups of vegetables and fruits per day is associated with a reduced risk of cardiovascular disease, including heart attack and stroke. Additionally, some vegetables and fruits may be protective against certain types of cancer. Third, most vegetables and fruits, when prepared without added fats or sugars, are relatively low in calories. Eating them instead of higher calorie foods can help adults and children achieve and maintain a healthy weight.

Very few Americans ages 2 years and older consume the amounts of vegetables recommended as part of healthy eating patterns. Similarly, although most Americans 2–3 years of age consume recommended amounts of total fruits, most Americans ages 4 years and older do not. Children ages 2–18 years and adults ages 19–30 years consume more than half of their fruit intake as juice. Although 100% fruit juice can be part of a healthful diet, it lacks dietary fiber and can contribute extra calories when consumed in excess. The majority of the fruit recommended should come from whole fruits, including fresh, canned, frozen, and dried forms, rather than from juice. When juices are consumed, 100% juice should be encouraged.

Grains

Whole grains are a source of nutrients such as iron, magnesium, selenium, B vitamins, and dietary fiber. Moderate evidence indicates that whole-grain intake may reduce the risk of cardiovascular disease and is associated with a lower body weight. Limited evidence also shows that consuming whole grains is associated with a reduced incidence of type 2 diabetes. Consuming enough whole grains helps one meet his or her nutrient needs. Additional health benefits are offered by whole grains that are higher in fiber.

At least half of recommended total grain intake should be whole grains. Less than 5% of Americans consume the minimum recommended amount of whole grains, which for many is about 3 oz-eq/day. On average, Americans eat less than 1 oz-eq of whole grains per day.

Americans should aim to replace many refined grain foods with whole-grain foods in their nutrient-dense forms (i.e., few added sugars or fats) to keep total calorie intake within limits. Individuals may choose to consume more than half of their grains as whole grains.

Milk and Milk Products

Milk and milk products (also known as dairy products) contribute many nutrients, such as calcium, vitamin D (for products fortified with vitamin D), and potassium, to the diet. Moderate evidence shows that intake of milk and milk products is linked to improved bone health, especially in children and adolescents. Moderate evidence also indicates that intake of milk and milk products is associated with a reduced risk of cardiovascular disease and type 2 diabetes and with lower blood pressure in adults.

Intake of milk and milk products, including fortified soy beverages, is less than the recommended amounts for most adults, children, and adolescents ages 4–18 years, and many children ages 2–3 years. The majority of current fluid milk intake comes from reduced fat (2%) or whole (full-fat) milk, with smaller amounts consumed as fat-free (skim) or low-fat (1%) milk. Cheese, little of which is consumed in a lower fat form, comprises almost half of the dairy intake in the United States. Choosing fat-free or low-fat milk and milk products should be encouraged because they provide the same nutrients with less fat and thus fewer calories.

Protein Foods

Protein foods include seafood, meat, poultry, eggs, beans and peas, soy products, nuts, and seeds. In addition to protein, these foods contribute B vitamins (e.g., niacin, thiamin, riboflavin, and B_6), vitamin E, iron, zinc, and magnesium to the diet. However, protein is also found in some foods that are classified in other food groups (e.g., milk and milk products).

Some Americans need to increase their total intake of protein foods, while others are eating more than is recommended. Americans should consume protein foods in amounts recommended for their nutrient and calorie needs. Meat, poultry, and eggs are the most commonly consumed protein foods, while seafood, beans and peas, soy products, nuts, and seeds are consumed in proportionally smaller amounts. The fats in meat, poultry, and eggs are considered solid fats, while the fats in seafood, nuts, and seeds are considered oils. Meat and poultry should be consumed in lean forms to decrease intake of solid fats.

In recent years, evidence has emerged about the health benefits of consuming seafood. Therefore, the 2010 Dietary Guidelines include a new quantitative recommendation for seafood intake. An intake of 8 or more ounces per week (less for young children) of a variety of seafood is recommended; this represents approximately 20% of recommended intake of protein foods. Seafood contributes a range of nutrients, notably the omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Moderate evidence shows that consumption of about 8 oz/week of a variety of seafood, which provide an average consumption of 250 mg/day of EPA and DHA, is associated with reduced cardiac deaths among individuals with and without preexisting cardiovascular disease.

Moderate, consistent evidence shows that the health benefits from consuming a variety of seafood in the amounts recommended outweigh the health risks associated with methyl mercury, a heavy metal found in seafood in varying levels. Eating a variety of seafood, as opposed to just a few choices, is likely to reduce the amount of methyl mercury consumed from any one seafood type. Seafood varieties that are commonly consumed in the United States are higher in EPA and DHA and lower in mercury including salmon, anchovies, herring, sardines, Pacific oysters, and trout.

In addition to the health benefits for the general public, the nutritional value of seafood is of particular importance during fetal growth and development, as well as in early infancy and childhood. Moderate evidence indicates that intake of omega-3 fatty acids, in particular DHA, from at least 8 oz of seafood per week for women who are pregnant or breastfeeding is associated with improved infant health outcomes, such as visual and cognitive development. Therefore, it is recommended that women who are pregnant or breastfeeding consume at least 8 and up to 12 oz of a variety of seafood per week, from choices that are lower in methyl mercury. Women who are pregnant or breastfeeding should not eat tilefish, shark, swordfish, and king mackerel because they are high in methyl mercury. Women who are pregnant or breastfeeding can eat all types of tuna, including white (albacore) and light canned tuna, but should limit white tuna to 6 oz/week because of methyl mercury content.

Oils

Fats with a high percentage of monounsaturated and polyunsaturated fatty acids are usually liquid at room temperature and are referred to as "oils." Oils are not a food group, but are emphasized because they contribute essential fatty acids and vitamin E to the diet.

Oils are naturally present in foods such as olives, nuts, avocados, and seafood. Many common oils are extracted from plants, such as canola, corn, olive, peanut, safflower, soybean, and sunflower oils. Foods that are mainly oil include mayonnaise, oil-based salad dressings, and soft (tub or squeeze) margarine with no *trans*-fatty acids. Coconut oil, palm kernel oil, and palm oil are high in saturated fatty acids and partially hydrogenated oils contain *trans*-fatty acids and, thus, are considered solid fats.

Americans consume more solid fats (saturated and *trans*) but less oil than is desirable. Replacing some saturated fatty acids (such as those in solid fats) with unsaturated fatty acids (such as those in oils) lowers both total and LDL blood cholesterol levels. Oils are a concentrated source of calories; therefore, Americans should replace solid fats with oils, rather than add oil to the diet, and should use oils in small amounts.

Nutrients of Concern

Because consumption of vegetables, fruits, whole grains, milk and milk products, and seafood is lower than recommended, intake by Americans of some nutrients is low enough to be

of public health concern. These are potassium, dietary fiber, calcium, and vitamin D. In addition, intake of iron, folate, and vitamin B_{12} is of concern for specific population groups.

Potassium. The recommended intake level for potassium ranges from 3000 to 5100 mg/day, depending on age and lactation status; the general recommendation for adults is 4700 mg/day [9]. Dietary potassium can lower blood pressure by blunting the adverse effects of sodium on blood pressure. Other possible benefits of an eating pattern rich in potassium include a reduced risk of developing kidney stones and decreased bone loss. Dietary sources of potassium are found in all food groups, notably in vegetables, fruits, and milk and milk products. Americans should select a variety of food sources of potassium to meet recommended intake rather than relying on supplements.

Dietary fiber. The recommended intake level for fiber is 14 g/1000 cal for all ages [7]. Dietary fiber is the nondigestible form of carbohydrates and lignin. Dietary fiber naturally occurs in plants, helps provide a feeling of fullness, and is important in promoting healthy laxation. Some of the best sources of dietary fiber are beans and peas, such as navy beans, split peas, lentils, pinto beans, and black beans. Additional sources of dietary fiber include other vegetables, fruits, whole grains, and nuts. Bran, although not a whole grain, is an excellent source of dietary fiber. Dietary fiber that occurs naturally in foods may help reduce the risk of cardiovascular disease, obesity, and type 2 diabetes. Children and adults should consume foods naturally high in dietary fiber in order to increase nutrient density, promote healthy lipid profiles and glucose tolerance, and ensure normal gastrointestinal function. Fiber is sometimes added to foods, although it is unclear if added fiber provides the same health benefits as naturally occurring sources.

Calcium. Individuals of all ages are encouraged to meet their Recommended Dietary Allowance (RDA) for calcium [10]. The RDAs for calcium range from 700 to 1300 mg for children and from 1000 to 1200 mg for adults. Adequate calcium status is important for optimal bone health. In addition, calcium serves vital roles in nerve transmission, constriction and dilation of blood vessels, and muscle contraction. Milk and milk products contribute substantially to calcium intake by Americans. Calcium recommendations may be achieved by consuming recommended levels of fat-free or low-fat milk and milk products and/or consuming alternative calcium sources. Removing milk and milk products from the diet requires careful replacement with other food sources of calcium, including fortified foods. Calcium in some plant foods is well absorbed, but consuming enough plant foods to achieve the RDA may be unrealistic for many.

Vitamin D. Adequate vitamin D status is important for health. The dominant function of vitamin D, in the form of the active metabolite, calcitriol, is its involvement in the regulation of serum calcium and phosphate homeostasis and, subsequently, the development and maintenance of bone health. Vitamin D is unique in that sunlight on the skin enables the body to make vitamin D. The RDAs for vitamin D, which assume minimal sun exposure, are 600 IU (15 mcg)/day for children and most adults and 800 IU (20 mcg) for adults older than 70 years [10]. In the United States, most dietary vitamin D is obtained from fortified foods, especially fluid milk and some yogurts. Some other foods and beverages, such as breakfast cereals, margarine, orange juice, and soy beverages, are also commonly fortified with vitamin D. Natural sources of vitamin D include some kinds of fish (e.g., salmon and tuna) and egg yolks, which have smaller amounts. It is also available in the form of dietary supplements. Although dietary intakes of vitamin D are below recommendations, recent data from the National Health and Nutrition Examination Survey (NHANES) indicate that more than 80% of Americans have adequate vitamin D blood levels. As intake increases above 4000 IU (100 mcg)/day, the potential risk of adverse effects increases.

Additional Nutrients of Concern for Specific Groups

- *Iron*: Iron is a component of a number of proteins, including hemoglobin, and thus, is important for the transport of oxygen to body tissues. Substantial numbers of women who are capable of becoming pregnant, including adolescent girls, are deficient in iron. They can improve their iron status by choosing foods that supply heme or nonheme iron; heme iron is more easily absorbed by the body. Sources of heme iron include lean meat and poultry, and seafood. Additional iron sources are nonheme iron in plant foods, such as white beans, lentils, and spinach, as well as foods enriched with iron, such as most breads and cereals. Absorption of nonheme iron can be increased by iron enhancers, such as vitamin C-rich foods. Women who are pregnant are advised to take an iron supplement as recommended by an obstetrician or other health care provider.
- *Folate*: Folic acid fortification of grain products in the United States has been successful in reducing the incidence of neural tube defects. However, many women capable of becoming pregnant still do not meet the recommended intake for folic acid. Dietary sources of folate include beans and peas, oranges and orange juice, and dark-green leafy vegetables such as spinach and mustard greens. Women who are capable of becoming pregnant are encouraged to consume synthetic folic acid (from fortified foods and/or supplements) in addition to food forms of folate from a varied diet.
- *Vitamin B_{12}*: Vitamin B_{12} is a cofactor for enzymes needed to support blood formation and neurological function. On average, Americans ages 50 years and older consume adequate vitamin B_{12}. Nonetheless, a substantial proportion of individuals ages 50 years and older may have reduced ability to absorb naturally occurring vitamin B_{12}. The crystalline form of the vitamin is well absorbed; therefore, individuals ages 50 years and older are encouraged to include foods fortified with vitamin B_{12}, such as fortified cereals, or take dietary supplements.

BUILDING HEALTHY EATING PATTERNS

The purpose of this section of the 2010 Dietary Guidelines is to integrate individual recommendations from previous sections into overall healthy eating patterns. An eating pattern is the combination of foods and beverages that constitute an individual's complete dietary intake over time. Many eating patterns have been associated with health benefits, and their variety demonstrates that people can eat healthfully in a number of ways.

Key Recommendations

- Select an eating pattern that meets nutrient needs over time at an appropriate calorie level.
- Account for all foods and beverages consumed and assess how they fit within a total healthy eating pattern.
- Follow food safety recommendations when preparing and eating foods to reduce the risk of foodborne illnesses.

Common Elements of Healthy Eating Patterns

The study of eating patterns is complex, but evidence from international scientific research has identified various eating patterns that may provide short- and long-term health benefits, including a reduced risk of chronic disease. Among the eating patterns with supporting evidence are the Dietary Approaches to Stop Hypertension (DASH) eating pattern, Mediterranean-style eating patterns, and various vegetarian eating patterns. Although healthy eating patterns around the world are diverse, some common threads exist. They are abundant in vegetables and fruits. Many emphasize whole grains. They include moderate amounts and a variety of foods high in protein (seafood, beans and peas, nuts, seeds, soy products, meat, poultry, and eggs). They include only limited amounts of foods high in added sugars. Most are low in full-fat milk and milk products; however, some include substantial amounts of low-fat milk and milk products. Compared to typical American diets, these patterns tend to have a high unsaturated to saturated fatty acid ratio, high dietary fiber and potassium content, and are relatively low in sodium.

Average eating patterns among Americans currently bear little resemblance to recommendations. Figure 10.1 graphically shows how the typical American diet compares to recommended intakes or limits. Americans eat too many calories and too much solid fat, added sugars, refined grains, and sodium. Americans also consume too little potassium; dietary fiber; calcium; vitamin D; unsaturated fatty acids from oils, nuts, and seafood; and other important nutrients. These nutrients are mostly found in vegetables, fruits, whole grains, and low-fat milk and milk products.

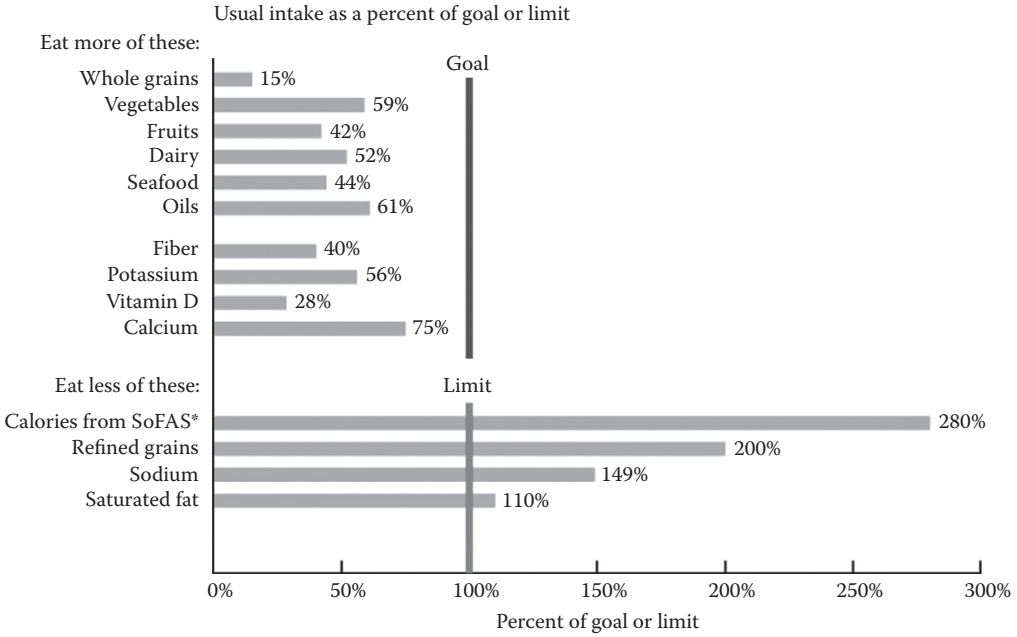


FIGURE 10.1 How do typical American diets compare to recommended intake levels or limits? *SoFAS, solid fats and added sugars. *Note*: Bars show average intakes for all individuals (ages 1 or 2 years or older, depending on the data source) as a percent of the recommended intake level or limit. Recommended intakes for food groups and limits for refined grains and solid fats and added sugars are based on amounts in the USDA 2000 cal food pattern. Recommended intakes for fiber, potassium. vitamin D, and calcium are based on the highest AI or RDA for ages 14–70 years. Limits for sodium are based on the UL and for saturated fat on 10% of calories. The protein foods group is not shown here because on average intake is close to recommended levels. (Based on data from U.S. Department of Agriculture, Agricultural Research Service and U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. What We Eat in America. NHANES 2001–2004 or 2005–2006.)

Principles for Achieving a Healthy Eating Pattern

A healthy eating pattern is not a rigid prescription, but rather an array of options that can accommodate cultural, ethnic, traditional, and personal preferences and food cost and availability. Americans have flexibility in making choices to create a healthy eating pattern that meets nutrient needs and stays within calorie limits. The following are principles that can assist individuals in achieving a healthy eating pattern:

1. *Focus on nutrient-dense foods*—Nutrient-dense foods include vegetables, fruits, whole grains, fat-free or low-fat milk and milk products, lean meats and poultry, seafood, eggs, beans and peas, and nuts and seeds that are prepared without added solid fats, sugars, starches, and sodium. Combined into an eating pattern, these foods can provide the full range of essential nutrients and fiber, without excessive calories.
2. *Reduce intake of calories from solid fats and added sugars*—Most people's eating patterns can accommodate only a limited number of calories from solid fats and added sugars. These calories are best used to increase the palatability of nutrient-dense foods (i.e., adding a small amount of flavored syrup to fat-free milk) rather than to consume foods or beverages that are primarily solid fats, added sugars, or both.
3. *Remember that beverages count*—Beverages contribute substantially to overall dietary and calorie intake for most Americans. Their consumption should be planned in the context of total calorie intake and how they can fit into the eating pattern of each individual. The calorie content of beverages varies widely, and some of the beverages with the highest intake, including regular sodas, fruit drinks, and alcoholic beverages, contain calories but provide few or no essential nutrients. Other beverages, however, such as fat-free or low-fat milk and 100% fruit juice, provide a substantial amount of nutrients along with the calories they contain. Water and unsweetened beverages contribute to total water intake without adding calories. To limit excess calories and maintain healthy weight, individuals are encouraged to drink water and other beverages with few or no calories, in addition to recommended amounts of low-fat or fat-free milk and 100% fruit juices.
4. *Follow food safety principles*—Ensuring food safety is an important principle for building healthy eating patterns. The four basic food safety principles that work together to reduce the risk of foodborne illnesses are
   a. *Clean* hands, food contact surfaces, and vegetables and fruits.
   b. *Separate* raw, cooked, and ready-to-eat foods while shopping, storing, and preparing foods.
   c. *Cook* foods to a safe temperature.
   d. *Chill* (refrigerate) perishable foods promptly.

   In addition, some foods pose high risk of foodborne illness. These include raw (unpasteurized) milk, cheeses, and juices; raw or undercooked animal foods, such as seafood, meat, poultry, and eggs; and raw sprouts. These foods should be avoided.
5. *Consider the role of supplements and fortified foods*—A fundamental premise of the Dietary Guidelines is that nutrients should come primarily from foods. Dietary supplements or fortification of certain foods may be advantageous to increase intake of a specific vitamin or mineral. In some cases, fortification can provide a food-based means for increasing intake of particular nutrients or providing nutrients in highly bioavailable forms. Examples include vitamin D, folic acid, vitamin B_{12}, and iron.

Sufficient evidence is not available to support a recommendation for or against the use of multivitamin/mineral supplements in the primary prevention of chronic disease for the healthy American population. Supplements containing combinations of certain nutrients may be beneficial in reducing the risks of some chronic diseases when used by special populations. For example, calcium and vitamin D supplements may be useful in postmenopausal women who have low levels of these nutrients in their diets, to reduce their risk of osteoporosis. In contrast, high levels of certain nutrient supplements may be harmful.

Putting the Principles for a Healthy Eating Pattern into Action

The 2010 Dietary Guidelines provide healthy eating templates that can be used or adapted to suit individual and cultural preferences. The illustrations of varied approaches to healthy eating that are provided include the USDA Food Patterns (with lacto–ovo vegetarian or vegan adaptations) and the DASH Eating Plan. These eating patterns apply the Dietary Guidelines recommendations and provide flexible templates for making healthy choices within and among various food groups. They include recommended amounts from all food groups, targets for total calorie intake, and limits on calories from solid fats and added sugars.

USDA Food Patterns

The USDA Food Patterns identify daily amounts of foods, in nutrient-dense forms, to eat from five major food groups and their subgroups. The patterns also include an allowance for oils and limits on the maximum number of calories that should be consumed from solid fats and added sugars. The food patterns were developed to meet nutrient needs, as identified by the Dietary Reference Intakes and the Dietary Guidelines, while not exceeding calorie requirements.

Recommended amounts and limits in the USDA Food Patterns are provided at 12 cal levels, ranging from 1000 to

3200 cal. Individuals should follow a pattern that meets their estimated calorie needs. Patterns at 1000, 1200, and 1400 cal levels meet the nutritional needs of children ages 2–8 years. Patterns at 1600 cal and above meet needs for adults and children ages 9 years and older. A sample USDA Food Pattern at the 2000 cal level is provided in Table 10.2. Additionally, Appendix 7 of the 2010 Dietary Guidelines provides recommendations for the remaining calorie levels.

The USDA Food Patterns recommend selecting a variety of foods within each food group. This allows for personal choice, and helps to ensure that the foods and beverages selected by individuals over time provide a mix of nutrients that will meet their needs. Recommended weekly intake amounts are specified for the five vegetable subgroups (dark-green, red and orange, beans and peas, starchy, and other vegetables). In the protein foods group, ≥8 oz/week of seafood is recommended (less in patterns for young children), and in the grain group, selecting at least half of all grains as whole grains is recommended. In the fruit and dairy groups, there are no quantitative recommendations for making selections within the group. However, selecting more fruit rather than juice, and more fat-free or low-fat vitamin D-fortified milk or yogurt than cheese is encouraged.

Vegetarian Adaptations of the USDA Food Patterns

The types of vegetarian diets consumed in the United States vary widely. Vegans do not consume any animal products, while lacto–ovo vegetarians consume milk and eggs. Some individuals eat diets that are primarily vegetarian but may include small amounts of meat, poultry, or seafood. The USDA Food Patterns allow for additional flexibility in choices through their adaptations for vegetarians—a vegan pattern that contains only plant foods (Appendix 9 of the 2010 Dietary Guidelines) and a

TABLE 10.2
Sample USDA Food Pattern at the 2000 cal Level

Food Group or Subgroup	Amount	Description (All Foods Are Assumed to Be in Nutrient-Dense Forms, Lean or Low-Fat, and Prepared without Added Fats, Sugars, or Salt)
Fruits[a]	2 c	All fresh, frozen, canned, and dried fruits and fruit juices
Vegetables[a]	2½ c	All fresh, frozen, and canned vegetables and vegetable juices
Dark-green vegetables	1½ c/week	Examples: broccoli, spinach, romaine, and collard, turnip, and mustard greens
Red and orange vegetables	5½ c/week	Examples: tomatoes, red peppers, carrots, sweet potatoes, winter squash, and pumpkin
Beans and peas (legumes)	1½ c/week	Examples: kidney beans, lentils, chickpeas, and pinto beans (does not include green beans/peas)
Starchy vegetables	5 c/week	Examples: white potatoes, corn, and green peas
Other vegetables	4 c/week	Examples: iceberg lettuce, green beans, and onions
Grains[b]	6 oz-eq	All grain products and grains used as ingredients
Whole grains	3 oz-eq	Examples: whole-wheat bread, whole-grain cereals and crackers, oatmeal, and brown rice
Enriched grains	3 oz-eq	Examples: white bread, enriched grain cereals and crackers, enriched pasta, and white rice
Protein foods[c]	5½ oz-eq	All meat, poultry, seafood, eggs, nuts, seeds, and processed soy products. Beans and peas are considered part of this group as well as the vegetable group, but should be counted in one group only (vegetarian adaptations available).
Seafood	8 oz/week	Examples: *fish*, such as salmon, tuna, trout, and tilapia, and *shellfish*, such as shrimp, crab, and oysters
Meat, poultry, eggs	26 oz/week	Examples: chicken, turkey, beef, pork, lamb, and eggs
Nuts, seeds, soy products	4 oz/week	Examples: walnuts, almonds, peanuts, and pistachios
Dairy[d]	3 c	All milks, including reduced lactose products and fortified soy beverages, yogurts, frozen yogurts, dairy desserts, and cheese (excluding cream, sour cream, and cream cheese)
Oils	27 g	Includes oils found naturally in foods such as olives, nuts, avocados, and seafood; oils extracted from plants, such as canola, corn, olive, peanut, safflower, soybean, and sunflower oils; and foods that are mainly oil such as oil-based salad dressings and soft table spreads that have no *trans*-fats
Maximum SoFAS limit, calories (% of calories)	258 (13%)	Added sugars are sugars, syrups, and other caloric sweeteners added to foods during processing, preparation, or consumed separately. Solid fats may be naturally occurring in foods such as beef fat or added to foods during processing or preparation such as butter

Notes: For each food group or subgroup, recommended average daily intake amounts for a 2000 cal level are provided. Recommended intakes from vegetable and protein foods subgroups are per week. Amounts are shown in cups (c), ounce-equivalents (oz-eq), or grams (g).

[a] Fruits and vegetables, 1 cup equivalent is 1 c raw or cooked; ½ c dried; 1 c juice; 2 c leafy salad greens.

[b] Grains, 1 oz-eq is 1 oz slice of bread; 1 oz uncooked pasta or rice; ½ c cooked rice, pasta, or cereal; 1 tortilla (6 in. diameter); 1 oz ready-to-eat cereal.

[c] Protein foods, 1 oz-eq is 1 oz lean meat, poultry, seafood; 1 egg; 1 Tbsp peanut butter; ½ oz nuts or seeds; ¼ c cooked beans or peas.

[d] Dairy, 1 cup equivalent is 1 c milk, fortified soy beverage, or yogurt; 1 ½ oz natural cheese; 2 oz processed cheese.

lacto–ovo vegetarian pattern that includes dairy products and eggs (Appendix 8 of the 2010 Dietary Guidelines). The adaptations include changes in the protein food group and, in the vegan adaptation, in the dairy group. These vegetarian variations represent healthy eating patterns, but rely on fortified foods for some nutrients. In the vegan patterns especially, fortified foods provide much of the calcium and vitamin B_{12}, and either fortified foods or supplements should be selected to provide adequate intake of these nutrients.

DASH Eating Plan

The DASH Eating Plan was developed based on findings from the DASH research studies. This plan limits sodium, saturated fatty acids, and cholesterol and focuses on increasing intake of foods rich in potassium, calcium, magnesium, protein, and fiber. The DASH Eating Plan is another approach to meeting the Dietary Guidelines recommendations. A sample DASH eating pattern at the 2000 cal level is provided in Table 10.3. Eating patterns at six additional calorie levels are provided in Appendix 10 of the 2010 Dietary Guidelines.

TABLE 10.3
Sample DASH Eating Plan at the 2000 cal Level

Food Group	Amount	Serving Sizes
Grains (mostly whole grains)	6–8	1 slice bread; 1 oz dry cereal; ½ c cooked rice, pasta, or cereal
Vegetables	4–5	1 c raw leafy vegetables; ½ c cut-up raw or cooked vegetable; ½ c vegetable juice
Fruits	4–5	1 medium fruit; ¼ c dried fruit; ½ c fresh, frozen, or canned fruit; ½ c fruit juice
Fat-free or low-fat milk and milk products	2–3	1 c milk or yogurt; 1 ½ oz cheese
Lean meats, poultry, and fish	6 or less	1 oz cooked meats, poultry, or fish; 1 egg
Nuts, seeds, and legumes	4–5 per week	1/3 c or 1 ½ oz nuts; 2 Tbsp peanut butter, 2 Tbsp or ½ oz seeds; ½ c cooked legumes (dried beans, peas)
Fats and oils	2–3	1 tsp soft margarine; 1 tsp vegetable oil; 1 Tbsp mayonnaise; 1 Tbsp salad dressing
Sweets and added sugars	5 or less per week	1 Tbsp sugar; 1 Tbsp jelly or jam; ½ c sorbet, gelatin dessert; 1 c lemonade
Maximum sodium limit	2300 mg	

Notes: Daily servings recommended for each food group at a 2000 cal level are provided. Amounts of nuts, seeds, and legumes and sweets and added sugars are provided per week.

HELPING AMERICANS MAKE HEALTHY CHOICES

The preceding sections of the 2010 Dietary Guidelines include strategies that *individuals and families* can adopt to achieve dietary intake recommendations. In contrast, the purpose of this section is to outline actions that can be implemented by *various sectors of society* (e.g., educators, health professionals, communities and organizations, small and large businesses and policymakers) to support individuals and families in their daily nutrition and physical activity decisions.

Two points are emphasized: (1) the nutrition and physical activity environment influences individual decisions regarding food and beverage intake and activity level and (2) reversal of the current epidemic of overweight/obesity and related health outcomes will require a coordinated, system-wide approach spanning all sectors of society. For the first time, the 2010 Dietary Guidelines also includes a societal call to action.

This call to action is framed by an adapted Social–Ecological Model (Figure 10.2), one theoretical approach to explaining how the current food and physical activity environment evolved and exploring how it can be improved. This model describes the various elements of society and how they work together to influence individual behaviors. The elements include

1. Individual factors (e.g., age, socioeconomic status, psychosocial factors, knowledge, skills)
2. Environmental settings (e.g., schools, workplaces, foodservice/food retail establishments)
3. Sectors of influence (e.g., government, health care systems, agriculture, media, food/beverage industry, entertainment industry)
4. Social and cultural norms and values (e.g., belief systems, priorities, body image, heritage)

The model can help define the roles that various segments of society can play in making healthy choices more widely accessible and desirable. Thus, it can be used to develop, implement, and facilitate the use of multiple, coordinated primary prevention strategies. Efforts to improve dietary intake and increase physical activity are more likely to be successful when using this type of coordinated, system-wide approach. Building on the Social–Ecological Model, the 2010 Dietary Guidelines' call to action is based on three guiding principles:

1. Ensure that all Americans have access to nutritious foods and opportunities for physical activity.
2. Facilitate individual behavior change through environmental strategies.
3. Set the stage for lifelong healthy eating, physical activity, and weight management behaviors.

Each of these principles is explored and sample action steps for implementation by various elements of society are provided within this section of the 2010 Dietary Guidelines.

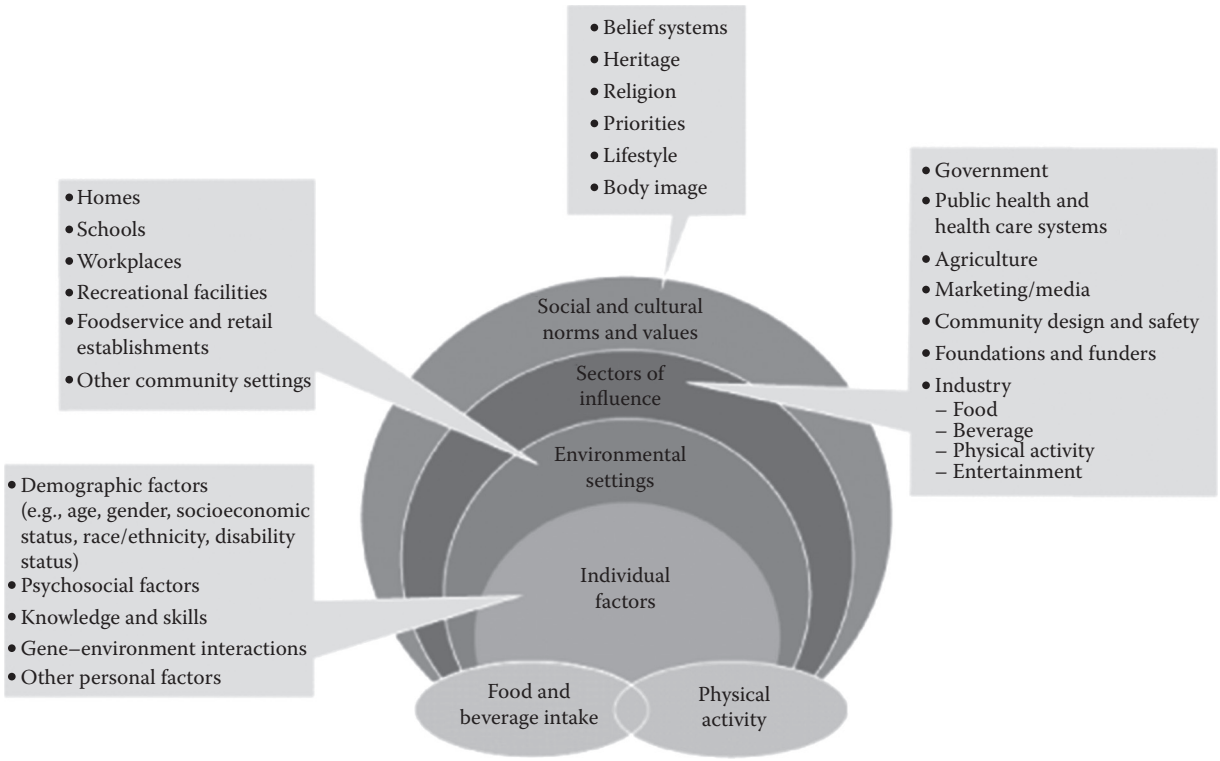


FIGURE 10.2 A social ecological framework for nutrition and physical activity decisions. (Adapted from Centers for Disease Control and Prevention, Division of Nutrition, Physical Activity and Obesity, State Nutrition, Physical Activity and Obesity (NPAO) Program: Technical Assistance Manual, January 2008, p. 36; http://www.cdc.gov/obesity/downloads/TA_Manual_1_31_08.pdf; Institute of Medicine, *Preventing Childhood Obesity: Health in the Balance*, National Academies Press, Washington DC, 2005, p. 85; Stroy, M., et al., *Annu. Rev. Public Health*, 29, 253, 2006.)

ADDITIONAL RESOURCES

The 2010 Dietary Guidelines also provides 16 appendices as resources that can be used in developing policies, programs, and educational materials. Examples of information provided in these appendices include a table of nutrition goals for age–gender groups (based on Dietary Reference Intakes and Dietary Guidelines recommendations); estimated calorie needs by age, gender, and physical activity level; examples of eating patterns at various calorie levels; estimated EPA and DHA and mercury content in certain seafood varieties; and food sources of the nutrients of concern (potassium, dietary fiber, calcium, and vitamin D). One appendix elaborates on the four basic food safety principles to reduce the risk of food-borne illness—Clean, Separate, Cook, and Chill—while another provides information on food labels, including discussion about Daily Values and the Ingredients List.

These resources are intended to complement existing Federal nutrition information and guidance that can be found at websites such as www.healthfinder.gov, www.nutrition.gov, www.mypyramid.gov, and www.dietaryguidelines.gov. Additional information on vitamin, mineral, and macronutrient recommendations are available in the Dietary Reference Intakes, accessible at http://fnic.nal.usda.gov/DRIreports and through an interactive tool at http://fnic.nal.usda.gov/interactiveDRI/

IMPLEMENTATION BY HEALTH PROFESSIONALS

The 2010 Dietary Guidelines emphasizes that everyone has a role in the movement to make America healthier. Health care professionals obviously play a particularly important and unique role as providers; however, they can also serve as trusted educators, respected advocates, and facilitators of change.

As providers, health care professionals engage in direct interactions with the American public, and can therefore serve as message purveyors. Health care providers should view the Dietary Guidelines as the authoritative source for evidence-based nutrition information, and should thus base any nutrition-related advice on the Guidelines' recommendations. Ideally, even providers who do not routinely dispense nutrition advice could incorporate the two main themes of the 2010 Dietary Guidelines (i.e., "Maintain calorie balance over time to achieve and sustain a healthy weight" and "Focus on consuming nutrient-dense foods and beverages") into their communications with patients, as a broad prevention effort. Nutrition messages should be brief, direct, and actionable; example nutrition messages (with consumer-tested wording) include

- Enjoy your food, but eat less.
- Avoid oversized portions.
- Make half your plate fruits and vegetables.
- Switch to fat-free or low-fat (1%) milk.

- Compare sodium in foods like soup, bread, and frozen meals—and choose the foods with the lower numbers.
- Drink water instead of sugary drinks.

Basing nutrition communication directly on the Dietary Guidelines reduces the risk of conflicting messages from authoritative sources and the resulting confusion for consumers. Outside of the direct provider role, health care professionals may facilitate the communication and implementation of the Dietary Guidelines in a number of ways. Potential examples include

- Collaborating to develop local, state, and national strategic plans to achieve Dietary Guidelines recommendations among individuals, families, and communities
- Recognizing health disparities among subpopulations and ensuring equitable access to safe and affordable healthy foods and opportunities for physical activity for all people
- Advocating for legislation, policies, and systems in key sectors such as public health, health care, retail, schools, and transportation to prevent obesity and associated health outcomes
- Supporting future research that will further examine the individual, community, and system factors that contribute to the adoption of healthy eating and physical activity behaviors; identifying best practices; and facilitating adoption of those practices
- Identifying approaches for assessing and tracking children's body mass index (or other valid measures) to identify overweight and obesity and implementing appropriate interventions
- Supporting effective policies to limit food and beverage marketing to children

The ultimate goal of the *Dietary Guidelines for Americans* is to improve the health of the nation's current and future generations by facilitating and promoting healthy eating and physical activity choices among all individuals. Meeting this goal will require comprehensive and coordinated system-wide approaches across the nation; health care professionals are vital to this endeavor and provide a uniquely influential role in behavioral and environmental change.

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11 Nutritional Considerations for the Active Adolescent

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CONTENTS

Introduction 149
Adolescence 149
Calories In 150
- Energy Intake 150
- Macronutrients 151
  - How Intakes Are Calculated 151
  - Carbohydrates 152
  - Fiber 152
  - Sugar 152
  - Fat 153
  - Protein 153
- Micronutrients 154
  - Vitamins 154
  - Minerals 154
  - Other Micronutrients 155
- Supplements 155
- Fluid Ingestion 156
  - Hydration Timing 157
  - Sports and Energy Drinks 157
  - Alcohol 157

Dietary Behaviors 157
- Special Considerations: Weight Status and Eating Disorders 158

Current Food Environment 158
Conclusion 158
References 159

INTRODUCTION

Adolescent nutrition is complicated. This stage of development is marked by rapid changes that occur at different times for different individuals, and nutrient and energy needs are exceptionally demanding; it is challenging for parents and practitioners to know how much of which nutrients are essential for healthy growth, and when and how nutritional needs change. Dietary considerations for an active adolescent are even more complex given the additional physical and biological strains being placed on their bodies. While physical activity is critical for promoting cardiovascular endurance, as well as skeletal and muscular growth, these positive effects can be either enhanced or hindered by inappropriate dietary practices. Given research suggesting that adolescent dietary habits can predict lifelong health behaviors[1] and youth's dietary behaviors tend to worsen as they age,[2,3] it is critical to establish healthy dietary behaviors as early as possible. Accordingly, this chapter will start by providing a context for youths' nutrient needs by presenting an overview of the psychosocial and biological changes that occur during adolescence, followed by a discussion of which nutrients are important for growth and development, as well as those that tend to be consumed in insufficient and excessive amounts, and lastly provide practical knowledge for practitioners to help adolescents eat better given the context of their current food environment.

ADOLESCENCE

Adolescence is an important time in our maturation process, as our bodies, social relationships, self-identities, and lifestyle health behaviors are developing simultaneously.[4] This period can be conceptualized as three distinct stages: early adolescence (ages 11–14 years), middle adolescence (ages 15–17 years), and late adolescence (ages 18–21 years).[5] Different phases of development occur within each of these time periods. Early adolescence is marked by the onset

of physiological and physical changes related to puberty (e.g., menarche, gains in height and weight); during middle adolescence, teens begin to increase their social and psychological autonomy; puberty ends, and growth slows for females and continues for males. Lastly, in late adolescence, females' growth and development is usually complete while males are still experiencing growth in body mass. Both genders are typically more independent, have a more established self-identity, and are more future-oriented, having increased concern about life decisions, such as college or career choices.

Essentially, throughout this decade, adolescents experience rapid changes in hormonal composition, secondary sexual characteristics, brain development, and height and weight. During their peak 1 year growth spurt, males can gain an average of 4.1 in. and females, 3.5 in.[6] Females tend to experience this rapid growth before males, with their changes occurring during the ages of 10–13 years, vs. 12–15 years for males.[7] In terms of body composition, females tend to increase both their fat and muscle mass as they gain weight, whereas males tend to gain mostly lean mass. Both sexes experience gains in bone; in fact, 85%–90% of adult bone mass is accrued by the end of the adolescent years.[8,9] This growth spurt is especially important because it has been shown to predict 15% of ideal adult height and 50% of ideal adult weight.[10,11]

Given these significant changes, teens need more sleep. However, while the recommended amount of sleep for the average adolescent is 9.2 h,[12] 61% of youth ages 13–18 years report getting less than 8 h on school nights. To make up for this, on average, the typical adolescent consumes 3.1 caffeinated drinks/day[13]; more specifically, the consumption of caffeine was found to be 76% higher in adolescents (ages 12–18 years) who had difficulties falling asleep at night and staying awake during school.[14]

Sleep is also critical for supporting healthy brain development in adolescents, as their prefrontal, neuronal connections (between mental, physical, and emotional abilities) are not fully developed.[15] These emotional and behavioral alterations can result in heightened sensitivity to peer influence and opinion. Because adolescents tend to compare themselves with their peers, there are a number of psychological disturbances, such as depression, which can develop. For example, the prevalence of depression among adolescents is 5%–8%,[16] and has been associated with the onset of early menarche[17]; as a point of reference, the prevalence of depression among children is 2%,[16] and adults is 9%.[18]

Participation in athletics puts an even greater demand on adolescents' developing self-concepts, physical appearance, and biological changes; in fact, during different stages of adolescence, youth may present with increased insulin resistance and different physiological responses to exercise, such as glycolytic and metabolic rates, and higher fat oxidation levels.[19] Given the rapid growth in muscle and bone, adequate consumption of high-quality protein, carbohydrates, and fats, as well as vitamins and minerals such as vitamin D, calcium, and iron is especially important. Conversely, high intakes of some micronutrients, such as sugar and salt, can adversely influence healthy development.

To provide a more detailed context for how to support positive growth and development by maximizing the practice of good nutrition, the next section will focus on "energy balance," which generally refers to "calories in" equaling "calories out." More specifically, "calories in" refers to the amount and quality of nutrients that are consumed, whereas "calories out" refers to the expenditure of those calories, either through physical activity, exercise, metabolism, or the Thermic Effect of Food (TEF; the energy expended to digest food, 3%–10% of daily expenditure). Accordingly, the next section will be broken down according to the "calories in" part of this energy balance equation: first by discussing adolescents' total calorie needs; then going more in-depth about the quality and quantity of nutrients consumed; and ending with more information about contextual considerations, particularly as they relate to the active adolescent.

CALORIES IN

Energy Intake

Since adolescents move through developmental stages at different rates, setting energy requirements for this population is particularly difficult. The Food and Nutrition Board establishes estimated energy requirements (EERs) based on individuals' age, gender, height, weight, and activity level (sedentary, moderately active, active, and very active). Table 11.1 presents these equations used to calculate the EERs, and Table 11.2 provides the associated physical activity coefficients. Using these calculations, Table 11.3 outlines calorie intake ranges based on age and gender, within the context of three different levels of activity: sedentary, moderately active, and active.[20]

Notably, these energy reference values are organized by age category and not by sexual maturation stage; the latter are rarely available despite possibly being a better predictor of physical development. Accordingly, it is difficult to determine, more specifically, how many calories an adolescent of a given maturation stage needs. An additional challenge, then, becomes calculating how many more calories are needed to compensate for additional exercise to meet needs above and beyond adolescents' natural growth and development, given their maturation stage instead of age, as well

TABLE 11.1
EER Equations[a]

Females (9–18 years): EER = 135.3 – (30.8 × age [years]) + PA × [(10.0 × weight [kg]) + (934 × height [m])] + 25
Males (9–18 years): EER = 88.5 – (61.9 × age [years]) + PA × [(26.7 × weight [kg]) + (903 × height [m])] + 25

[a] Based on doubly labeled water experiments measuring the energy expenditure of normal-weight individuals.

TABLE 11.2
Physical Activity Coefficients for EER Equations by Gender

	Sedentary[a]	Low Active[b]	Active[c]	Very Active[d]
Females	1.0	1.16	1.31	1.56
Males	1.0	1.13	1.26	1.42

[a] Typical day-to-day activities, such as walking to school.
[b] Typical day-to-day activities, and 30–60 min of moderate activity/day (e.g., walking 3–4 mph).
[c] Typical day-to-day activities, and at least 60 min of moderate activity/day.
[d] Typical day-to-day activities, at least 60 min of moderate activity/day and 60 min of vigorous or 120 min of moderate activity/day.

TABLE 11.3
Calorie Estimates of Adolescents Based on Gender and Activity Level

Gender	Adolescent Stage	Sedentary[a]	Moderately Active[b]	Active[c]
Females	Early (9–13 years)	1400–1600	1600–2000	1800–2200
	Mid (14–18 years)	1800	2000	2400
	Late (19–30 years)	1800–2000	2000–2200	2400
Males	Early (9–13 years)	1600–2000	1800–2200	2000–2600
	Mid (14–18 years)	2000–2400	2400–2800	2800–3200
	Late (19–30 years)	2400–2600	2600–2800	3000

[a] Typical day-to-day activities.
[b] Walks 1.5–3.0 miles/day at 3–4 mph, in addition to typical day-to-day needs.
[c] Walks 3+ miles/day at a 3–4 mph pace, in addition to typical day-to-day needs.

as for an exercise level that is more vigorous than the "very active" category. Active adolescent energy needs will vary depending on the duration, intensity, and frequency of the sport in addition to maturation stage, as well as dietary patterns and/or restrictions. More specifics about these will be provided later.

Macronutrients

There are three macronutrients: carbohydrates, fats, and protein. They are called macronutrients because of the quantities required by our bodies, and because they are our only sources of energy. This section will discuss these three nutrients in more detail, including recommended intakes, roles in the body, and food sources.

How Intakes Are Calculated

In order to frame the following section, it is important to start with a context for how intake recommendations are calculated. The Food and Nutrition Board of the Institute of Medicine (IOM) establishes the dietary reference intakes (DRIs). These reflect intake reference values for macronutrients and micronutrients. There are five subcategories: estimated average requirement (EAR), recommended dietary allowance (RDA), the adequate intake (AI), and the tolerable upper limit (UL), as well as the acceptable macronutrient distribution ranges (AMDRs). The EAR reflects the average daily intake amount that is estimated to meet the needs of half of healthy individuals in a particular life stage and gender category. The RDA is the average daily intake amount that is sufficient to meet the needs of nearly the entire population (97%–98%) of healthy individuals in a particular life stage and gender category. An AI is calculated when there is insufficient data to establish an EAR (and thus an RDA); this amount is calculated from epidemiological data, and reflects the estimated intake of a given nutrient consumed by a group of apparently healthy people. The UL represents the maximum average intake amount of a given nutrient that is unlikely to cause an adverse health effect to a majority of the population; as intakes increase beyond this amount, the likelihood for an undesirable effect may also increase. The AMDR represents the range of intakes for a given macronutrient that provides a sufficient amount of essential nutrients while reducing the risk for a given chronic disease or condition. Intakes above or below these amounts may elevate risk for chronic diseases, and may result in the under- or overconsumption of micronutrients.

These reference values are based on research studies using biological data, as well as dietary data typically quantified by self-report, including 24 h food recalls, food journals, 3 day diet records, and food frequency questionnaires. Measurement errors implicit in these tools can lead to incorrect conclusions about the nutrient amounts consumed by a given target population. Examples of issues with dietary assessment include (1) respondent error (e.g., incorrect recall or social desirability bias); (2) interviewer error; (3) intake estimation errors (most people underestimate their intake); (4) failure to include food types—on the measure and in diet analysis computer programs; (5) errors in data entry and analysis; (6) intra- and inter-rater variability; and (7) insufficient recall duration to account for reporting errors.

Awareness of these limitations is particularly important given that most available data on measurement error is limited to adults. While there is little research validating the accuracy of adolescents' dietary recall, in their review of the literature, Livingstone et al. found that adolescents' nutrient intake variance ratios were twice that of adults, with males being more accurate in their reported vs. actual nutrient intake than females.[21] The variance ratio captures the discrepancy between within subject and between subject nutrient intakes. Moreover, validation studies of adolescents' reported vs. actual dietary intakes have consistently found biased results, which are associated with the type of diet assessment, weight, and adolescent age[21]; in fact, one study found adolescent girls' recall accuracy declines as they age, with greater underreporting occurring.[22]

Despite these limitations, there is a breadth of research dedicated to adolescent nutritional needs; using this data, the following sections will provide an overview of the roles of both macro- and micronutrients in the body, and more specifically, in the context of active adolescents.

Carbohydrates

Carbohydrates are chains of glucose molecules, either simple (sugars) or complex (fibers and starches). Carbohydrates, or more specifically glucose, are the human brain's and muscles' primary energy source. Accordingly, the AMDR for carbohydrates for adolescents is 45%–65% of total calorie needs; this is equivalent to an RDA of 130 g/day for all adolescents, and represents the amount of glucose needed for brain metabolism. While most youth consume enough carbohydrates, dietary sources tend to come from refined or processed food products, such as candy or sugar-sweetened beverages (SSBs), and fewer from whole foods, such as grains, legumes, fruits, and vegetables. Data from the federal government's Centers for Disease Control and Prevention's Youth Risk Behavior Surveillance System (YRBSS) found that, nationwide, 29% of adolescents report drinking at least one glass, can, or bottle of sugared (non-diet) soda/day.[23] Another study found that on any given day, 58% of adolescent males ages 11–13 years and 73% of males ages 14–17 years consume at least one soft drink; the figures for adolescent females were similar, with 63% of females ages 11–13 years and 62% of females ages 14–17 years.[24] Moreover, only 22% of high-school students reported consuming fruits and vegetables five times or more in the previous 7 days (excluding fried potatoes and potato chips).[23]

While carbohydrates are stored in the body as glycogen, it is noteworthy that adolescents' glycolytic capacity is still growing (only 0.4%–0.5% of body weight).[25] Accordingly, their muscle glycogen stores are 50%–60% less than adults and they have lower levels of circulating lactate[26]; this means "carb-loading" and other associated training tactics that increase glycogen stores may not have the same beneficial effect in adolescents, as they rely more on aerobic metabolism.[26] Thus, the source of carbohydrate is important because while all ingested glucose activates the release of the hormone insulin, which then signals cellular receptors to take up the glucose; the amount of insulin secreted, the time it takes for cells to absorb the glucose, and the time it takes for blood sugar levels to decline to normal (collectively referred to as the "glycemic index" or GI) vary across foods. Given that research also suggests adolescents may have greater insulin sensitivity,[25] it is important to choose foods with a lower glycemic load, such as those containing greater amounts of fiber. The next section will discuss fiber in more detail.

Fiber

While fiber represents parts of plants that are indigestible by humans, it provides the following benefits to the growing body: supports healthy GI function (by both promoting excretion and slowing digestion to encourage maximal nutrient absorption); provides a feeling of fullness; can be metabolized by gut bacteria to synthesize B vitamins; and binds to bile, which can lower cholesterol. In fact, too little fiber can lead to digestive problems, excessive calorie intake, and peaks in blood sugar levels; too much fiber, on the other hand, can lead to GI distress and micronutrient deficiencies (as fibers bind to minerals such as calcium and iron; heating grains weakens these bonds and encourages maximal absorption). Good sources of fiber include beans, whole grains (such as whole oats and whole wheat bread), as well as fruits and vegetables. Accordingly, there are different types of fibers; for example, fibers can be categorized by their water solubility: insoluble or soluble.

The AI for fiber is 31 g/day for males ages 9–13 years, and 38 g/day for males ages 14–18 years. For females ages 9–18 years, the AI is 26 g/day. Using National Health and Nutrition Examination Survey (NHANES) 2005–2006 data, Van Horn found that adolescents were consuming insufficient amounts of fiber. Males, ages 9–13 years ($n = 1009$) consumed 14.6 ± 0.59 g/day, and males ages 14–18 years ($n = 1351$) consumed 15.3 ± 0.39 g/day. Females ages 9–13 years ($n = 1039$) consumed 12.9 ± 0.39 g/day, and females ages 14–18 years ($n = 1250$) consumed 11.8 ± 0.34 g/day.[27]

Sugar

While sugars can provide a good source of quick energy—and are naturally occurring in fruits, vegetables, whole grains, and dairy products—added sugars in the diet are a major contributor to the nearly 40% of energy consumed in the form of empty calories (low nutrient value) among youth ages 2–18 years.[2] Using 2005–2006 NHANES data, this same analysis found that the primary source of energy for youth between the ages of 9 and 13 years was grain desserts; for youth between the ages of 14 and 18 years, it was soda (this category also included energy drinks, sports drinks, and sweetened bottled water).[2] As youth aged, the caloric contribution of SSBs to their added sugar consumption also increased from 169 kcal/day for 9–13 year olds to 260 kcal/day for 14–18 year olds.

In total, the average adolescent intakes of added sugars are as follows (measured in teaspoons): 29.2 ± 0.92 (males 9–13 years); 34.3 ± 1.03 (males 14–18 years); 23.2 ± 0.82 (females 9–13 years); and 25.2 ± 0.71 (females 14–18 years)[28]; notably, for both genders, intakes increase as they age. This equates to almost 400 kcal/day[2], with SSBs, alone, contributing an additional 173 kcal/day (soda: 116 kcal/day, fruit drinks: 55 kcal/day); as a point of reference, for an active adult male the (highest) intake reference for added sugar is 9 tsp/day, or 144 cal.[28] Excess sugar consumption has been linked with weight gain, dental carries, type II diabetes, micronutrient deficiencies, and a host of other adverse health effects.

To address the need for guidance on how much added sugar adolescents should be consuming, the American Heart Association (AHA) published dietary recommendations, which offered the following: "sweetened beverages and naturally sweet beverages, such as fruit juice, should be limited to … 8–12 oz per day for children 7–18 years old"[29]; in the AHA's 2009 report, adolescent-specific guidelines were not

published. Parents, coaches, and practitioners should seek to limit intakes of added sugars in adolescents' diets, including sources such as SSBs, sugar-sweetened cereals, candy, and baked goods.

Fat

Fats play an important role in human health: they protect internal organs and bones, are needed for vitamin absorption and storage, help regulate body temperature, and are used in cells' membrane and structure. There are different kinds of fats: unsaturated fats (including poly- and monounsaturated), saturated, and *trans*-fats (each of these prefixes refer to its chemical structure), as well as cholesterol. The AMDR for total fat is between 25% and 35% of total calories (with <10% from saturated and 0 g *trans*-fat); the AI is not determined. However, AIs are established for the two essential, unsaturated fatty acids: linoleic acid (n−6) and α-linolenic acid (n−3). For males ages 9–13 years, they are 12 and 1.2 g/day, respectively; males ages 14–18 years, the amount increases to 16 and 1.6 g/day, respectively. For females 9–13 years, the AI is 10 and 1.0 g/day for linoleic acid and α-linolenic acid, respectively; females ages 14–18 years, the amount increases to 11 and 1.1 g/day, respectively.

Most adolescents are consuming a sufficient amount of fat, and it appears, too much fat. A 2007 study using an ethnically diverse adolescent population found 68% of subjects were not meeting Healthy People 2010 Guidelines for <30% of calories from fat.[30] More recently, using data from the third School Nutrition Dietary Assessment Study (SNDA-III), Clark and Fox found middle-school students (n = 787) consumed 32.0% ± 0.35% of their total calories from fat and, more specifically, 11.0% ± 0.16% of their calories from saturated fat. High-school students (n = 795) consumed 32.8% ± 0.35% of their calories from fat; 11.1% ± 0.14% of total calories were from saturated fat.[31]

Too much dietary fat can lead to an increase in body weight and elevated cholesterol levels. Too little fat can impair vitamin absorption, metabolism and storage, increase risk of fracture after a fall, and impair body temperature regulation (e.g., increase perceived extremes of hot and cold). It is important for adolescents to pay attention to the kind of fat they are consuming: unsaturated fats are preferable given their role in neurological and visual development, and in the fluidity and permeability of cell walls; saturated fat, on the other hand, has been shown to increase low-density lipoprotein (LDL; "bad cholesterol"), and *trans*-fats have been shown to concurrently increase LDL and decrease high-density lipoprotein (HDL; "good cholesterol"). Good sources of dietary fat include fatty fish, such as salmon and sardines, nuts, avocado, and oils (e.g., canola, olive, and coconut).

Saturated fat has received much attention given its relationship to heart disease.[32,33] In light of research finding that adolescents exceed the recommended intake, it is worth briefly discussing the controversy. An April 2011 review of the literature found that when polyunsaturated fats replace saturated fats, risk for coronary heart disease (CHD) is reduced.[34] The evidence for monounsaturated fats, however, is mixed; carbohydrates as a replacement may be beneficial if the source is minimally processed and has a low GI (this relationship also works in its converse), such that a diet high in refined grains can adversely influence cholesterol, as well as blood glucose, levels. It is difficult to assess the effects of certain foods since their molecular interactions, and thus influence on CHD risk, vary; again, the quality of the nutrients matters. Accordingly, there seems to be consistent confounding by food type; most dietary assessments are based on self-report and not biological data, which makes it difficult to parse the influence of fat and other macronutrient types.[34]

Protein

Protein is needed in the body for multiple physiological and biological processes, including antibody synthesis, tissue repair, and cell structure. Proteins comprise amino acids. There are 20 amino acids, 9 of which are "essential." Animal products (e.g., meat and dairy) are considered to be "complete proteins" since they contain all nine essential amino acids, nonmeat, complete protein sources including quinoa and soy. Notably, it is possible to create a complete protein by pairing complementary proteins. Food pairing examples include beans and rice, peanut butter and whole wheat bread, and pasta with beans.

The RDA for protein ranges from 1.2 to 2.0 g/kg of body weight for the average adolescent,[35] and reflects the amount needed to maintain adequate nitrogen balance; the range reflects varying needs based on gender, age, height, weight, and physical activity. However, the evidence is inconclusive (and research is ongoing) about how much protein the active adolescent actually needs. Research does suggest that with increased physical activity, protein utilization efficiency improves,[36,37] which means greater intakes are likely unnecessary (and not research-supported), and needs may be met from dietary intake alone. Accordingly, any substantive and intentional increase in protein intake—especially from supplements—should be preceded by a dietary analysis given the consequences of excess protein consumption. More specifically, while insufficient intakes of protein can lead to an irregular heartbeat, impairments in blood clotting and tissue repair, and poor immune health, high intakes of protein can lead to renal damage and increased fat mass. There is an additional concern that too much protein can lead to increased urinary calcium excretion, and thus adversely influence bone health; however, the research findings on this are also mixed, and the effects seem to be influenced by the interaction of multiple variables including source (food or supplement) and intake amounts for both protein and calcium.[38]

Typically, adolescents consume a sufficient amount of protein. Using NHANES (2003–2004) data, Fulgoni found the average adolescent protein intake was 1.7 ± 0.7 g/kg body weight (ages 9–13 years) and 1.5 ± 0.6 g/kg body weight (ages 14–18 years); notably, nearly 8% of adolescent females ages 9–18 years were consuming less than the EAR[39] (contrasted with <3% of males).

Micronutrients

Micronutrients are those nutrients our body requires in much smaller amounts (micro- and milligrams instead of grams), noncaloric, and include vitamins and minerals. Vitamins are organic substances that our body uses for fundamental and essential physiological processes, such as cholesterol synthesis, vision, immune function, and blood clotting. Minerals are inorganic compounds that are also important for biological processes, including blood pressure and pH balance, hemoglobin synthesis, muscle contractions, and bone structure. This section will discuss a few key micronutrients for the active adolescent: vitamin D, iron, and calcium.

Vitamins

Vitamin D

Vitamin D is a fat-soluble vitamin that is essential for calcium absorption, cholesterol synthesis, cell differentiation, and insulin secretion. Human beings are able to absorb vitamin D from sunlight, and can also consume it from our diet. Egg yolks, fatty fish (such as salmon, herring, mackerel) are the only naturally occurring food sources; fortified milk, cereals, and orange juice also contain vitamin D. The vitamin D RDA for adolescents is 600 IU (15 μg).[40] Because sunlight has such a potent effect on vitamin D status, dietary intake is not as useful an indicator of nutritional status as it is for some other nutrients. For this reason, serum 25 hydroxy vitamin D (25OH D) is the standard for nutritional status. Until recently, a reference standard for 25OH D was not available; therefore, values obtained in many clinical settings were not always valid indicators of deficiency or excess. The serum measurement of vitamin D is currently used to establish the RDA, but there is controversy surrounding the methods used and what levels are most appropriate. An additional challenge is the body's compensatory mechanisms for responding to low levels, and the widespread perception that many individuals are deficient or insufficient. These considerations make establishing an optimal range difficult; thus, the definitions for optimal levels remain controversial.[41]

Currently, the definition for deficiency is <20 ng/mL,[42] and for insufficiency it is between 21 and 29 ng/mL.[43] There appears to be a high prevalence of both vitamin D insufficiency and deficiency among adolescents and athletes; now that a reference standard for serum 25OH D is present it will be important to confirm these findings. Using NHANES data, Reis et al. found the mean serum 25OH D level was 24.8 ng/mL (23.8–25.9), with the highest levels in non-Hispanic whites (28.0; 27.0–29.0) and the lowest levels in non-Hispanic blacks (15.5; 14.6–16.4).[44] In an athletically diverse, young population (mean age: 14.7 ± 3.0 years) Constantini et al. found 73% of subjects had insufficient vitamin D levels (25.3 ± 8.3 ng/mL), with a significant insufficiency prevalence difference between indoor and outdoor athletes (80% vs. 40%; $p = 0.002$).[45]

Low levels of vitamin D can increase risk of fracture, impair athletic performance, lead to a softening of the bones, and osteoporosis later in life; it can also cause increased muscle pain and weakness. Other populations at risk for deficiency include overweight and obese individuals (as excess body fat sequesters vitamin D, making it less available to the body); vegans and vegetarians (whose vitamin D intakes are often very low unless they drink fortified cow's milk or soy milk); and individuals with dark skin (who do not synthesize as much of the vitamin in their skin). In order to absorb enough vitamin D from the sun, it is recommended to expose face, arms, and legs, without sunscreen, twice/week between 10:00 a.m. and 3:00 p.m. for 5–30 min, depending on the season, latitude, and skin color, as SPFs of 8 and greater reduce skin synthesis by 95%.

Minerals

Iron

Given their rapid growth and development, adolescents need a sufficient amount of iron. The RDA is 8 mg for both males and females ages 9–13 years; it increases to 11 mg for males and 15 mg for females ages 14–18 years. Iron is used in the body for hemoglobin synthesis, cell growth, and oxygen transport. There are different kinds of iron: heme and nonheme. Heme iron is bound in hemoglobin, so it is found in animal products, such as fish and poultry; this form is the most bioavailable. Sources of nonheme iron include fortified cereals, dark green leafy vegetables (e.g., spinach, kale), and nuts. One of the concerns with nonheme iron is that its bioavailability is limited by multiple inhibitors such as polyphenols, phytates, and fiber. Accordingly, nonheme food sources should be consumed with vitamin C (red bell peppers, strawberries, citrus fruits), which maximizes its absorption; blanching dark green leafy vegetables can also improve iron bioavailability.

Iron intakes vary by gender. For example, using cross-sectional data, Juzwiak et al. found that among a population of male tennis players, 100% of youth ages 10–13 years and 85% of those ages 14–18 years were either meeting or exceeding the iron RDA.[46] Conversely, using 2006 NHANES data, Cogswell e al. found that the prevalence of iron deficiency was 15.6% ± 1.2% among females ages 12–19 years.[47] The low intakes observed in the female population could be explained by a combination of factors, including diet (low calorie and/or low meat), high iron turnover from increased activity, and increased losses through sweat and urine. Vegetarians are also at risk for deficiency given the limited bioavailability of nonheme iron. Consistently low intakes of iron can lead to chronic fatigue and decreased immune function, as well as impaired aerobic capacity and athletic performance. It has been recommended that populations at risk for deficiency take a low-dose iron supplement during intense training and with guidance from a physician.[48]

Calcium

Calcium performs multiple roles in the body. It is necessary for muscle contractions, nerve transmissions, blood vessel volume regulation, and bone health; bone mineral content (BMC) is about 80% calcium.[49] For adolescents, calcium

consumption is particularly important; Martin et al. found in a group of 228 youth, maximal calcium accretion occurs at rates of 282 mg/day for males at age 13.3 years, and 212 mg/day for females at age 11.4 years.[50] In fact, total body BMC more than doubles in children between the ages of 8 and 15 years, with peak gains attained between the ages of 12.5 (girls) and 14.0 (boys) years,[51] resulting in 85%–90% of total bone accrual by the age of 18 years for females and 20 years for males. Given the critical role calcium plays in laying down adequate bone, the RDA is 1300 mg/day (males and females ages 9–18 years).

Since blood levels of calcium are homeostatic, insufficient intakes from the diet can lead to the leeching of calcium from the bone, resulting in soft bones and elevated risk for stress fractures, as well as muscle cramps and arrhythmias. Calcium deficiency is of particular concern for adolescents, since, as a demographic, they tend to consume insufficient amounts. Larson et al. found an average intake of 1014 ± 17 mg in an ethnically diverse cohort of adolescents (n = 1521; mean age: 15.9 years), with more than 72% of females and 55% of males consuming less than the recommended intake.[52] There are many reasons for this, but most notably is the displacement of milk for SSBs.[53] More specifically, using 10 year data from the National Heart, Lung, and Blood Institute Growth and Health Study, Striegel-Moore et al. found the consumption of SSBs increased almost three times, while consumption of milk decreased >25% among a group of black and white female adolescents (n = 2371).[3] Thus, while activities that increase skeletal demand, such as running and gymnastics, positively contribute to BMC,[54] if adolescent athletes do not consume a sufficient amount of calcium, they increase their risk for injury and impaired performance.

Aside from dairy products such as milk, yogurt, and cheese, other good sources include calcium-fortified beverages such as orange juice and soy milk, as well as dark green leafy vegetables (e.g., spinach and kale). Calcium absorption can be maximized by consuming it concurrently with a source of vitamin D (such as eggs or salmon), and waiting an hour ingesting between a calcium-rich source and an iron-rich source, as they compete for absorption. In fact, Malczewska et al. found that iron-deficient female endurance athletes had greater calcium levels than their nonathletic peers with adequate iron status.[55] This underscores the importance of AI of all micronutrients—especially those that compete for absorption—among adolescent athletes in order to avoid deficiencies. This is especially important for vegans, as they are at risk for both iron and calcium deficiency.

Other Micronutrients

While the nutrients outlined earlier are of the most concern for active adolescents, other nutrients are also important for growth and development. Tables 11.4 and 11.5 provide an overview of intake recommendations for all the vitamins and minerals.

Supplements

Americans spend more than $20 billion on dietary supplements.[57] Hoffman et al. found 71% of adolescents (n = 3248, grades 8–12; 48% males) reported using at least one supplement.[58] According to their data, the most popularly used supplement was a multivitamin (59.3%), followed by high-energy drinks (31.5%). The use of weight gain aids (e.g., protein powders, creatine) was reported by 17.3% of students, and 35.1% used weight loss aids (e.g., ephedra, caffeine pills). The use of supplements increased as students aged for high-energy drinks (β = 0.19, SE = 0.09, p = 0.04, OR = 0.83), protein powders (β = 0.65, SE = 0.14, p = 0.000, OR = 1.92), creatine (β = 0.87, SE = 0.25, p = 0.000, OR = 2.38), weight gain aids (β = 0.80, SE = 0.22, p = 0.000, OR = 2.22), and anabolic steroids (β = 1.32, SE = 0.38, p = 0.000, OR = 3.75).

Research, however, has yet to consistently support the reliability, efficacy, and safety of dietary supplements.[59] This is especially true for adolescents. For example, research in

TABLE 11.4
Vitamin Needs of Adolescents

	A[a]	D[a]	E[b]	K[a]	C[b]	Thiamin[2]	Riboflavin[2]	Niacin[b]	B6[b]	Folate[a]	B12[a]	Panto. Acid[b]	Biotin[a]	Choline[b]
Females														
9–13 years	600	15	11	60	45	0.9	0.9	12	1.0	300	1.8	4	20	375
14–18 years	700	15	15	75	65	1.0	1.0	14	1.3	400	2.4	5	25	550
Males														
9–13 years	600	15	11	60	45	0.9	0.9	12	1.0	300	1.8	4	20	375
14–18 years	900	15	15	75	75	1.2	1.3	16	1.2	400	2.4	5	25	400

Sources: Institute of Medicine, Dietary reference intakes for calcium and vitamin D, National Academy of Sciences, Washington, DC, 2010, http://www.iom.edu/~/media/Files/Report%20Files/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Vitamin%20D%20and%20Calcium%202010%20Report%20Brief.pdf; Otten, J.J. et al., eds., *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*, National Academies Press, Washington, DC, 2006. Otten JJ, Pitzi Hellwig J, Meyers LD, eds. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington, DC: National Academies Press, 2006.

[a] µg/day.

[b] mg/day.

TABLE 11.5
Mineral Needs of Adolescents

	Ca^{+}	Cr^{a}	Cu^{a}	F^{-b}	I^{a}	Fe^{b}	Mg^{b}	Mn^{b}	Mo^{a}	P^{b}	Se^{a}	Zn^{b}	K^{c}	Cl^{-c}
Females														
9–13 years	1300	21	700	2	120	8	240	1.6	34	1250	40	8	4.5	2.3
14–18 years	1300	24	890	3	150	15	360	1.6	43	1250	55	9	4.7	2.3
Males														
9–13 years	1300	25	700	2	120	8	240	1.9	34	1250	40	8	4.5	2.3
14–18 years	1300	35	890	3	150	11	410	2.2	43	1250	55	11	4.7	2.3

Source: Institute of Medicine, Dietary reference intakes for calcium and vitamin D, National Academy of Sciences, Washington, DC, 2010. Available from: http://www.iom.edu/~/media/Files/Report%20Files/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Vitamin%20D%20and%20Calcium%202010%20Report%20Brief.pdf

Note: While there is no recommended intake for sodium, the reference value is 1500 mg for males and females between the ages of 9 and 18 years.

[a] µg/day.

[b] mg/day.

[c] g/day.

adults suggests creatine has positive effects on both changes in total body and fat-free mass, and performance in sports that require short, intense bursts of energy (e.g., power lifting)[60]; safety data for youth is limited.[61] In fact, the American College of Sports Medicine (ACSM) does not recommend supplements for persons under 18 years of age due to insufficient, supportive data, and the risk for developmental problems. Similarly, the widespread use of multivitamins is not generally medically warranted; in fact, consistent use of multivitamins could put some individuals at risk for nutrient toxicities.[62] Moreover, people who use multivitamins tend to lead a healthier lifestyle than nonusers.[63] Consequently, supplements should be taken by adolescent athletes with the consultation of a dietician or physician, and only in cases where there is an established nutrient deficiency (or significant risk for one).

Fluid Ingestion

Our body is about 60% water; our brain is 75%–85%. Water is needed for the digestion, absorption, metabolism, and transportation of nutrients; regulation of body temperature, physiological/biological reactions, and electrolyte balance; and adequate lubrication of joints. Being well-hydrated boosts cognitive and physical performance, helps protect against illness, and encourages the maximal use of dietary nutrients. The IOM's AI for water is 2.4 L/day for males ages 9–13 years, 2.1 L/day for females ages 9–13 years; 3.3 L/day for males ages 14–18 years, and 2.3 L/day for females ages 14–18 years.[64]

It is important to pay attention to hydration, as water losses of as little as 1%–2% can cause fatigue and negatively impact performance.[65] Water is lost through respiration, GI excretions, and sweat; electrolytes are also lost in perspiration. Consequently, appropriate fluid replenishment is important; this is particularly true when exercising in hot climates, as heat stress can both impair performance and increase risk for heat-related illness.[35,66] The body's ability to regulate temperature, maximize cardiorespiratory function, and otherwise adapt to increasing physical demands is largely predicted by hydration status, and are impaired when athletes are not sufficiently hydrated.[67]

While there is little data on the amount of water consumed by adolescents, a recent (2010) study used NHANES data to describe water consumption among young adults.[68] The findings are presented in Table 11.6.

The NHANES data in Table 11.6 show that ~70% of adolescents are consuming an insufficient amount of water. Accordingly, it is important to encourage the consumption of *water* as adolescents' first choice of beverage—especially if they are active—in lieu of sports drinks, juice, coffee, and soda.

TABLE 11.6
Mean Usual Water Intakes of Adolescent Americans and Percentages That Meet or Exceed the AI

Gender	Age (*n*)	Mean Usual Intake (L) (95% CI)	AI (L)	% ≥ AI (95% CI)
Females	9–13 years (525)	1.79 (1.64, 1.94)	2.1	26 (16, 36)
	14–18 years (643)	1.97 (1.84, 2.10)	2.3	24 (16, 32)
	19 years (112)	2.02 (1.82, 2.21)	2.7	10 (3, 17)
Males	9–13 years (522)	1.88 (1.73, 2.03)	2.4	15 (6, 23)
	14–18 years (654)	2.89 (2.65, 3.13)	3.3	29 (19, 39)
	19 years (126)	3.35 (3.07, 3.63)	3.7	33 (24, 43)

Source: Kant, A.K. and Graubard, B.I., *Am. J. Clin. Nutr.*, 92, 887, 2010.

Hydration Timing

The timing of water consumption is also important. Between 1 and 2 h prior to exercise, adolescent athletes should consume 2½ cups (~20 oz) of fluid; 15–30 min before, they should consume 1½ cups (12 oz). The purpose of drinking before exercise is to ensure that the athlete is sufficiently hydrated, and that his or her electrolyte balance is maximized for performance. During exercise, water consumption is needed to prevent drastic changes in electrolyte balance, as well as excess dehydration (>2% of body weight). For workouts lasting longer than 1 h, adolescent athletes should consume 6%–8% carbohydrate–electrolyte beverages frequently (about ½ cup every 10–15 min), as this will maintain appropriate fluid balance by replenishing sodium and potassium levels (thus preventing dehydration), and spare glycogen stores (particularly important if participating in multiple training sessions in 1 day).[69]

Due to differences in variables such as duration, frequency, type, and intensity of activity, training quality, hydration status, sweat rate, and exercise environment, individuals should monitor their hydration status in order to determine their appropriate rehydration strategy. For example, in a cohort of high-school football players, Yeargin et al. used urine osmolality analysis and found mild–moderate dehydration both before (881 ± 285 mOsmol/kg) and after (856 ± 259 mOsmol/kg) practice. While the researchers found the players adequately replenished during practice (approximately two-thirds of sweat loss), they insufficiently hydrated between practices.[70] Adolescent athletes can calculate their own replacement needs by calculating weight loss during workouts. For each pound lost, individuals should consume 16 oz of water and avoid caffeine.

Sports and Energy Drinks

Sports and energy drinks, in particular, have become a popular source of hydration among adolescents. With the recent surge of energy drinks available on the market, these beverages have become synonymous with sports drinks; this is especially problematic since these drinks contain significant amounts of caffeine and added sugar. Furthermore, while consuming sports drinks (containing protein, carbohydrates, or electrolytes) can be helpful for adolescent athletes, particularly if exercising for longer than 60 min,[35,71] a recent (2011) statement by the American Academy of Pediatrics found that energy drinks have "no place in the diets of children or adolescents."[35]

Sports drinks are appropriate, however, when adolescents are engaging in prolonged activity, especially if it requires short bursts of energy (e.g., soccer, basketball). As discussed earlier, adolescents' glycolytic capacity is still developing, which means they are relying on circulating carbohydrates (in the blood) for energy needs; sports drinks can satisfy this need. There are concerns with improper and unguided consumption of sports drinks; these include the displacement of calorie-free—and essential—water, which means an overall increase in daily caloric intake, as well as the displacement of other health-promoting beverages such as milk. Some strategies that can ensure adolescents are replenishing their electrolytes while hydrating properly include using sports drinks only during prolonged activity, diluting the sports drink with water (50/50), drinking seltzer water instead of soda, and tea instead of coffee.

Alcohol

While not an essential nutrient, alcohol provides a source of "empty calories" at 7 cal/g of intake. In adolescents and young adults, excessive drinking of alcohol can stunt cognitive and physical development and performance, impair judgment, and lead to increased engagement in risky behaviors such as drunk driving and unprotected sexual intercourse.[72–74] Therefore, it is concerning that consumption among adolescents is widespread, and increases linearly as youth age. More specifically, according to a 2010 Monitoring the Future Report (National Institute on Drug Abuse), 37% of current 8th graders, 59% of 10th graders, and 72% of 12th graders had tried alcohol. Heavy drinking for this report was defined as five or more drinks in a row at least once in the prior 2 weeks; reported percentages for this behavior were as follows: 8% of 8th graders, 18% of 10th graders, and 25% of 12th graders.[75]

Adolescents who play sports have been shown to drink more than their nonathlete peers. More specifically, using data from the 2005 YRBS, Mays and Thompson found male athletes were more likely to report having drinking in the past month (OR 1.204; 1.021, 1.419), and drinking and driving in the previous month (OR 1.428; 1.160, 1.757). This finding was the converse in females, however, with female athletes being less likely to drink than nonathlete peers (OR 0.807; 0.681, 0.958), drinking at 12 or earlier (OR 0.824; 0.691, 0.982), and drinking in the previous month (OR 0.843; 0.734, 0.969).[76] Given these data, and the documented mal effects of consumption on healthy growth and development, practitioners, parents, and coaches should explicitly talk with adolescents about the dangers of excess consumption.

DIETARY BEHAVIORS

Fluid and food consumption patterns are particularly important for the active adolescent, as intake habits have physiological and biological implications, and can serve to either impair or improve athletic and academic performance. Especially while in-season, dietary behaviors should be seen as part of training; athletes should be encouraged to "practice" eating in order to see the effects different foods have on them. Athletes' meal timing also matters. Prior to competitions, athletes should consume 1–4 g of carbohydrate/kg of body weight: 1 h prior, consume 1 g/kg; 4 h prior, 4 g/kg. While the meal should be high in carbohydrate, it should also be low in protein, fat, and fiber, and moderate in salt.

For athletes playing endurance sports that require short bursts of energy (e.g., soccer, volleyball), consuming a combination of simple sugars has been shown to be beneficial[69]; however, discretionary calories should be kept under 200. For every hour of exercise, adolescents should ingest 30–60 g of

carbohydrate, and drink 4–8 oz of fluid every 15 min. After an event, athletes should consume a mixed carbohydrate/protein meal or snack within 15–20 min; this will boost glycogen storage by as much as 300%. Waiting 2 h postexercise before refueling can reduce glycogen synthesis by 50%, thus impairing recovery.

Special Considerations: Weight Status and Eating Disorders

As adolescents grow older, the prevalence of eating disorders increases; dieting to lose weight is often a strong predictor of onset.[77] Using cross-sectional data from a nationally representative sample of 10,123 adolescents (ages of 13–18 years), Swanson et al. found that the lifetime prevalence of anorexia nervosa, bulimia nervosa, and binge eating disorder was 0.3%, 0.9%, and 1.6%, respectively.[78] Even for teens that do not meet the standard psychiatric DSM-IV criterion for an eating disorder, body image may still be an issue, which means they may exhibit disordered eating patterns. Ackard et al. found that among an ethnically diverse group of adolescents, many reported disturbances in body shape perception (41.5% females; 24.9% males) and unwarranted influence of body shape/weight on self-esteem (36.4% females; 23.9% males).[79] Moreover, data from the Youth Risk Behavior Surveillance System (YRBSS) found that in the 30 days prior to the survey, 39.5% of students had eaten fewer calories, less food, or more lower fat food to prevent weight gain; and 10.6% of students had not eaten for a 24 h period in order to either lose or prevent from gaining weight.[23]

Some sports, such as wrestling and martial arts, place competitors in certain weight classes. Others, such as gymnastics, ice skating, and dance, place a strong emphasis on a lean and slender physique. Since growth and development are so rapid during adolescence, it can be difficult for youth to maintain their status in a given weight class or sustain a certain body type. Accordingly, these athletes may need additional guidance to ensure that they are consuming a sufficient amount of nutrients (within potentially restrictive calorie allowances) in order to meet the demands being placed on their body.

Similarly, while active adolescents are at lower risk for becoming overweight or obese compared with their sedentary peers, they are still at risk for developing disordered eating and weight adjustment patterns such as anorexia, bulimia, and muscle dysmorphia (the self-perception that an individual lacks enough muscle, often characterized by excess usage of protein supplements and weight gainers), as well as behavioral patterns intended to lose water weight, such as wearing plastic suits, using diuretics, and sitting for long periods of time in saunas. For example, some athletes engage in purging or dietary restrictive behaviors prior to competition in order to "make weight." After competition, these athletes then compensate by consuming an excess amount of calories (binge), which leads to rapid weight gain. This dietary pattern can place such a strongly negative demand on the body that adverse physiological and developmental changes can occur.[80] Other athletes restrict calories as the competition nears. Using data from nine 16 year old female judo competitors, Boisseau et al. found a significant 19.7% decrease in daily caloric intake between 3 weeks and 1 week prior to competition (1076 ± 206 vs. 1666 ± 156, $p < 0.01$). Total water consumption also decreased significantly, from 4.22 L ± 0.41 to 3.87 L ± 0.18, $p < 0.01$.[80]

CURRENT FOOD ENVIRONMENT

A last critical consideration for practitioners, coaches, and parents is the current food environment; it has been referred to as "toxic" and "obesogenic."[81,82] Contributors to this include excessive advertising, crop subsidies that encourage the cheap creation of energy-dense, but nutrient-poor products, and a cultural lifestyle that is conducive to sedentary living. Aggregated, these variables make it difficult to make healthy choices, especially for heavily marketed-to populations, such as adolescents. Using data from 44 companies, it was found that they spent $1.6 billion on the marketing of food and beverages to adolescents and children; of that, $1 billion was spent specifically on adolescents.[83] Moreover, 89% of food advertisements seen by adolescents are for products high in sodium, fat, and sugar.[84]

This type of marketing increases the likelihood that adolescent athletes will consume products that may be high in calories, added sugars, fat, and salt, as well as ergogenic (performance) aids, such as creatine and caffeine. Moreover, the regular consumption of these high calorie foods and beverages as part of an adolescent's dietary intake can offset his or her energy balance—even if they are active—and lead to unhealthy weight gain over time. In fact, the prevalence of overweight and obesity has reached epidemic proportions in the United States; according to NHANES data (2007–2008), 18% of youth ages 12–19 years are obese.[85] There are racial trends as well; there is a higher prevalence of obesity among Mexican American boys (27%) than among non-Hispanic white adolescents (17%), and 29% of non-Hispanic black adolescent females were obese compared with 14% of non-Hispanic white females.[85] These changes could be resultant from the obesogenic food environment adolescents find themselves in, as it is increasingly difficult for teens to make healthy dietary choices, especially if they live in areas where access to affordable fruits and vegetables is limited. Recognizing that proper nutrition for adolescent athletes does not happen in a vacuum, and that youth are a heavily marketed-to population, is critical for adapting recommendations.

CONCLUSION

While adolescent athletes may have performance needs to consider when establishing their dietary intake patterns, their needs do not appear to warrant the default consumption of additional nutrients, such as sports nutrition supplements or ergogenic aids. On the contrary, research appears to support the need for adolescent athletes to pay increasing attention to

the quality of their diets—ensuring they are consuming a sufficient quantity of calories and micronutrients to meet their developmental and athletic performance needs, and limiting the intake of "empty calories" often found in SSBs and salty snack foods. Practitioners can support this by encouraging adolescent athletes to consider their food and fluid intake as part of their training, and by educating youth on the role nutrition plays in their competitive performance. Awareness of the challenges and social constraints placed on this population can aid practitioners in successfully communicating with this population.

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12 Nutrition for the Elite Athlete

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CONTENTS

Introduction: What Is an *Elite* Athlete? 163
Optimizing Health and Performance via Adequate Energy Intake 164
CHO Recommendations 164
Daily CHO Requirements 164
CHO for Pretraining and Competition 164
CHO Intake during Training and Competition 164
CHO for Posttraining and Competition 165
PRO Recommendations 166
Daily PRO Requirements 166
PRO Timing, Type, and Amount 166
Fat Recommendations 167
Fat and Athletic Performance 167
Hydration and Electrolyte Recommendations 167
Daily Hydration and Electrolyte Requirements 168
Hydration for Pretraining and Competition 168
Hydration during Training and Competition 168
Hydration for Posttraining and Competition 169
Vitamin and Mineral Recommendations 169
B-Vitamins and Energy Metabolism 169
Antioxidant Vitamins–Vitamin C, E, and Beta-Carotene 170
Bone Nutrients–Calcium and Vitamin D 170
Hematopoietic Nutrients–Iron, Folate, and Vitamin B_{12} 171
Special Considerations 171
Ergogenic Aids: Classification, Effectiveness, and Dangers 171
Weight Management 171
Extreme Environments Heat and Humidity, Cold, and Altitude 173
Summary 173
References 173

INTRODUCTION: WHAT IS AN *ELITE* ATHLETE?

In the world of sport the title "elite" is typically reserved for those athletes who are the *best*. While this title might be given to a wide range of athletes based on subjective judgments, a more systematic classification might categorize elite athletes as those competing at the collegiate, professional, world-class, or Olympic level. Competition at these levels demands a lifestyle, including a nutrition and training program, that promotes optimal performance. Such a lifestyle may also be associated with a host of desirable health benefits [1]. Indeed, available research suggests that former elite athletes, especially those involved in endurance type sports, are at decreased risk for a number of chronic diseases including heart disease, stroke, diabetes, and certain types of cancer and on average live 3–6 years longer than the general population [2–4].

At the same time, however, the unique physical demands required of an elite athlete's lifestyle can create special nutritional needs and challenges, which under certain circumstances may negatively impact health. For example, heavy training loads require additional calories and nutrients to support performance and recovery. Demanding competition schedules often require frequent travel and may disrupt an athlete's normal eating and sleeping patterns and access to familiar foods. Competition in extreme environments (i.e., extreme temperature and/or altitude) may adversely affect appetite, energy requirements, and/or the ability of the athlete to properly hydrate. Furthermore, personal or outside pressure to perform may lead to risky lifestyle practices such as extreme weight-loss methods or use of dangerous or banned ergogenic supplements. Left unchecked, these factors may not only compromise the

short-term health of these athletes, but they may also have unintended long-term health consequences.

Unfortunately, even though athletes acknowledge the value of sports nutrition, relatively few are knowledgeable about current recommendations and even fewer achieve them [5–8]. This chapter provides a practical review of current nutrition recommendations that serve as the basis of elite performance while addressing the potential nutrition-related health risks associated with the elite athlete's lifestyle.

OPTIMIZING HEALTH AND PERFORMANCE VIA ADEQUATE ENERGY INTAKE

When energy requirements are met, individual requirements for the major macronutrients and micronutrients (i.e., carbohydrate [CHO], protein [PRO], fat, vitamins, and minerals) are typically achieved provided a well-balanced diet is consumed. A well-balanced diet that provides adequate energy supports the demands of training and competition, aids in the maintenance of an appropriate body composition, promotes recovery, sustains immune function, and reduces the risk of injury [9].

Unfortunately, however, elite athletes face several challenges that may prevent them from meeting their daily energy requirements, thus increasing their risk for inadequate intakes of other nutrients. To begin with, the frequency, intensity, and duration of physical activity may change dramatically over the course of a training cycle leading to inadequate or excessive energy intake. Additionally, an athlete may sustain an unexpected injury or illness that prevents a normal level of activity, travel to a culture where the food is unfamiliar, or simply restrict energy intake in an attempt to manipulate body composition. When presented with these challenges, a registered sports dietitian becomes an invaluable resource for the athlete by helping to ensure that appropriate dietary accommodations are made so that energy and nutrient requirements are met and health and performance do not suffer. The following sections provide an overview of the major macro and micronutrient requirements of elite athletes.

CHO Recommendations

As the primary substrate used during exercise intensities >65% of VO_{2max}, CHO is arguably the single most important nutrient for an elite athlete. The availability of CHO during exercise dictates both the intensity and duration at which an athlete is able to train and compete and has been directly related to subjective indices of fatigue [10,11]. Because the body's storage capacity for CHO is limited (approximately 100 g in the liver and another 300–400 g in the muscle) regular CHO consumption is imperative. Thus, current CHO recommendations seek to ensure a high level of CHO availability during training and competition by maximizing muscle glycogen stores prior to, during, and after training or competition.

Daily CHO Requirements

Table 12.1 summarizes the most recent general daily CHO requirements for athletes according to intensity and duration of activity. These general guidelines should be fine-tuned to the individual needs of the athlete taking into account total energy requirements and feedback from training performance [12]. For athletes with ≥24 h between glycogen depleting training or competition, meeting total daily CHO requirements is the most important factor that ensures adequate muscle glycogen repletion after strenuous exercise [13]. Two classic studies conducted by Costill and associates illustrated that after strenuous running, muscle glycogen stores were only maintained by runners who consumed adequate daily CHO and the results were independent of timing of CHO ingestion [14,15]. However, for athletes with fewer than 24 h between training sessions or those who engage in multiple training sessions per day, timing of CHO ingestion becomes more important to ensure adequate replenishment of glycogen stores between training sessions (see section on "CHO for Posttraining and competition" recommendations as follows).

CHO for Pretraining and Competition

CHO intake prior to training or competition seeks to "top off" muscle glycogen stores and has been shown to improve performance during subsequent exercise [10]. The amount and timing of CHO intake prior to training or competition depends largely on scheduling of training sessions or competition as well as on individual tolerance (Table 12.1). Events lasting longer than 90 min or those that involve repeated high-intensity sprints may benefit from CHO feeding strategies that provide CHO within 1–4 h prior to the event. To avoid any potential gastrointestinal distress during training or competition, it is recommended that the CHO, calorie, and fiber content of the pretraining or competition meal be reduced as the training session or competitive event nears. Furthermore, better designed and well-controlled studies have demonstrated that glycogen super-compensation (i.e., CHO loading) may be achieved without the traditional depletion phase and with as little as 24–36 h of high CHO intake and rest (Table 12.1) [12].

CHO Intake during Training and Competition

Exogenous CHO ingestion during endurance or intermittent high-intensity type training or competition lasting longer than 45–60 min supports performance and prevents fatigue [10,12,16,17]. The current recommendation for CHO consumption during exercise is based on the maximum rate of endogenous CHO oxidation (~1 g min^{-1}) and is set at 30–60 g of CHO per hour of exercise (Table 12.1) [17,18]. Athletes are encouraged to develop a personalized plan that provides CHO within this range, maintains adequate hydration, and is amenable to their individual tolerance and opportunities for intake during training or competition noting that consumption of ~15 g CHO at 15–20 min intervals is optimal [10,17].

An emerging body of evidence, however, suggests that the rate-limiting step of endogenous CHO oxidation occurs

TABLE 12.1
Nutrient Recommendations and Timing

	Daily Requirements	Pre-Training/Competition	During Training/Competition	Recovery
Carbohydrate Recommendations	• 3–5 g·kg^{-1}·day^{-1}; Light-intensity or skill based activity • 5–7 g·kg^{-1}·day^{-1}; Moderate-intensity short duration (~1 hr·day^{-1}) • 6–10 g·kg^{-1}·day^{-1}; Moderate-to-high intensity moderate duration (1–3 hr·day^{-1}) • 8–12 g·kg^{-1}·day^{-1}; Moderate-to-high intensity long duration (4–5 hrs·day^{-1})	Days prior to event: • 7–12 g·kg^{-1} per 24–36 hrs prior to event lasting <90 min • 10–12 g·kg^{-1} per 36–48 hrs prior to event lasting >90 min Hours prior to event: • 1–4 g·kg^{-1} 1–4 hrs prior to training or event lasting >60 min	• <45 min Exogenous CHO not needed • 45–75 min High intensity intermittent type exercise may benefit from small amounts of CHO or a CHO mouth rinse • 1–2.5 hrs Endurance or stop-and-go type sports 30–60 g·hr^{-1} • >2.5–3 hrs Ultra endurance exercise up to 90 g·hr^{-1}	• ≥24 hr recovery period ensure total daily CHO requirement is met • <8 hr recovery period 0.8–1.2 g CHO·kg^{-1}·hr^{-1} + 0.4 g PRO·kg^{-1}·hr^{-1} for the first 4 hrs then resume normal CHO feedings
Protein Recommendations	Endurance athletes • 1.2–1.6 g·kg^{-1}·day^{-1} Strength athletes • 1.2–1.7 g·kg^{-1}·day^{-1} Early training/Power athletes • 1.5–1.7 g·kg^{-1}·day^{-1} Steady state strength athletes • 1.2–1.4 g·kg^{-1}·day^{-1}	• 0.3–0.5 g PRO·kg^{-1} (~20–40 g) along with 0.8–1.5 g CHO·kg^{-1} ~ within 1 hr prior to, during, or within 1hr post resistance type exercise • Consuming a combination of whey and casein proteins may provide an anabolic advantage over other types of protein or consuming either protein individually		
Hydration and Electrolyte Balance	• Due to differences in sport, environment, and individual sweat rates no single total daily fluid and electrolyte recommendation is appropriate for all athletes • To maintain euhydration elite athletes should closely monitor daily hydration status • Several markers of hydration (BW, urine color, USG) should be used to ensure adequate hydration is being obtained	• Consume adequate fluids to begin euhydrated • Consume 5–7 mL·kg^{-1} (0.08–0.11oz·lb^{-1}) fluid 4 hrs before exercise, especially important for athletes with <24 hrs between events • If no urine is produced or is dark in color consume an additional 3–5 mL·kg^{-1} (0.05–0.08 oz·lb^{-1}) 2 hrs prior to event	• Drink periodically to prevent >2% body weight loss and excessive changes in electrolyte balance • Amount should be customized to each athlete according to individual sweat rate, sport, intensity, duration, and environment • For events lasting >1–2 hrs use of a CHO electrolyte beverage containing 6–8% CHO (~14–19 g·8 oz^{-1}), 20–30 mEq·L^{-1} sodium (~110–165 mg·8 oz^{-1}), and 2–5 mEq·L^{-1} potassium (~20–45 mg·8oz^{-1}) is warranted	• If the recovery period is >~12 hrs normal meals and snacks with adequate water will typically restore euhydration • For recovery periods lasting <~12 hrs consuming ~1.5 L·kg lost BW^{-1} (~24 oz·lb lost BW^{-1}) will promote rapid rehydration • Consuming sodium during the recovery period will help retain ingested fluids and stimulate thirst

at the site of intestinal absorption and that this rate is fluid depending on the form of CHO ingested [12]. Differences in the transport mechanism at the site of intestinal absorption between glucose and fructose, for example, allows for absorption rates that exceed 1.5 g min^{-1} (90 g h^{-1}) when these different CHOs are consumed in a 2:1 ratio [12]. The practical application of this finding, however, may be limited to those athletes with extreme fuel requirements during exercise that can also easily consume food and fluids during exercise (e.g., cycling events during the Tour De France or Ironman Triathlon).

Still, further interesting data is emerging regarding the use of a CHO mouth rinse for intermittent high-intensity short duration (45–75 min) events that are not limited by the availability of endogenous CHO [12]. Initial hypotheses postulate that CHO receptors in the oral space may signal the central nervous system and promote an enhanced sense of well-being and improved pacing [12]. In fact, some studies have reported a 2%–3% improvement in performance with very small amounts of CHO ingestion or use of a CHO mouth rinse, suggesting that a nonmetabolic role for CHO ingestion during exercise and improved performance exists [19].

CHO for Posttraining and Competition

As noted previously, muscle glycogen stores are typically replenished to preexercise concentrations within 24 h if total daily CHO needs are met. For athletes with <24 h between training or competition, however, rapid replenishment of muscle glycogen stores is critical to support activity during multiple training sessions or competitions on the same or successive days. For optimal short-term glycogen repletion ensuring adequate CHO availability seems to be dependent on the amount and frequency of CHO ingestion. Muscle glycogen content was 150% greater in glycogen-depleted cyclists who consumed 1.2 g kg^{-1} h^{-1} at 30 min intervals during postexercise recovery than those who consumed only 0.8 g kg^{-1} h^{-1} [20]. Additionally, no further benefits have been demonstrated with intakes up to 1.6 g kg^{-1} h^{-1} or by manipulating the form of CHO (i.e., liquid vs. solid) [13].

Adding PRO to the postexercise feedings, however, decreases the total need for postexercise CHO. Results from a study conducted by van Loon and Wagenmakers (2000) found no difference between muscle glycogen synthesis rates over a 5 h recovery period when glycogen depleted cyclists ingested 0.8 g CHO kg^{-1} h^{-1} plus 0.4 g PRO kg^{-1} h^{-1} or 1.2 g CHO kg^{-1} h^{-1} at 30 min intervals [20]. Since the majority of athletes do not consume solely CHO postexercise ingesting at least 0.8 g CHO kg^{-1} h^{-1} plus 0.4 g PRO kg^{-1} h^{-1} offers a more practical approach to optimizing glycogen repletion between strenuous exercise bouts spaced closely together when time does not allow for normal glycogen replenishment (Table 12.1).

PRO Recommendations

While PRO has many physiological roles (e.g., structure, transport, hormonal signaling, fluid balance, immune function, etc.) the role of PRO in the maintenance and building of lean body mass (LBM) in the form of skeletal muscle is of particular importance and interest for elite athletes. This section describes what is known about the PRO needs of athletes and offers practical recommendations regarding the amount, timing, and type of PRO.

Daily PRO Requirements

Although some controversy exists regarding PRO needs of athletes, data derived from both nitrogen balance and amino acid tracer studies suggests that athletes have greater PRO requirements than their sedentary counterparts [21,22]. The current PRO recommendations for endurance and strength/power athletes are summarized in Table 12.1. These recommendations should be modified to meet the individual needs of the athlete depending on the intensity, duration, and frequency of exercise as well as training status.

It should be emphasized, however, that while PRO requirements are likely higher for elite athletes compared to sedentary individuals, dietary intake surveys among both endurance and strength/power athletes reveal that the large majority of athletes either meet or exceed the current PRO recommendations. For example, habitual PRO intakes among endurance-trained athletes tend to fall within the recommended range of 1.2–1.6 g PRO kg^{-1} day^{-1} [21–24]. Furthermore, habitual PRO intakes among strength/power athletes in the range of 2–2.5 g PRO kg^{-1} day^{-1} to as high as 3 g PRO kg^{-1} day^{-1}, a level well above recommended intakes [21–24]. Even so, certain athletic populations such as female endurance athletes, vegetarians, weight-class athletes, or those restricting energy intakes may be at risk for inadequate PRO intakes [17].

Some concern has been raised among health professionals regarding the potential negative effects of chronically high PRO intake among athletes. In particular, excessive PRO intake may *crowd out* other nutrients, especially CHO, potentially impairing performance particularly for endurance-type athletes. Other concerns that excessive PRO intake may impair renal function or negatively impact bone health, however, remain largely unsubstantiated [22,25]. In fact, high PRO intakes have only been associated with impaired renal function in individuals with concurrent renal insufficiency [22,25]. Additionally, even though high PRO intakes tend to increase urinary calcium excretion, mounting evidence suggests that high PRO intakes actually result in greater peak bone mass and may actually reduce the risk of osteoporosis and related fractures [26].

PRO Timing, Type, and Amount

Since most athletes appear to be meeting or exceeding daily PRO recommendations, a more practical concern might be identifying the significance of the timing and type of PRO consumed as well as the effect that co-ingestion of other nutrient such as CHO might have on skeletal muscle hypertrophy, strength gains, and performance. From a timing stand point, research suggests that there is an *anabolic window* (approximately 1 h prior to and/or after exercise) during which PRO should be consumed to optimize strength gains and muscle hypertrophy [13,22,27–31]. However, whether consuming PRO prior to, during, or after exercise would be more advantageous remains unclear. Tipton and Wolfe (2001) showed a benefit on net PRO status only when 35 g of CHO with 6 g of essential amino acids (EAA) was consumed *immediately prior to training* as opposed to *immediately posttraining* [32]. A separate follow-up study, however, found no difference in PRO status regardless of whether 20 g of whey PRO was consumed *immediately prior to or immediately after* the training bout [32,33].

Other studies have highlighted possible performance benefits when PRO is consumed along with CHO *during* endurance type exercise. For example, Saunders and Herrick (2007) showed improvements in cycling performance and attenuation of muscle damage when PRO was added to a standard 6% CHO solution or CHO gel [34,35]. A major criticism of these studies, however, is that isoenergenic controls were not used and the caloric difference between the treatment vehicles likely accounts for the difference between treatment groups. Indeed, studies that have used isoenergenic controls have found no significant endurance performance benefits when PRO is added to a CHO solution consumed during endurance-type exercise [36–38]. For strength/power athletes, on the other hand, ingesting PRO plus CHO during prolonged resistance training (approx. >45 min) may ameliorate muscle catabolism, preserve muscle glycogen, and enhance muscle PRO accretion [31]. Although the mechanism by which CHO positively affects PRO status is not precisely known and is likely multifaceted, at least part of the effect is attributed to insulin which has been shown to be a potent inhibitor of muscle PRO breakdown (MPB) [39].

PRO type also seems to have an effect on muscle PRO synthesis (MPS). Interestingly, only EAA seem to be needed to effectively stimulate postexercise MPS [13,40]. In fact, leucine alone has been shown to independently stimulate expression of PROs that regulate MPS [41]. The majority of research, however, centers on common supplemental forms

of PRO such as whey, casein, soy, egg, and milk, or some combination thereof. The milk PROs whey and casein are particularly popular and seem to have unique anabolic properties. The soluble PRO whey elicits a rapid rise in plasma amino acid concentration and leads to both higher MPS and AA oxidation rates while the insoluble PRO casein clots in the stomach, delaying gastric emptying, leading to a slower more sustained rise in plasma AA that supports MPS over a longer period of time [42–44]. Despite these differences, however, both whey and casein seem to affect net PRO balance similarly [45].

Even so, it makes sense that some combination of these PROs might provide an anabolic advantage. Indeed, consuming milk, which is composed of approximately 80% casein and 20% whey PROs, after resistance-type exercise effectively stimulates MPS and has been shown to be superior to plant PROs (i.e., soy PRO) in eliciting strength gains and muscle hypertrophy [46–48]. Two studies have shown that consuming milk immediately after resistance-type exercise significantly increased muscle fractional synthetic rate and muscle fiber size ($p < 0.05$) when compared to an isonitrogenous isocaloric soy beverage or placebo [27,49]. Conversely, Candow and Burke (2006) found no difference in LBM, strength, or muscle damage between those who consumed a whey or a comparable soy supplement immediately postexercise [50].

The ideal amount of PRO needed to maximize MPS and strength gains has also been an area of interest. Recently Moore and Phillips (2009) demonstrated that MPS responded in a dose–response manner and was maximally stimulated by ingestion of 20 g of PRO after resistance exercise [51]. Ingestion of 40 g of PRO resulted in a significant increase in leucine oxidation, suggesting that a PRO intake ≥40 g exceeds the amount that may be incorporated into muscle tissue [51].

Based on the research presented previously, it is clear that much still stands to be elucidated regarding the optimal PRO prescription for the elite athlete seeking to optimize LBM and improve performance. Still, from a practical point of view the current research suggests that athletes seeking to maximize gains in LBM and strength and/or accelerate recovery should aim to consume between 0.3 and 0.5 g PRO kg^{-1} (~20 to 40 g) along with 0.8–1.5 g CHO kg^{-1} within 1 h prior to, during, or within 1 h post resistance and/or endurance type exercise [31,40,51].

Fat Recommendations

Dietary fat is a critical component of every elite athlete's diet. Aside from being calorically dense (9 cal g^{-1} of fat compared to 4 cal g^{-1} for CHO and PRO), fats play integral roles in cell structure, nervous function, hormone synthesis, insulin action, prostaglandin production, absorption and transport of the fat-soluble vitamins, and much more [52]. Fat requirements for athletes must be considered within the context of energy and macronutrient balance and typically fall within 20%–35% of total calories depending on the athlete's individual CHO and PRO requirements [17]. For example, a 90 kg (~200 lb) American football linebacker may require 3600 cal, 6 g CHO kg^{-1} (545 g CHO or ~60% CHO), and 1.6 g PRO kg^{-1} (145 g PRO or ~15% PRO) during a certain training cycle. It follows then that the fat recommendation for this athlete would be about 100 g (1.1 g fat kg^{-1}) or ~25% of total calories from fat.

Additionally, very-low-fat diets (<20% of total calories from fat) are not recommended for the athletes. Very-low-fat diets are typically too low in energy to support the demands of training and can lead to a lower intake of other nutrients, both of which can be detrimental to health and performance [53]. Like the general population, elite athletes should focus on obtaining adequate dietary fat from heart healthy sources such as low-fat dairy products, avocadoes, nuts, seeds, and olive oil and canola oil. Fish is also an excellent source of healthy fats and athletes should aim for at least two 3.5 oz servings of fatty fish such as salmon, herring, lake trout, and tuna per week [54].

Fat and Athletic Performance

Elite athletes have a greater ability to utilize fat than their untrained counterparts. Trained athletes typically have elevated levels of muscle lipoprotein lipase, muscle lipase, fatty acid acyl CoA synthetase and reductase, carnitine acyl transferase, and 3-hydroxyl acyl CoA dehydrogenase, all of which enhance fatty acid oxidation [55]. Furthermore, trained athletes store more intracellular fat, which leads to enhanced fatty acid availability and oxidation during exercise, potentially conserving glycogen stores helping to stave off fatigue during endurance-type exercise [55]. This potential performance-enhancing effect of glycogen sparing due to increased fat oxidation has led to the development of dietary strategies that might enhance fat utilization during endurance-type exercise. Some of these strategies include *fat adaptation* diets (>40% of energy from fat), supplementation with medium chain triglycerides (MCTs), or L-carnitine. Unfortunately, research has shown these strategies to be largely ineffective at best and, in the case of MCT supplementation, can actually impair performance due to gastrointestinal distress [56–59].

Hydration and Electrolyte Recommendations

Proper hydration mirrors adequate energy and CHO intake in terms of importance and the effect on performance and the overall health of elite athletes. Maintenance of euhydration during exercise is critical for normal thermoregulatory, metabolic, and nervous system function. Dehydration resulting in a little as a 2% body weight (BW) loss as water increases body core temperature, heart rate, glycogen utilization, perceived exertion, and, consequently negatively impacts performance [60]. If fluid loss continues, metabolic, nervous system, and cognitive functions become impaired and the likelihood of heat exhaustion or heat stroke dramatically increases [60].

Furthermore, excessive electrolyte loss, which often accompanies dehydration, may alter normal nervous system and cardiac function, lead to the development of muscle

cramps, and/or cause life-threatening shifts between extra- and intracellular fluid compartments [60]. Conversely, excessive consumption of hypotonic beverages may precipitate dilutional hyponatremia, resulting in cerebral, or pulmonary edema, and even death [60]. Clearly the importance of adequate hydration and electrolyte balance among the athletic population cannot be overstated. This section addresses the hydration needs of elite athletes, discusses practical ways of assessing hydration status, and summarizes current fluid and electrolyte recommendations.

Daily Hydration and Electrolyte Requirements

To avoid decrements in performance or adverse health outcomes elite athletes must maintain euhydration and electrolyte balance by matching daily fluid and electrolyte loss with intake. Inter-individual variability in sweat rate and electrolyte losses, differences in sport type, environment, and heat acclimation make it not only difficult, but also inappropriate to assign a universal fluid and electrolyte intake recommendation for all athletes. Consider that a football player practicing in the heat in full pads may lose as much as 8 L (~1.6 $L \cdot h^{-1}$) of fluid and greater than 9000 mg of sodium or the equivalent of 23 g of NaCl over the course of a 5 h practice, while a swimmer training only 1 h may lose less than 0.5 L of fluid and minimal amounts of sodium [61]. Obviously, in this situation the fluid and electrolyte needs of the football player are much greater than that of the swimmer and a standard fluid recommendation for both athletes would be inappropriate.

Since daily fluid requirements vary widely among athletes, it is imperative that each athlete monitor his/her individual daily hydration status to ensure adequate amounts of fluid is being ingested. Tracking chronic changes in first morning BW after voiding (BW should fluctuate by <1%) and monitoring urine color of the first void are simple methods athletes can employ to monitor their hydration status on a daily basis. Ideally, however, BW and urine color should be used in combination with other more objective status measures, such as urine specific gravity (USG) or plasma osmolality, to minimize any possible confounding factors that might affect BW or urine color [60]. Additionally, athletes should be reminded that both fluids and foods can serve as hydrating agents. Water, milk, fruit juices, sport drinks, coffee, tea, soup, and fruits, and vegetables all provide significant amounts of fluid and can contribute to daily fluid intake needs and help to maintain euhydration [61].

With regard to electrolyte needs, sodium is the electrolyte that is lost to the greatest extent during exercise and, thus, should be of most concern for elite athletes [61,62]. Potassium, magnesium, and calcium, along with several other organic compounds, are also lost with sweat; however, the amounts lost are relatively low and constant relative to the higher more variable loss of sodium [61,62]. Not unlike fluid losses, variability in sodium losses between athletes and challenges in accurately assessing sodium losses during exercise makes it difficult to establish a specific, universal sodium recommendation.

It is important to note that the current adequate intake (AI) for sodium (1500 mg Na^+ day^{-1} or ~3.8 g NaCl day^{-1}) set forth in the 2004 dietary reference intake (DRI) is likely inadequate for the athletic population [63]. Even so, the average athlete consuming a normal diet generally consumes adequate amounts of sodium making hyponatremia due to insufficient dietary intake rare. In contrast, sodium losses among athletes who lose large volumes of sweat on a daily basis (e.g., distance runners, tri-athletes, football players, etc.) and/or those who may be considered *salty sweaters* may be at increased risk of hyponatremia. For these athletes strategic consumption of salty snacks and electrolyte containing sports drinks will help to offset sodium losses and maintain electrolyte balance.

Hydration for Pretraining and Competition

Elite athletes should aim to enter a training session or competition euhydrated and in normal electrolyte balance. As noted previously, these conditions are typically met if adequate fluid and food is consumed over a prolonged recovery period (>12 h) [60]. For athletes who have not adequately hydrated between training sessions or for whom time between training does not allow for sufficient consumption of fluid and electrolytes, hydrating prior to training or competition is advocated. Hydration strategies set forth by the American College of Sports Medicine (ACSM) are summarized in Table 12.1 [60]. Following these recommendations, a 70 kg (154 lb) distance runner seeking to prehydrate should consume approximately 350–490 mL (~12 to 16 oz) of fluid about 4 h prior to training. Beverages containing sodium or sodium-containing foods may also help stimulate thirst and enhance retention of the consumed fluids [60].

Hydration during Training and Competition

The goal of hydrating during training or competition is to prevent excessive fluid loss (>2% BW) and drastic changes in electrolyte balance that may compromise performance or lead to more serious complications such as heat illness or rhabdomyolysis. Optimally, fluid intake and electrolyte intake should equal fluid and electrolyte loss. This scenario, however, is often not possible for many athletes. Bear in mind that the maximal rate of gastric emptying and subsequent intestinal absorption approximates 1 L fluid h^{-1}, while the average athlete may lose as many as 1–3 L of fluid in the form of sweat every hour [61,62].

Additionally, athletes with low gastric tolerance for fluids during exercise may find it difficult to consume the volume of fluid required to prevent excessive fluid losses even at sweat rates <1 L h^{-1}. Other athletes simply may not have the opportunity to drink depending on the nature of the sport. To prevent excessive fluid loss, athletes must develop a customized hydration program depending on the amount of fluid lost (i.e., sweat rate), sport, different training environments, and individual tolerance. An athlete's sweat rate may be calculated easily by routine measurement of pre- and postexercise BW. This method assumes that the amount of BW lost during exercise approximates fluid losses [60].

In contrast, consumption of copious amounts of fluid during training or competition that result in BW gains is

contraindicated. Excessive water consumption without adequate electrolyte replacement has the net effect of *diluting* plasma sodium. Dilutional hyponatremia (plasma sodium levels that rapidly drop to <130 mmol L^{-1}) has been reported in slow marathon runners consuming excessive amounts of hypotonic beverages (e.g., plain water) before, during, and after a race [60]. As plasma sodium levels drop symptoms such as headache, vomiting, fatigue, swelling in the extremities, confusion, and disorientation are common [60]. If not properly treated, dilutional hyponatremia eventually leads to cerebral and pulmonary edema, seizure, coma, respiratory arrest, and death [60].

In short, a reasonable hydration strategy for the elite athlete during exercise should aim to prevent BW loss >2% due to water deficits, while avoiding excessive fluid consumption that results in BW gains. The strategy should be customized to the individual needs of the athlete depending on sweat rate, sport, environment, and tolerance. Sodium-containing beverages and/or snacks are recommended to maintain electrolyte balance, stimulate thirst, and promote fluid retention, especially for endurance-type athletes exercising >1 h or other athletes with large fluid and sodium losses.

Hydration for Posttraining and Competition

The goal of postexercise hydration is to replenish fluid and electrolytes that were not adequately replaced during exercise and, thus, prepare for the next exercise session. Recall that for many athletes dehydration during training or competition is an inevitable situation since sweat rates (~1 to 3 L h^{-1}) often exceed the physiological ability (~1 L h^{-1}) to ingest and absorb fluid. Still, not unlike replenishment of glycogen stores, if adequate meals, snacks, and plain water are ingested over a long enough recovery period (>12 h) euhydration and lost electrolytes are typically restored. Situations in which recovery time is limited, however, may require more aggressive hydration tactics. When recovery time is limited (<12 h), athletes should aim to consume at least 1.5 L of fluid for every kilogram BW lost (24 oz lb^{-1} BW or 150% of BW lost) [60]. The additional fluid required during the recovery period is needed to offset losses due to increased urine production that occurs in response to ingestion of large volumes of fluid [60]. For that reason, it is recommended that fluids be consumed over time as opposed to immediate ingestion of the prescribed volume of fluid. Additionally, as mentioned previously, simultaneous ingestion of sodium in the form of food or as part of a sports drink can help to retain fluid and stimulate thirst throughout the recovery period, helping to restore euhydration and replace lost electrolytes more rapidly [60].

Vitamin and Mineral Recommendations

There is no question that micronutrients (i.e., vitamins and minerals) play a critical role in supporting training, competition, and the overall health of the elite athlete [17,64]. It remains unclear, however, whether or not training for sport increases micronutrient requirements or whether micronutrient intakes exceeding the RDA can enhance performance [65–67]. Theoretically, strenuous physical activity may alter micronutrient needs by increasing vitamin and mineral turnover or increasing losses via sweat, urine, or feces [17,67]. Moreover, higher micronutrient requirements may be needed to support physiological training adaptations such as the building, maintenance, and repair of LBM [17,65–67]. However, difficulty in accurately assessing micronutrient intake and status as well as fundamental differences in experimental design between studies has made it difficult to draw conclusions regarding the micronutrient needs of athletes.

The DRI published by Institute of Medicine (IOM) state that athletes do not have micronutrient needs that differ from the general population and that the elevated energy requirements among athletes more than likely compensate for any micronutrient deficit incurred as a result of regular strenuous exercise provided energy needs are met and a variety of foods are consumed [65,66,68]. Conversely, athletes who restrict energy, avoid or eliminate certain foods from their diet, or consume an overall poor diet may have marginal micronutrient intakes that could lead to poor status and negatively impact performance and/or health [17]. This section highlights common micronutrients found to be of concern among athletes, namely, certain B-vitamins, antioxidants, calcium and vitamin D, and iron.

B-Vitamins and Energy Metabolism

Although the water-soluble B-vitamins (thiamin, riboflavin, niacin, pantothenic acid, pyridoxine [B_6], and biotin) are essential for energy metabolism, limited research exists that regular strenuous exercise increases B-vitamin requirements [65,67,69]. Even so, dietary intake surveys often reveal marginal intakes of vitamin B_6, B_{12}, and folate among the athletic population, especially among vegetarian female athletes and/or those with disordered eating patterns [17]. Still, short-term deficiencies do not seem to negatively impact athletic performance and B-vitamin requirements are likely met when energy availability is adequate and a variety of foods are consumed [67].

Nevertheless, several sport supplements and energy drinks fortified with B-vitamins, often times at several times the recommended intake, are commonly marketed to athletes as a quick source of energy. This marketing scheme is misleading since vitamins do not in fact provide energy. Additionally, supplementing with B-vitamins has not been shown to enhance energy metabolism or improve performance [17,67].

In contrast, excessive supplementation of certain B-vitamins such as niacin, riboflavin, or pyridoxine can negatively impact both health and performance. Niacin supplementation >1 g day^{-1} has vasodilatory effects that may cause burning, itching, and tingling and/or gastrointestinal distress potentially impairing performance [69]. Riboflavin, a fluorescent yellow compound, in excess of only 1.7 mg day^{-1} is readily excreted by the kidneys producing a fluorescent yellow urine, thereby confounding the use of urine color as a marker of hydration [69]. Moreover, excessive long-term pyridoxine supplementation has in certain cases led to irreversible peripheral neuropathy [69].

Antioxidant Vitamins–Vitamin C, E, and Beta-Carotene

Oxidative stress occurs when endogenous and/or environmental oxidants (e.g., reactive oxygen and nitrogen species [RONS], pollution, solar radiation, etc.) surpass the body's inherent antioxidant capacity. Left unchecked RONS damage cellular macromolecules and interfere with cellular signaling pathways, ultimately resulting in cellular dysfunction [70]. It has been hypothesized that the cellular damage caused by RONS plays a major role in the pathophysiology of a majority of chronic disease states, including coronary artery disease (CAD), certain forms of cancer, and dementia and that increasing intake of dietary antioxidants vitamins may effectively prevent or slow this process [70]. Since regular exercise may result in a 10- to 20-fold increase in whole body oxygen consumption, and, thus an increase endogenous RONS formation, it has been hypothesized that athletes might require or could benefit from additional dietary antioxidants vitamins C, E, and beta-carotene [71].

Despite the logic of this hypothesis, however, research does not support a performance or health benefit from antioxidant vitamin supplementation in athletes who are meeting the recommended requirements. In fact, supplementation with antioxidant vitamins may actually impair performance by blocking and/or delaying many of the beneficial physiological adaptations that occur in response to regular exercise [72,73]. Ristow and Blüher (2009) observed that supplementation with a combination of vitamin C and E (1000 mg and 400 IU day^{-1}, respectively) over a 4 week training period effectively blocked induction of the antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx) among healthy young men [74]. Moreover, a number of other recent studies have shown that supplementation with high doses of various antioxidant vitamin combinations actually delays recovery from exercise by slowing the increase in exercise induced stress PROs and delaying muscle recovery [72,75,76]. Finally, interventions that have investigated the use of antioxidant supplementations in the treatment of chronic disease have either shown no effect or actually shown an increase in the risk of mortality [70].

Bone Nutrients–Calcium and Vitamin D

While many nutrients are important for bone health, none are more important than calcium and vitamin D. Calcium and vitamin D work together to maintain calcium homeostasis by regulating bone metabolism and calcium absorption. Adequate calcium is also important for normal muscle contraction, nerve conduction, and blood clotting, while vitamin D has several other roles involving gene expression, immune function, modulation of inflammation, and potentially enhancement of muscular and athletic performance [77–81]. Current calcium and vitamin D recommendations are summarized in Table 12.2 [82].

TABLE 12.2
Calcium, Vitamin D, and Iron Recommendations

Age Group	Calcium[a]	Vitamin D[b]	Iron[c]
14–18 years	1300–1500 $mg \cdot day^{-1}$	600 $IU \cdot day^{-1}$	Males: 11 $mg \cdot day^{-1}$ Females: 15 $mg \cdot day^{-1}$
19–50 years	1000–1500 $mg \cdot day^{-1}$	600 $IU \cdot day^{-1}$	Males: 8 $mg \cdot day^{-1}$ Females: 18 $mg \cdot day^{-1}$
Dietary Sources	Excellent Sources: Low-fat dairy products and fortified cereals, juices, and soy products Poor Sources[d]: Dark green leafy vegetables and legumes	Good Sources: Fatty fish such as salmon, mackerel, and tuna as well as fortified dairy products and ***sensible sun exposure*** of arms and legs to 0.5 MED[e]	Excellent Sources: Red meat, shell fish and fortified grain and soy products Poor Sources[d]: Dark green leafy vegetables and legumes

Source: Coyle EF. *J Sports Sci*, 22, 39, January 2004; Tenforde AS, Sayres LC, Sainani KL et al. Evaluating the relationship of calcium and vitamin D in the prevention of stress fracture injuries in the young athlete: A review of the literature. PM R. 2, 945, October 2010; Holick MF, Binkley NC, Bischoff-Ferrari HA et al. *J Clin Endocrinol Metab* 96, 1911, June 2011; Quaglio G, Fornasiero A, Mezzelani P et al. *Intern Emerg* Med 4, 289, August 2009.

[a] The standard practice for athletes with disordered eating, low energy availability, and/or amenorrhea is to recommend 1500 mg elemental calcium daily; The tolerable upper intake level (UL) for calcium is set at 2500 $mg \cdot day^{-1}$ [16,86].

[b] While 600 $IU \cdot day^{-1}$ is recommended to optimize bone health, some experts argue that as much as 1500–2000 $IU \cdot day^{-1}$ may be required to maintain 25(OH)D levels above 30 $ng \cdot mL^{-1}$; The UL for vitamin D is set at 4000 $IU \cdot day^{-1}$ [86,87].

[c] Iron requirements for distance runners have been estimated to be increased by as much as 30–70%; Vegetarians, blood donor, and endurance athletes should aim to consume more than their respective RDAs; The UL for iron is set at 45 $mg \cdot day^{-1}$ [16,92].

[d] Oxylates and phytates present in dark green leafy vegetables and legumes significantly decreases the bioavailability of calcium and iron [86,92].

[e] One minimal erythemal dose (MED) is defined as the amount of UVB exposure that produces redness of the skin 24 hrs after exposure; Exposure of arms and legs to 0.5 MED (~5–10 min depending on time of day, season, latitude, and skin sensitivity) is equivalent to ~3000 IU vitamin D_3 [87].

Although the IOM deemed athletes to have no greater requirement for calcium or vitamin D than their sedentary counterparts, research indicates that many athletes do not obtain adequate amounts of these two key bone nutrients [79–81,83–85]. In particular female athletes with inadequate energy availability and/or who have low-intake of or avoid dairy products are at an increased risk for low calcium intake [17]. Similarly, athletes at greatest risk for suboptimal vitamin D status (<30 ng mL^{-1} 25(OH)D) include those who primarily train or compete indoors, live or train at high latitudes (>37°N–40°N) during the winter months, have darkly pigmented skin, or regularly use sunscreen [79–81]. Inadequate calcium and vitamin D among this population significantly increases the risk of stress fractures and development of osteopenia or osteoporosis later in life [17,86]. A registered sports dietitian should be consulted to determine the adequacy of dietary calcium as well as develop strategies for meeting calcium needs via food or if appropriate recommendation of a suitable calcium supplement.

Additionally, assessment of serum 25(OH)D concentrations may also be warranted for athletes at risk for suboptimal vitamin D levels. For athletes with suboptimal 25(OH)D status, daily supplementation with 2000–6000 IU of vitamin D_3 for 6–8 weeks followed by a maintenance period of 600–2000 IU vitamin D_3 day^{-1} may be required to achieve and maintain a blood level of 25(OH)D > 30 ng mL^{-1} [87]. Because dietary sources of vitamin D are limited to a few foods (salmon, tuna, mackerel, and fortified dairy), and assessment of serum 25(OH)D concentrations may not be practical or affordable for all athletes, supplementation with 1500–2000 IU vitamin D_3 day^{-1} may be appropriate for the majority of athletes at risk for vitamin D deficiency [87].

Hematopoietic Nutrients–Iron, Folate, and Vitamin B_{12}

Iron, folate, and vitamin B_{12} play important roles in the formation and function of red blood cells (RBC) and thus oxygen transport. Maintaining adequate iron status, in particular, is not only important for optimal aerobic efficiency and endurance capacity but also affects mental acuity and immune function [17,88]. Current iron recommendations are summarized in Table 12.2 [89]. A detailed description of the prevention, diagnosis, and treatment of anemia is discussed in Chapter XXXX. In short, female athletes, especially adolescent females, distance runners, vegetarians, and/or those who avoid red meat are at the highest risk for iron deficiency [88]. At risk athletes should undergo routine iron status assessments. For athletes found to be deficient, increasing the intake of iron-rich foods (Table 12.2) should be encouraged. In most cases, however, dietary alterations are insufficient to correct the deficiency and supplementation is necessary [17].

SPECIAL CONSIDERATIONS

Elite athletes are faced with several unique challenges that may potentially have dire consequences for health and performance. This section addresses three common areas of concern for elite athletes namely, use of ergogenic aids, weight management, and extreme environments.

Ergogenic Aids: Classification, Effectiveness, and Dangers

An ergogenic aid may be defined as anything that is intended to enhance physical performance, stamina, or recovery. Using this definition, a wide range of dietary and herbal supplements, stimulants, as well as pharmaceutical drugs (e.g., human growth hormone [HGH], erythropoietin [EPO], diuretics, etc.) may be considered ergogenic. The American Dietetic Association (ADA) and ACSM categorize ergogenic aids into four separate categories based on supporting scientific evidence: (1) ergogenic aids that perform as claimed, (2) ergogenic aids that may perform as claimed, but for which there is insufficient evidence, (3) ergogenic aids that do not perform as claimed, and (4) ergogenic aids that are dangerous, banned, or illegal [17]. Similarly, the Australian Institute of Sport has devised a grading system (Grades A–D) for ergogenic aids used in sport based on safety, legality, and effectiveness (Table 12.3) [90]. From a quick review of Table 12.3, it is evident that the vast majority of ergogenic aids used in sport are ineffective at best or dangerous to an athletes career and health at worst [91–93]. Notwithstanding, use of some form of ergogenic aid is almost ubiquitous among the athletic population [94–97]. In one recent survey, more than 87% of elite athletes surveyed reported using at least one dietary supplement [94].

Furthermore, use of ergogenic aids such as anabolic steroids, HGH, and diuretics can result in serious side effects that not only put the athlete's career at risk but, also, jeopardize the short- and long-term health of the athlete [91,98]. Unfortunately, some athletes knowingly turn to ergogenic aids known to contain dangerous, banned, or illegal substances, while others inadvertently consume these substances via adulterated dietary supplements [99–102]. Both the National Collegiate Athletic Association (NCAA) and the World Anti-Doping Agency (WADA) ban certain substances known to adversely affect health and/or provide an unfair advantage and routinely test for such substances. Nevertheless, qualified health professionals (i.e., medical doctors and registered sports dietitians) must remain open-minded and well-educated regarding the use of ergogenic aids in order to most effectively assess, recommend, and educate athletes regarding responsible use of such products [17]. Many online resources are available for health professionals, trainers, coaches, and athletes alike that provide evidence-based information regarding safe and prudent use of ergogenic aids (see References).

Weight Management

While BW and body composition influence athletic performance, there is no singular ideal body composition that correlates with optimal athletic performance [17]. Genetics, gender,

TABLE 12.3
Ergogenic Aid Classification

Grade A-Perform as Claimed	Grade B-May Perform as Claimed
Caffeine	β-alanine
Creatine	HMB[a]
Probiotics	Colostrum
Protein and AA Supplements[a]	Glutamine
Sodium Bicarbonate and Citrate	Glucosamine
Sports Drinks, Gels, and Bars	Melatonin
Vitamin and Mineral Supplements (i.e. calcium, iron, vitamin D)	Ribose

Grade C-Do Not Perform as Claimed[b]		Grade D-Dangerous, Banned, or Illegal[c]
Individual AAs	Gamma Oryzanol	19-norandrosteneediol
Bee Pollen	Ginseng	19-norandrostenedione
BCAA[a]	Inosine	Androstenedion
Carnitine	MCT[a]	Dehydroepiandrosterone[a]
Chromium Picolinate	NO Supplements[a]	Ephedra
Coenzyme Q10	Pyruvate	Glycerol
CLA	Oxygenated Water	HGH[a]
Cordyceps	Vadium	Methylhexaneamine
Cytochrome C	Vitamin & Mineral Supplements (not listed in Grade A)	Tribulis Terrestris
Dihydroxyacetone		Strychnine

Source: Rodriguez NR, DiMarco NM, Langley S et al. *J Am Diet Assoc*, 109, 509, 2009; Sport AIo. AIS sports supplement program. 2009. Accessed: May 5, 2011. Available from: http://www.ausport.gov.au/ais/nutrition/supplements

[a] Abbreviations: AA = amino acid; BCAA = Branched chain amino acids; CLA = conjugated linoleic acid; DHEA = Dehydroepiandrosterone; HGH = Human growth hormone; HMB = β-Hydroxymethylbutyrate; MCT = Medium chain triglyceride; NO = Nitric oxide.

[b] Not a conclusive list; Most sports supplements not found in this table fall into this category.

[c] Not a conclusive list; For an extensive list of banned substances see references blank and blank.

and environmental factors heavily influence an athlete's natural body composition. Moreover, elite athletes train and compete successfully over a wide range of body compositions. Body fat percentages between 5% and 20% for male athletes and 16% and 28% for female athletes are considered optimal depending on sport, position, and body type [103]. Still, a higher LBM to body fat ratio may be advantageous for many elite athletes in that it provides greater strength-to-weight ratio, may increase speed, agility, and/or endurance, and provides aesthetic appeal for sports in which appearance is important [103].

Ideally the best time to make changes in body weight and/or composition is during the off-season or precompetitive period versus during the competitive season when energy and performance demands are more critical [17,103,104]. Athletes seeking to lose weight should aim for a slow and steady weight loss (no more than 1 kg week^{-1}) and may benefit from a diet slightly higher in PRO (1.5–2.0 g PRO kg $^{-1}$) to minimize losses in LBM while still promoting fat loss [21]. Theoretically an energy deficit of 500 kcal day^{-1} obtained via a combination of reduced energy intake and increased energy expenditure will result in the loss of 1 lb of body fat per week (3500 kcal lb body fat^{-1}) [104].

Conversely, athletes seeking to gain weight or muscle mass must consistently consume calories in excess of those expended. In fact, a positive energy balance has been shown to be more important than increasing PRO intake when attempting to gain LBM [21]. It is generally recommended that male athletes increase their caloric intake by 400–500 cal day^{-1} to support an increase of ∼0.5 kg (∼1 lb) of muscle tissue per week, while females should increase their caloric intake to a somewhat lesser extent [104].

To ensure energy and nutrient needs are being met and body composition changes occur in a healthy fashion, body composition changes should be monitored by a qualified medical practitioner or registered sports dietitian. Supervision is especially important among athletes participating in weight-class/aesthetic sports or sports where a lower weight may provide a competitive advantage (e.g., wrestlers, light-weight rowers, jockeys, gymnastics, diving, figure skating, distance running and cycling, etc.). Inadequate direction or supervision may result in the athlete utilizing extreme and/or dangerous methods of weight control.

For example, weight-class athletes have been reported to exercise in sweat suits, sit for long periods in saunas, abuse

diuretics and laxatives and/or engage in severe caloric restriction and self-induced vomiting in order to lose weight quickly for a competition [105]. These tactics not only lead to dehydration, impaired cognitive function, difficulty recovering, and building LBM, but they may also compromise bone health and in some cases have even resulted in death [105]. Moreover, athletes who engage in chronic weight cycling (i.e., rapid weight-loss followed by rapid weight-gain) are more likely to be over-weight later in life putting themselves at an increased risk for weight-related chronic diseases [106].

Similarly, research indicates that athletes who participate in aesthetic and endurance sports often engage in unhealthy dieting practices to reduce body weight and/or change body composition in the hopes of improving performance [107]. Not only can these pathogenic weight control practices be dangerous to health and performance, but they may develop into more clinical conditions including body image distortion and eating disorders (i.e., anorexia nervosa and bulimia nervosa) [107]. A team approach (i.e., medical doctor, mental health professional, and sport dietitian) is highly recommended for effective treatment of such athletes.

Extreme Environments Heat and Humidity, Cold, and Altitude

Elite athletes are often faced with the challenge of competing under extreme environmental conditions (i.e., heat, humidity, cold and/or altitude). Exercise in hot and/or humid environments significantly increases physiological heat stress that may lead to excessive water and sodium losses, thereby decreasing the body's ability to thermoregulate. As previously described (see section on "Hydration and Electrolyte recommendations"), excessive fluid and sodium losses may result in anything from performance-inhibiting heat cramps to life-threatening heat exhaustion. Similarly, athletes who exercise in cold environments experience increased water losses via the lungs and sweat, have blunted thirst reflexes, and may even voluntary fluid restrict in an attempt to decrease the need to urinate [17]. For elite athletes training or competing in such environment's adherence to established hydration guidelines as well as routine monitoring for heat-related illness or hypothermia is imperative.

Moreover, training or competing at altitude presents unique nutrition-related challenges. Athletes who exercise at >2500 m (8200 ft) have increased rates of CHO utilization, an elevated basal metabolic rate (BMR), altered fluid balance, suppressed appetite, and may experience cachexia [108]. As such, a diet that focuses on CHO and energy-rich foods is warranted and may even decrease the symptoms of acute mountain sickness [108]. Attention to fluid intake is also important as, exposure to high altitude results in an increase in ventilation that results in a loss of water to the environment and a concomitant loss of plasma volume. A sports drink that contains both CHO and electrolytes offer a practical option that helps to provide extra CHO and maintain the drive to drink and minimizes urine production helping to maintain fluid balance [108].

SUMMARY

In summary, while the active lifestyle of an elite athlete may afford long-term health benefits for some athletes, the unique physical demands required of an elite athlete's lifestyle can create special nutritional needs and challenges, which under certain circumstances may negatively impact health. Under such circumstances nutritional guidance and counseling from a qualified sports dietitian is imperative in helping elite athletes meet their unique nutritional requirements and prevent undue health issues and decrements in performance.

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13 Optimal Nutrition Guidance for Older Adults

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CONTENTS

Introduction 177
Current Recommendations 177
Nutrients of Concern 178
Vitamin D 178
Calcium 179
Vitamins E and K, and Potassium 179
Fiber 179
Special Dietary Considerations for Older Adults 179
Organ Systems 179
Taste and Smell 180
Vision, Dexterity, and Mobility 180
Social Factors 180
Physiological Changes of Concern in Older Adults 181
Dentition and Associated Senses 181
Cardiovascular Disease 181
Osteoporosis 181
Glucose Intolerance/Type 2 Diabetes 181
Hypertension 182
Immune Function 182
Cancer 182
Conclusions 182
References 182

INTRODUCTION

In 2010 approximately 14% of the U.S. population was over 65 years of age. This percentage is expected to increase to approximately 21% by the year 2030. Accompanying this shift in the demographic makeup of U.S. population is a greater need for specific nutrition guidance to achieve and maintain optimal physical and cognitive function with advancing years. Evidence suggests that within a population, older adults who score in the higher categories for diet quality [1–4] and physical activity measures [5,6] have the best survival rates.

CURRENT RECOMMENDATIONS

The revamp of the recommended dietary allowances (RDA) by the Food and Nutrition Board of the Institute of Medicine starting in the early 1990s brought about more precise recommendations for individuals above the age of 50 years [7–14]. The current recommendations, termed dietary reference intakes (DRI), include guidance for adults in categories of 31–50 years, 51–70 years, and greater than 70 years [15]. No further distinction is made for individuals aged 70 years and above. This lack of precise further guidance for those over 70 years is likely a consequence of limited information from the older aged groups [15].

DRIs for most nutrients, including vitamin A, vitamin C, vitamin E, vitamin K, thiamin, riboflavin, niacin, folate, vitamin B_{12}, pantothenic acid, biotin, choline, chromium, copper, fluoride, iron, magnesium, manganese, molybdenum, phosphorus, selenium, and zinc, do not differ between adults above and below the age of 50 years. The nutrient recommendations for three nutrients, vitamin D, calcium, and vitamin B_6, increase for older adults. The DRIs for vitamin D increase from 15 µg/day for females and males less than 70 years, to 20 µg/day for adults above 70 years [16]. The DRIs for calcium increases from 1000 to 1200 mg/day for females above the age of 50 years, and for males above the age of 70 years [16]. The DRIs for vitamin B_6 increase from 1.3 mg/day for both females and males below 50 years to 1.5 and 1.7 mg/day, respectively, for females and males 51 years and older [9]. Emerging evidence suggests future revisions in the DRIs for individuals over the age of 70 years may be

necessary [17], but any recommendations must await a thorough review of the new literature.

Although the DRIs for most nutrients do not increase with advancing age, with the exceptions of vitamin D, calcium, and vitamin B_6, it can become increasingly difficult to achieve the recommended intakes as one ages. In general, total energy need decreases with advancing years to compensate for the diminished need associated with lower levels of physical activity, and a higher proportion of fat mass relative to lean muscle mass and a lower basal metabolic rate [18]. Nutrient needs must be met within the context of lower food intakes. This can be accomplished ensuring that the nutrient density of the diet (nutrients per calorie) is relatively high. A food guide pyramid has been developed specifically for older adults (Figure 13.1). Differences from the food guide pyramid for Americans include a narrower base to reflect lower energy needs, examples that emphasize nutrient-dense foods within each category, illustrations of foods that are particularly useful to older adults (e.g., bags of frozen vegetables), and added to the base, one row containing water glasses to emphasize the importance of maintaining adequate fluid intake and a second row emphasizing the continued need for regular physical activity throughout the lifespan.

NUTRIENTS OF CONCERN

Adequacy of some nutrients can be a concern for older adults. These include calcium; vitamins D, E, and K; potassium; and fiber (Table 13.1) [19,20]. The mean intake for these nutrients ranges from 33% to 50% of the RDA, or adequate intake (AI) values for individuals over the age of 70 years. These data suggest that to ensure adequate nutrient intake, efforts should be focused on providing food-specific guidance for these essential components of the diet.

Vitamin D

Adequate vitamin D intake is of concern for older adults [21]. There are a number of factors that may compromise their vitamin D status. These include decreased efficiency of skin to synthesize vitamin D after exposure to sunlight [22] and the tendency to spend less time outdoors to accumulate sun exposure. Limited sun exposure due to latitude or concern about sun exposure because of skin cancer risk can minimize endogenous vitamin D synthesis, especially in older adults [23,24]. Additionally, overweight and obese individuals have been reported to have lower circulating vitamin D concentrations. As rates of excess body weight

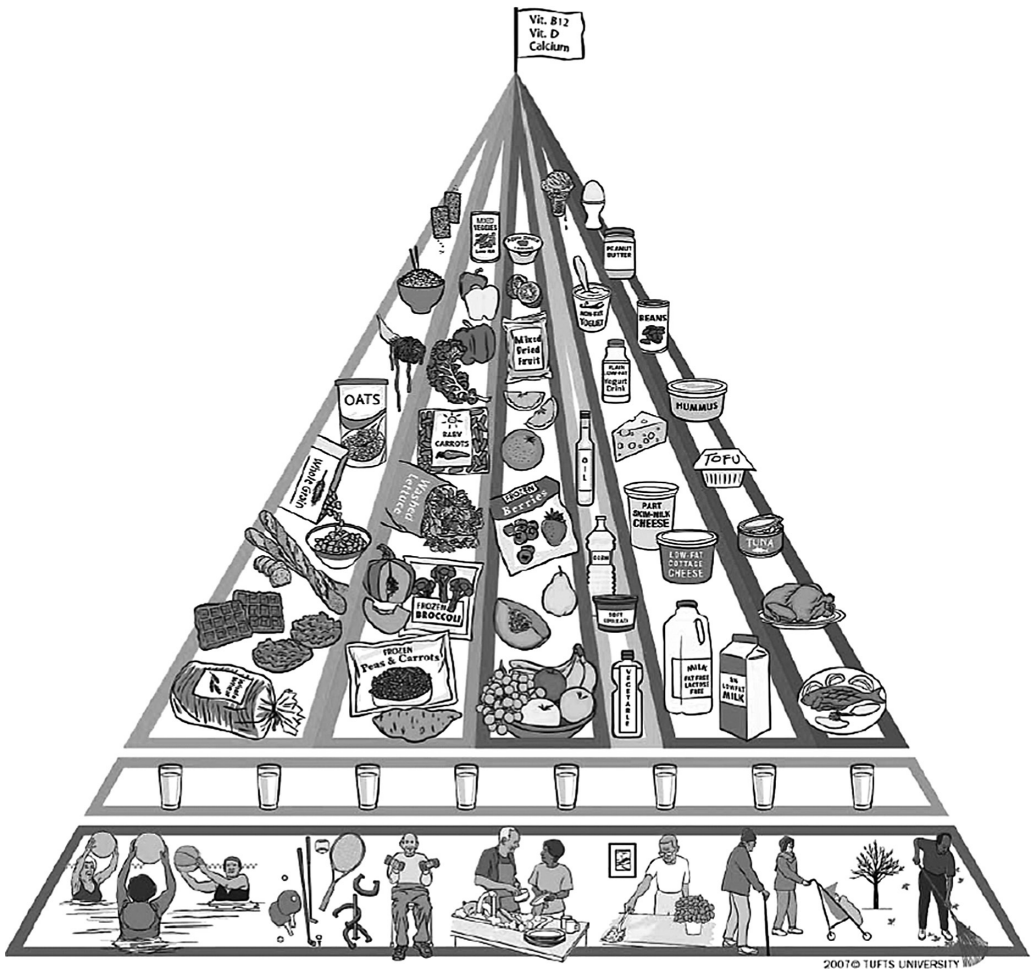


FIGURE 13.1 *MyPyramid* for older adults. http://nutrition.tufts.edu/docs/pdf/releases/ModifiedMyPyramid.pdf

TABLE 13.1
Shortfall Nutrients for Individuals 70 Years and Older

Nutrient	70 years+ Male RDA or AI[a]	RDA 70 years+ Female RDA or AI	NHANES 2003-04 Mean, Male 70+ (% of RDA or AI)	NHANES 2003-04 Mean, Female 70+ (% of RDA or AI)
Vitamin D µg/day	*15*	*15*	8.1[b]	8.0[b]
Calcium, mg/day	*1200*	*1200*	*743 (62%)*	*668 (56%)*
Vitamin E, mg/day	15	15	6 (40%)	5 (33%[c])
Vitamin K, µg/day	*120*	*90*	*92 (77%)*	*56 (62%)*
Potassium, mg/day	4700	4700	2441 (52%)	2332 (50%)
Fiber, g/day	*30*	*21*	*15 (50%)*	*14 (67%)*

Source: Adapted from Lichtenstein, A.H. et al., *J Nutr*., 138(1), 5, 2008.
RDA, recommended dietary allowances; AI, adequate intake.
[a] Italics indicates AI.
[b] Data include food plus supplements.
[c] Number in brackets refer to percent of the population below RDA or AI.

increase in the older population [18,25], this factor may also contribute to compromised vitamin D status [26]. Up until recently, fluid milk was the only reliable food source of vitamin D in the United States [21]. Recent changes to the vitamin D fortification regulation have resulted in an increased availability of vitamin D- and calcium-fortified juices and juice drinks, and vitamin D-fortified dairy products other than fluid milk [27,28].

Calcium

The richest naturally occurring and bioavailable source of calcium is dairy products. A wide range of low-fat and nonfat dairy products is currently available. There are two factors to take into consideration when recommending dairy products to older adults. The first is lactose intolerance. With increasing age, the rate of lactose intolerance increases [29–31]. Fortunately a wide range of lactose free and low lactose dairy products are now available, as well as enzyme preparations (lactase) that can be taken when consuming foods containing lactose to decrease the symptoms of lactose intolerance. It is important to note that although the prevalence of lactose intolerance increases with age, intolerance symptoms among lactose maldigesters tends to decease with age, suggesting that as people get older they may have more, rather than less, flexibility in their choice of calcium rich dairy foods [30]. The second consideration with regard to dairy products is saturated fat. Dairy products can be a major source of saturated fat. Saturated fat intake is associated with the increased risk of developing cardiovascular disease [32,33]. Older adults should be encouraged to take advantage of reduced fat versions of dairy foods. In addition to fat-free and low-fat dairy products, other good sources of dietary calcium are fortified drinks, such as calcium-fortified orange juice and soy milk.

Vitamins E and K, and Potassium

Rich dietary sources of vitamin E, vitamin K, and potassium, are plant foods, primarily vegetables and fruits. Depending on the individual food, they can be good sources of one or more of these nutrients. Higher fruit and vegetable intakes have been associated with a number of positive health outcomes including bone health, blood pressure, metabolic syndrome, stroke, and cardiovascular disease [34–43]. Older adults should be encouraged to choose deeply colored vegetables and fruits, as they tend to be nutrient dense. Liquid soybean and canola oils, and products made thereof, such as margarine spreads, are also a good source of vitamins, and are low in saturated and *trans* fatty acids.

Fiber

A major function of dietary fiber is its laxative effect in the gut. In addition to vitamins E, K, and potassium, vegetables and fruits are a good source of dietary fiber, along with whole grains and whole grain products. For this reason, older adults should be encouraged to consume whole fruits and vegetables rather than the juice form. They should also be encouraged to choose whole grain products rather than refined and processed grain products. In general, fiber supplements are not routinely recommended because excessive fiber can decrease the bioavailability of calcium, iron, zinc, copper, and magnesium [44,45].

SPECIAL DIETARY CONSIDERATIONS FOR OLDER ADULTS

The area of maintaining optimal nutrient status in older adults must be considered in terms of physiological factors and psychological factors. Special attention to both of these factors is critical for ensuring optimal health outcomes.

Organ Systems

The way the body handles nutrients can change with advancing age [46]. These changes are mostly due to changes in the functioning of organ systems, which impact the utilization of specific nutrients (Table 13.2). Interestingly, few adverse nutritional consequences resulting from advancing years have been noted that are independent of ancillary biological changes. These exceptions include vitamin B_{12}, vitamin D, and calcium. With increasing years, many individuals experience a decline in gastric hydrochloric acid secretion [46]. The resulting hypochlorhydria results in a decline in the bioavailability of vitamin B_{12}. As previously noted, due to changes in

TABLE 13.2
Potential Biologic Changes Contributing to Altered Nutrient Status in Older Adults

System	Change
Digestive system	↓ Hydrochloric acid secretion
	↓ Digestive juice secretion (pancreas and small intestine)
	↓ Absorptive capacity (malabsorption)
	↓ Muscles tone large intestine (↓ gastrointestinal motility)
	↓ Chronic blood loss due to ulcers and hemorrhoids
Liver	↓ Hepatic and biliary function
	↓ Rate detoxification
Heart	↓ Cardiac output
	↓ Strength and flexibility of blood vessels
Kidneys	↓ Blood flow
	↓ Glomerular filtration
Senses	↓ Acuity vision and hearing
	↓ Taste (loss taste buds, mainly salt and sweet)
	↓ Smell
Skin	↓ Synthesis vitamin D
Body composition	↓ Lean muscle mass and ↑ fat mass
	↓ Physical activity
Immune system	↓ T cell-mediated function
	↑ Susceptibility to infection and malignancy
Pharmacokinetics	↑ Prescription and nonprescription drug use
	↑ Chronic drug therapy
	↓ Capacity to metabolize drugs
Mouth	↓ Salivary secretion
	↑ Altered bite pattern due to tooth loss

skin and nutritional lifestyle, older adults may be at a compromised status for vitamin D and for calcium. Impairments or decreases in the function of the heart, blood vessels, and kidneys can stress the normal demands on everyday life. Changes in body composition (decreased lean muscle mass and increased fat mass) result in decreased basal metabolic rates, energy needs, and capacity for physical activity [47]. Increased use of prescription and nonprescription medications, chronic drug therapy, and decreased capacity of the liver to metabolize drugs can compromise nutrient unitization. All these factors need to be addressed on a regular basis by the health care provider.

Taste and Smell

Retaining the desire to eat a variety of foods is integral to ensure optimal nutrition for older adults. This issue is of particular concern because diminished taste and smell acuity associated with aging can lead to poor appetite. This change includes loss of taste buds, primarily those involving salt and sweet, resulting in greater sensitivity to acid and bitter [48]. Other changes frequently observed in older adults include a diminished sense of smell. Older adults with poor odor perception have lower nutrient intakes than those with good odor perception [49–51].

Vision, Dexterity, and Mobility

Diminished vision, dexterity, and mobility can make food accusation and preparation difficult, which severely impacts on variety and quality of foods (Table 13.3). Difficulty opening jars, cans, or packaged foods due to arthritis or diminished strength can lead to decreased variety and ability to consume preferred foods. Small accommodations in an individual's environment such as ergonomically designed kitchen aides (e.g., can openers and scissors), kitchen reorganization (e.g., eliminating clutter and moving frequently used items to most accessible places) and shifts to the use of partially prepared foods can minimize a decline in diet quality. For example, resealable bags of frozen vegetables and fruits are particularly good choices for older adults because they allow for easy apportioning of single or double servings, minimize prepreparation, which can be difficult or even painful with advanced years, eliminate waste due to spoilage, reduce the need for frequent trips to the market, and provide variety during winter months or long periods of inclement weather. Likewise, purchasing boneless chicken breasts can decrease preparation and cooking times, and is adaptable to preparation of individual small portions. Older adults may not automatically take advantage of newer forms of common food items (e.g., prewashed and cut salad, shredded cheese) and require some regular guidance in this area.

Social Factors

In addition to adapting with declines in physical capacity associated with the aging process, there are also changes in the social environment of older adults that can have an impact on nutritional status (Table 13.4). With increasing years, the loss of a spouse or other family members with whom an individual shared and prepared meals is common. This can lead to social isolation, especially during mealtime, and diminished desire to prepare well-balanced and varied meals. Due to deterioration in mental or economic status, older adults are

TABLE 13.3
Activity of Daily Life Factors Contributing to Compromised Food Intake in Mature Adults

Factor	Change
Oral cavity	↑ Peritoneal disease
	↑ Ill-fitting dentures
	↓ Salivary gland function
Mobility	↓ Physical activity
	↓ Respiratory capacity
	↓ Lean muscle mass (strength, physical disability)
	↑ Physical isolation
Senses	↓ Acuity (taste, smell, sight)
Dexterity	↑ Arthritic involvement finger and hand joints
	↑ Tremor
	↓ Manual dexterity
Energy needs	↓ Energy requirements
	↓ Caloric intake
	↓ Volume

TABLE 13.4
Psychosocial Factors Contributing to Compromised Food Intake in Mature Adults

Factor	Change
Companionship	↑ Loss of spouse
	↑ Social isolation
	↑ Loss of companions
	↓ Social interaction secondary to ↓ mobility
Mental State	↑ Depression
	↑ Mental deterioration (dementia)
	↑ Alcoholism
	↑ Loneliness
	↑ Chronic disease
Economic	↑ Fixed income (poverty)
	↓ Choice and availability
	↓ Quantity needs
	↓ Variety
Nutrition knowledge	↑ Susceptibility to food fads
Housing	↑ Change in status (loss of home)

frequently faced with having to adapt to a new living environment. This can result in dramatic changes in meal times, food preparation, and foods available. The onset of chronic disease can further limit food choices and make older adults susceptible to the lures of food fads or dietary supplements promising a fountain of youth. At worst, these claims risk draining scarce resources from food purchases and overconsumption of individual nutrients. The latter can interfere with prescription drug actions or the utilization of essential nutrients. Depression frequently accompanies the aging process in individuals without adequate support to make the necessary adaptations that come with advancing age. Older adults are also at increased risk of alcohol abuse. All of these factors may contribute to poor food consumption patterns [52].

PHYSIOLOGICAL CHANGES OF CONCERN IN OLDER ADULTS

Nutrient-related chronic diseases particularly prevalent in middle and later years include cardiovascular disease, cancer, type 2 diabetes, hypertension, osteoporosis, disorders of dentition and associated senses, and declines in immune function. In some cases, the goals of nutrient recommendations for older adults are aimed at delaying the onset of chronic disease while in other cases they are intended to treat or accommodate to the disorder.

Dentition and Associated Senses

Salivary secretions decrease with increasing age. Changes in bite pattern from partial or complete extraction/loss of teeth are common. Poorly fitted dentures can make eating painful and distasteful. The prevalence of root canals is higher in older than younger adults [53,54]. Increased incidence of tooth disease in older adults has been related, in part, to high levels of sugar consumption [55]. Any one, or a combination of these factors, can restrict the type and variety of foods consumed. For example, chewing and swallowing fibrous foods may be difficult due to poor dentition, resulting in a shift toward highly processed foods or juices that are low in fiber content [56]. It is critical when evaluating dietary intakes of older adults to consider possible concerns regarding food textures and preparation methods, and to assess dentition.

Cardiovascular Disease

The rate of cardiovascular disease increases with age, especially after menopause in females [57]. Higher saturated fat coupled with lower polyunsaturated fat intakes has consistently been associated with higher rates of cardiovascular disease [58]. The American Heart Association [33], the National Cholesterol Education Program [59], and the 2010 Dietary Guidelines for Americans [60] recommend dietary patterns that are rich in vegetables and fruits, whole grains, legumes (beans), fat-free and low-fat dairy products, fish, and lean meat. No specific recommendations for dietary change are made for adults as they age. The response to these recommendations in terms of plasma lipids appears consistent for both genders and age groups [32].

Osteoporosis

Age-related or type II osteoporosis (bone loss) is positively associated with the aging process. It has been estimated that osteoporotic fractures affect 50% of females and 30% of males over the age of 50 years [61]. Age-associated bone loss is attributed to diminished estrogen production, decreased calcium absorption from the gastrointestinal tract, decreased calcium resorption by the kidney, decreased rates of physical activity, compromised vitamin D status, and decreased calcitriol production secondary to hyperparathyroidism [61,62]. In older adults, calcium balance is favorably affected by vitamin D intake and negatively affected by high sodium, protein, alcohol, and caffeine intakes [62]. Supplemental calcium and vitamin D in postmenopausal women living in northern latitudes (42°N) may minimize bone loss [63]. Because serum osteocalcin, calcidiol, and vitamin D fluctuate seasonally due to sun exposure, vitamin D intake is particularly important during the period of winter and spring in this group. These data strongly support routinely screening older adults for vitamin D status.

Glucose Intolerance/Type 2 Diabetes

The incidences of glucose intolerance and type 2 diabetes mellitus increases with age [64,65]. The increased incidence has been strongly associated with weight gain in later years. Lifestyle interventions have been shown to be efficacious in preventing or delaying the onset of type 2 diabetes mellitus [66–68]. These include regular daily physical activity, weight loss, and dietary modification consistent with that advocated for the prevention and treatment of cardiovascular disease.

Hypertension

The incidence of hypertension increases with age [57]. This increase is associated with changes in the vasculature and kidneys, and is exacerbated by weight gain. A number of clinical trials have demonstrated clear benefits of dietary modification to treat hypertension in older adults. The dietary approaches to stop hypertension (DASH) type dietary pattern, rich in vegetables, fruits, and fat-free and low-fat dairy products, decreases blood pressure in a wide range of individuals [42]. Further coupling this dietary pattern with sodium restriction has been shown to further decrease blood pressure [43].

Immune Function

The most commonly associated age-related change in the immune response is cell-mediated function [69,70]. Limiting data suggests vitamin E supplementation may be beneficial in decreasing the incidence of respiratory infections in older adults [71].

Cancer

The incidence of cancer shows tremendous variability on the basis of worldwide distribution, type, and site in the body. The incidence of all types of cancer increases with age. Support for a diet/cancer incidence link comes from data suggesting associations between markedly divergent food consumption patterns and incidence rates of cancer among different population groups [72]. Some data have been reported for associations involving the following dietary component: alcohol intake (laryngeal), calcium and vitamin D intake (stomach, colon, breast), fat intake (breast, colon, prostate), fiber intake (breast), antioxidant vitamin and/or orange and dark green vegetable intake—vitamin A and beta-carotene, vitamin C, vitamin E, and trace elements (wide range of sites) [72–76]. Results from randomized controlled trials are limited [77]. At this time the general dietary guidance to reduce cancer risk is consistent with the dietary guidance to prevent the onset of chronic diseases of concern in the twenty-first century.

CONCLUSIONS

The aim of dietary guidance specifically targeted for older adults is to maintain optimal health and forestall the onset of chronic disorders. The actual dietary recommendations, for the most part, are consistent throughout the adult lifecycle. Evidence suggests that there is a direct relationship between the nutrient quality of the diet and survival rates. Due to decreased levels of physical activity, decreased metabolic rates, and increased proportions of fat to lean muscle mass, energy requirements decline with advancing years yet nutrient requirements remain unchanged, or increase. This situation requires a greater emphasis on choosing nutrient dense foods within each food category. Special attention needs to be given to adapting living environments with advancing years to retain the ability to acquire and prepare food. Changes in social situations that could impact on food intake should be monitored on a regular basis. Evidence suggests that diet and lifestyle interventions can forestall the onset of cardiovascular disease, osteoporosis, diabetes, hypertension, immune function, and possibly cancer. There are no data to suggest a person is too old to benefit from improvements in diet quality. The definitions for old age and expectations for the period of time individuals can remain active, productive, and live independently are expanding. Efforts toward improving diet quality and levels of physical activity with advancing years should keep up with this trend.

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14 Role of Communication in Changing Nutrition Behaviors to Promote Healthy Lifestyles

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CONTENTS

Introduction 185
People 186
Individual Level 186
Fundamental Importance of Taste 187
Cost, Convenience, and Self-Efficacy 188
Health Literacy: Special Case of Nutrition Communication 188
People Eat Diets, Not Foods or Nutrients 189
Everyone Is an Expert 189
Social Networks 189
Personal Network and Social Support 189
Opinion Leaders 190
Population/Community 190
Places 190
Shift in Communications Landscape 190
Other Challenges to Communication of Nutrition Messages for Behavior Change 191
Media Advocacy: Using Media to Get Behind Your Cause/Sway Public Opinion and Policymakers 191
Role of Nutrition Communication in Changing Behavior: Community-Level Interventions 192
Sisters Together: Move More, Eat Better 192
People-Based Campaign Components 192
Place-Based Campaign Components 193
Shape Up Somerville: Eat Smart, Play Hard 193
People-Based Campaign Components 193
Place-Based Campaign Components 193
General Nutrition Communication Recommendations 194
Acknowledgments 194
References 194

INTRODUCTION

An old saw says that "food is not food until it is eaten." To paraphrase, "a behavior is not a behavior until it is adopted." That is, science-based evidence, no matter how solid, is of little value until it is adopted by those to whom it applies. The Dietary Guidelines for Americans, first issued in 1980 by the U.S. Department of Agriculture (USDA) and the U.S. Department of Health, Education, and Welfare (USDHEW), later renamed Health and Human Services (HHS), articulate science-based recommendations for healthy diets that provide adequate amounts of all essential nutrients and at the same time minimize the risk of chronic diseases associated with dietary factors. The problem is that the gap between the recommendations, which have been modified relatively little since they were first released, and their adoption by the American public remains wide. The advisory committee that wrote the 2010 report observed that "now, as in the past, a disconnect exists between dietary recommendations and what Americans actually consume. On average, Americans of all ages consume too few vegetables, fruits, high-fiber whole grains, low fat milk and milk products, and seafood and they eat too much added sugars, solid fats, refined grains, and sodium. SoFAS (added sugars and solid fats) contribute approximately 35% of calories to the American diet" [1].

The power of nutrition to shape public health is indisputable. In a 2009 World Health Organization report describing

the ten leading risk factors for death in high-income countries, seven of the factors—high blood pressure, overweight and obesity, physical inactivity, high blood glucose levels, high cholesterol levels, low fruit and vegetable intake, and alcohol use—are related to diet and physical activity [2]. The same report estimated that in 2004 these risk factors contributed to an estimated 4.1 million deaths in high-income countries, and that modifying food intake and increasing physical activity (along with reducing tobacco use) could increase global life expectancy by 5 years.

There is no logical starting point to the discussion of why Americans have not made greater shifts toward the recommendations of the Dietary Guidelines, and there is no single approach to modifying eating behaviors at the population level. What people eat depends on individual factors, on interpersonal interactions through multiple networks, and on the environments in which eating behaviors occur. Simply telling people what to do or what not to do, no matter how well the advice is grounded in scientific evidence, is unlikely to lead to wholesale adoption of the Dietary Guidelines. More successful nutrition communications will likely evolve through identification of barriers to change and solutions to address those barriers, at both the individual and the environmental levels.

Public health communication has been defined as the production and exchange of information to inform, influence, or motivate individual, institutional, and public audiences. That definition can be applied to communication about nutrition-related health issues [3]. Importantly, it is not limited to the interaction between nutrition communicators and individual consumers of information, but also incorporates structural and social factors. Indeed, successful nutrition communications must be delivered in the context of multilevel interventions that promote and support behavior change. As such, this chapter addresses the role of nutrition communication in interventions incorporating individual, social, and environmental components.

The design of effective nutrition communications must include specification of the target audience(s) and behavioral objectives, a message strategy and execution plan, and a selection of dissemination channels and settings. It must also include ongoing formative research, campaign monitoring, and outcome evaluation that makes it possible not only to measure effectiveness but also to make course corrections. An IOM report on health communication strategies for diverse populations aptly describes the fluid nature of this work: "A campaign is not defined by a specific and static mix of messages, audiences, and channels. Rather, it is defined as a program that makes decisions about these operational details, decisions that will vary over time" [4].

What we know about the potential of public health media campaigns comes mainly from efforts to influence population behavior by targeting individual-level antecedents to the behavior of concern, factors such as knowledge, perceptions, and self-efficacy [3]. However, addressing individual factors alone may not be sufficient to drive health behavior change; indeed, the limited available evidence from national nutrition campaigns confirms that behavioral shifts require far more than messages promoting personal behavior change. For example, the 5-A-Day Campaign, launched jointly by the National Cancer Institute and the Produce for Better Health Foundation in 1991, was designed to increase public awareness of the importance of eating at least five servings of fruits and vegetables every day. Results from 5-A-Day program surveys 6 years after it was launched showed that the majority of the population still did not know the fruit and vegetable recommendation, and, more importantly, that there were no significant changes in fruit and vegetable consumption [5].

In the 20 years since the campaign was introduced there have been numerous communications efforts, extensive programming at the community level, and environmental and policy changes. Yet the most recent data available indicate that more than half of the U.S. population fails to consume recommended intakes. Approximately 33% of adults meet the recommendation for fruit consumption and 26% get the recommended servings of vegetables [6]. To add to the challenge, the 5-A-Day program was renamed "Fruits and Veggies: More Matters" to reflect the change in the 2005 Dietary Guidelines from five servings a day to five to nine servings a day. What effect, if any, this campaign branding shift had on consumer recognition of the fruit and vegetable message or on consumer reaction to a higher goal is unclear. There are many possible explanations for the limited shifts in fruit and vegetable consumption; further research is needed to identify the relative importance of taste, cost, convenience, accessibility, and of course, the role of communication in persuading Americans to eat more fruits and vegetables.

Over the past two decades, public health researchers have broadened their approach to understanding and influencing population health, including issues around eating behavior. Maibach, Abroms, and Marosits propose a framework which posits that population health is influenced by the attributes of, and interplay between people and place-based factors [3]. In their framework, people are analyzed through three levels: the individual field, the social network field, and the community or population field. Places are understood in terms of both local and distal influences (see Figure 14.1). Maibach et al. use this framework to discuss avenues for health communication within each field of influence. We will attempt to adapt this model to address challenges specific to nutrition communication, and particularly to address the gap between dietary recommendations and the public's behavior.

PEOPLE

Individual Level

In the ecological framework proposed by Story et al., individual factors such as cognitions, skills and behaviors, lifestyle, biology, and demographics are at the core of the model [7]. All are critical to understanding whether communication can have its intended effect, some because they are impossible

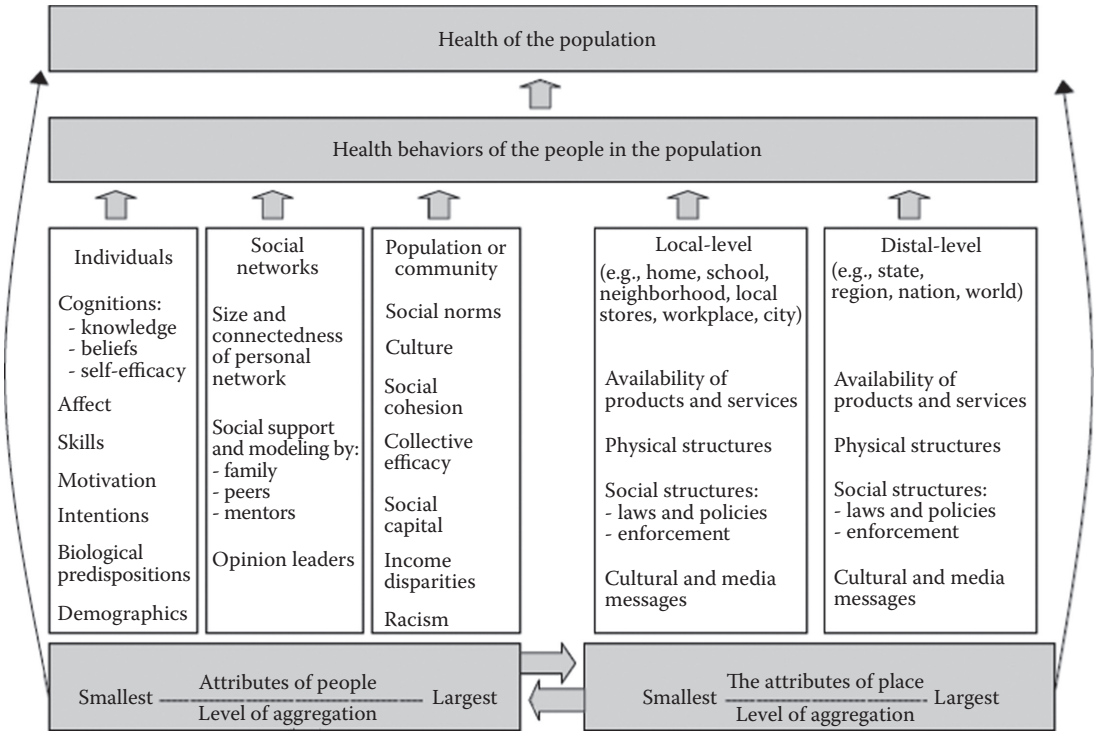


FIGURE 14.1 Maibach et al.'s People and Places framework for public health communication. (From Maibach, E.W. et al., *BMC Public Health*, 7, 88, 2007. With permission.)

to change, others because they can be modified. Whether a proposed intervention focuses solely on nutrition or includes nutrition among other components, formative research to identify both barriers to the recommended behavior and solutions to enable that behavior are critical. We will place greater focus on the barriers that evidence suggests can be modified. These include taste, cost, convenience, and self-efficacy, and health literacy or lack of it, with respect to the specific behavior being targeted.

Fundamental Importance of Taste

At the individual level, the disconnect between dietary recommendations and dietary intake is explained in large part by consumers consistently ranking taste as the major factor driving their food choices [8,9], with concern about health ranking third or fourth, behind cost and convenience. Unfortunately, for the majority of individuals, foods that taste good tend to be high in fat, sugar, and salt. In a food environment described in the extreme as "toxic" [10], these highly palatable foods are widely available at relatively reasonable prices, posing a challenge on the individual level as well as at the local and distal levels within the environment. In short, at the individual level, people make choices about whether to prepare and consume energy-dense foods, but policies affecting the cost and availability of these items serve as powerful place-based influences on behavior.

It follows, then, that attitudes toward taste must be addressed in any nutrition communication activities if we are to nudge the population toward more healthful diets. Some tastes, like sweetness, are innately preferred, while others, like bitterness, are innately rejected. Exposure to different flavors can modify these preferences [11]. Clearly, consumers' preferences for certain types of food are linked to market availability; for example, most Americans prefer refined grains over whole grains [12]. This preference has only emerged in the past 200 years, as commercial milling made refined grains more widely available [13]. Increasing recognition of the benefits of whole grains has led to the public health recommendation to "Make half your grains whole." However, that seemingly simple message requires modification of taste preferences and consumer understanding of the difference between whole and refined grains. In some cases, to get consumers to cook, buy, and eat more whole grains may require reformulation of products, a challenge to industry at the distal level.

Such change is possible, but, whether the recommendation focuses on alterations of fat, sugar, salt, or whole grain intake, population shifts require action at multiple levels. While we lack comprehensive studies to fully explain changes in consumption, examples such as the slow increase in low-fat and fat-free milk consumption and decrease in whole milk consumption in the United States over time are probably explained both by messages that promote lower fat milk and by changes in taste preferences as more palatable products appeared in the marketplace [14].

Unfortunately, taste preferences often conflict with nutrition advice. To compound the problem, most nutrition advice is based on evidence related to long-term outcomes, such as

reduced risk of heart disease and certain cancers. The dietary advice related to risk reduction, as well as to weight loss and maintenance, competes with the short-term gratification of indulging in energy-dense foods. There are no immediate, perceptible benefits to adopting nutrition recommendations and generally no immediate consequences to ignoring them either. The challenges, therefore, are to address the tension between the palatability of many unhealthful foods and the advice to cut back on them, and also to get people to increase their intake of foods they often find unpalatable. Which approach or combination of approaches will be most effective depends on understanding the target audience.

Cost, Convenience, and Self-Efficacy

Cost, convenience, and self-efficacy interact to affect food choice and food consumption. The relative importance of each of these factors varies from one individual to another and can change over time. They are related to family economics, time (or perceived time) available to purchase and prepare food, and skills and confidence to make cost-effective purchase decisions and to efficiently prepare appetizing food. At times of high unemployment and rising food prices, for example, it is reasonable to expect increased attention to low-cost shopping than during better economic times. Identifying whether cost, convenience, or self-efficacy is the strongest driver of food choice requires formative research. For example, formative research for the *Sisters Together* campaign, described more fully later in this chapter, identified self-efficacy, specifically the lack of kitchen skills, as a major barrier to preparing healthier meals. In turn, the intervention incorporated the promotion of a cable television cooking show hosted by a member of the *Sisters Together* Advisory Board, which supported the development of these needed skills.

Health Literacy: Special Case of Nutrition Communication

A key consideration in the development of any form of nutrition communication is the health literacy of the intended audience, or the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions [15]. In a national survey, 36% of adults exhibited basic health literacy, and only 12% demonstrated proficient health literacy [16].

Low health literacy has been called a silent killer, linked with higher mortality rates, poor utilization of preventive health care services, improper use of medications, and delayed or inadequate care for chronic diseases such as diabetes and heart disease [17,18]. Increased awareness of these adverse effects has made efforts to improve health literacy a high priority; the Healthy People 2020 objectives, for example, strongly advocate for improved health literacy among Americans [19].

Early efforts to improve health literacy focused on simplifying the language of health communication materials, but current approaches also address social, cultural, and environmental factors, all of which influence health literacy. Addressing health literacy in this multifaceted manner is difficult, especially given the diversity of the American public. The development of clear and usable nutrition communication presents a special health literacy challenge for a number of reasons. Most nutrition information does not lend itself to succinct, actionable messages, and scientifically sound information often competes with advertising and other messages that are concise and persuasive, but not necessarily accurate or balanced. Moreover, understanding of the role of nutrition in health promotion and chronic disease prevention continues to evolve, and so too must guidance to consumers about how to integrate that knowledge into their daily food practices. The role of fat in the diet illustrates the problem. Since the first edition of the Dietary Guidelines was released in 1980, there have been recommendations regarding fat intake. In the first two editions, the guidance was to "avoid too much fat, saturated fat, and cholesterol." In the next two editions, the guidance was modified to convey a positive tone: "Choose a diet low in fat, saturated fat, and cholesterol." Then, in 2005, it was modified to emphasize the need to limit saturated fat, to include "moderate amounts" of unsaturated fat, and to limit cholesterol to less than 300 mg/day. In the 2010 Guidelines, Americans are advised to "Consume less than 10% of calories from saturated fatty acids by replacing them with monounsaturated and polyunsaturated fatty acids" and to "Consume less than 300 mg of cholesterol" [1]. Evidence from periodic studies of consumer comprehension of these guidelines suggests that there is a wide gap between recommendations and consumer understanding of what they mean and, more importantly, how to translate them into actionable behaviors [20,21]. To be sure, the Guidelines were intended for use by health professionals whose challenge is to translate them into language that consumers—even those with limited health literacy—can understand and act on. Unfortunately, popular materials designed to translate the Guidelines into actionable steps tend to use the same scientific language found in the Guidelines themselves.

There is no simple solution to this problem. Information about dietary fats (and many other nutrition topics) is complex. It is not always possible to simplify complex information to a point where it remains accurate, actionable, and comprehensible to the target population. As a first step, it is probably logical to consider a basic question: what does the individual or group need to know in order to implement the dietary guidance? Given that not all information on a particular topic is equally important, it is the role of the health professional to determine which information is needed most urgently and to prioritize those messages accordingly. For example, it is probably more important to help people to understand how to substitute unsaturated for saturated fats than to focus on dietary cholesterol. It is also a good idea to take advantage of existing resources, but to evaluate such materials with members of the target population to ensure they are both accurate and clear. If no available materials are suitable for the target population, it may be possible to modify relevant sources to make them more

audience-appropriate. Many useful resources are now accessible on the Internet. For example, an article on the complex topic of salt-reduction strategies can be found at the Harvard School of Public Health's website "The Nutrition Source" (http://hsph.harvard.edu/nutritionsource/salt/). The article, which was developed to help individuals implement the recommendations of the National Academy of Sciences Report [22], is divided into reasonable "bites," which could easily be adapted to a series of instructional sessions. While some of the language may be above the literacy level of many audiences, and some critics might debate details of the recommendations, this comprehensive, modifiable mini curriculum provides specific steps necessary for the consumer to reduce sodium intakes. This translation of dietary guidance into actionable steps can serve as a model for development of materials on other nutrition-related topics.

People Eat Diets, Not Foods or Nutrients

Further complicating matters is that messages to promote dietary behaviors often address a singular focus. The environment is saturated with nutrition messages related to specific health conditions. People are told to consume a diet to reduce cardiovascular risk, or to promote bone health, or to prevent cancer, or of course, to lose weight. Other messages focus on one particular nutrient. Individuals are advised to eat for more vitamin C, vitamin D, or iron or to avoid trans fats or carbohydrates. These pointed messages, which appear on everything from printed public health materials to front-of-package food labels, neglect the fact that most individuals do not eat to reduce risk of one disease or another, but instead consume a group of foods commonly referred to as their "diet." With this in mind, nutrition communicators should as a general rule place information about individual foods or nutrients within the context of the total diet. The 2010 Dietary Guidelines Advisory Committee recently took steps in this regard, advocating for a "total diet approach to achieving dietary goals" and providing an evidence-based review of healthful eating patterns, such as the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean patterns [1].

Everyone Is an Expert

The challenge of influencing eating behavior begins at the most fundamental level: everyone eats. Consciously or unconsciously, people draw on their vast reservoir of experiences with food each time they decide to buy, prepare, and consume food. Further, in their role as caregivers, many individuals draw on those experiences to make decisions about the foods that they serve to their families. When new information conflicts with what they "know" about food (that is, their preferences) they engage in the process of deciding whether that information should be used to modify their choices. For example, a common concern expressed by participants in *Sisters Together* focus groups was that substitution of healthier choices would not be acceptable to family members. Therefore, the campaign needed to address women's reluctance to modify certain food practices based on family preferences [23].

Despite years of attempts to regulate who can say what about nutrition, it remains generally true that almost anyone can set themselves up as an expert and dispense nutrition advice even to broad audiences. The problem has grown as more and more individuals turn to the Internet for nutrition information. As a result, it is more difficult than ever for consumers to identify sound, unbiased nutrition information.

A challenge related to this proliferation of unchecked nutrition advice is that, when it comes to health messages, we accept or reject nutrition information depending on our experiences, beliefs, and biases. In the current nutrition communication landscape, we can easily find sources that confirm what we want to believe. For example, one might find any number of communications that extol the health benefits of dark chocolate, red wine, or fast food diets. Stumbling upon a source that affirms a favorite food as healthful may, in turn, prompt a consumer to ignore the less attractive, but accurate, advice communicated by more reputable sources [24]. That said, while TV, magazines, and the Internet represent the most frequently used sources of nutrition information, consumers rank registered dietitians, doctors, and nurses as the most credible sources [25,26]. Clearly, one-on-one interactions with patients are an important opportunity for health professionals to cut through the noise and establish themselves as providers of sound, actionable nutrition guidance.

Social Networks

Social networks, "the web of social relationships that surround individuals" [27], provide another avenue for meaningful nutrition communication. The relationship between social networks and health gained attention in the 1970s when researchers demonstrated that less connected individuals had a higher risk of all-cause mortality than well-connected individuals [28–30]. Since then, social networks have been studied for their effect on health issues as varied as smoking cessation, sexual behaviors, and obesity. Maibach and colleagues highlight the importance of the size and connectedness of one's personal network; the social support and modeling provided by family members, peers, and mentors within that network; and the role of opinion leaders as key influences on health behaviors [3].

Personal Network and Social Support

While well-connected individuals are generally healthier than less connected individuals, extending the size of individuals' social networks seems beyond the scope of most nutrition communication efforts. However, health providers should be sensitive to the fact that an individual's level of social support and day-to-day influences can have a significant impact on whether or not they adopt or maintain healthy eating behaviors. More important for the nutrition communicator is understanding how to engage with the social networks that individuals occupy in order to promote healthful behaviors. Evidence shows that having a friend who becomes obese can significantly increase one's own risk of obesity, yet this research also suggests that these same social influences

could be used to slow the spread of obesity [31]. Formative research with the target audience is a key step in integrating social support and modeling into a nutrition communications strategy, particularly by identifying the people who have the most influence (positive or negative) on eating habits within a social network. For example, if formative research shows that members of the target audience are most influenced by their mothers, messaging can be designed to invoke a mother's voice. Alternatively, if research shows that spouses most frequently undermine healthy eating habits, messaging can specifically target spouses.

Opinion Leaders

Opinion leaders, sometimes called champions, are individuals who influence the opinions, attitudes, beliefs, motivations, and behaviors of others. They can act as gatekeepers for interventions, help change social norms, and accelerate behavior change. In public health, they have been used to gain support for and implement community health programs in at least four different ways. They provide access for and legitimize external change agents, serve as the communication link between communities and external agencies that implement programs, act as role models for behavior change within a community, convey health messages, and serve as the "capital" that institutionalizes program goals after an outside agency has left a community. In the diffusion of innovation model, it is the opinion leaders who tend to monitor the climate of opinion and use their influence when the advantages of a new idea is apparent or when it is clear that norms will change [32]. Community opinion leaders often include clergy, teachers, legislators, and physicians. However, it is important to assess the primary influencers within each target audience through formative research.

Population/Community

The attributes of groups, communities, and populations that influence health behaviors are perhaps less well understood than are other factors in the people and places framework [3]. However, a large body of work is beginning to clarify how racial and socioeconomic disparities negatively influence health. Furthermore, a growing number of interventions based on community-based participatory models incorporate community organization and coalition building to create sustainable change. Within this context, it is critical to understand factors such as social norms, culture, social cohesion, collective efficacy, social capital, and income disparities. Both interventions described in some detail in this chapter, *Sisters Together: Move More, Eat Better* and *Shape Up Somerville*, addressed these factors in the planning and execution stages.

PLACES

Place-based factors outlined by Maibach and colleagues include the availability of products and services, the physical structure of the environment, the social structures within the environment, and media and cultural messages to which the target population is exposed. At the local level, these include home, school, neighborhood, local stores, workplaces, and the city. At the distal level they include state, regional, national, and even international factors. Health practitioners working at the local level must familiarize themselves with the community in which they work, identifying supportive individuals and groups as well as gaps in available resources. For example, if the goal is to increase fruit and vegetable consumption, then it is essential to understand the availability of food markets and seasonal farmer's markets that provide high-quality fruits and vegetables at fair market prices, as well as to help organize advocacy efforts to bring such resources to underserved neighborhoods. If the goal is to insure that public schools are following the mandated wellness policies with respect to nutrition and physical activity, it is important to know what these policies are, to identify where progress is being made and where it has lagged, and to actively participate in efforts to ensure progress. In the *Sisters Together* campaign, beauty salons were identified as an important component of the social structure of the community, so those businesses were engaged as partners to promote healthy eating by providing materials developed by the campaign. While attention to such place-based resources can enhance the effectiveness of nutrition communications, the challenges of engaging such resources are considerable.

Shift in Communications Landscape

As Abroms and Maibach aptly note, "A communication revolution has blurred traditional distinctions between mass and interpersonal communication, and changed in many ways how we must think about using the media to promote the public's health" [33]. The rise of the Internet has radically altered the way that information flows through our society. In an earlier era, communication occurred largely on a one-on-one or one-to-few basis and flowed in a somewhat linear fashion through one of two pathways. In the "treatment model" pathway, information flowed from research to medical practitioners and then to consumers as patients. In the wellness domain, it flowed through media and health professionals to consumers. The arrival of next-generation technologies has enabled dramatic shifts in that process, providing individuals and organizations with dynamic and powerful new communication tools to spread their influence to thousands, if not millions, of people, independent of traditional media channels and their associated gatekeepers. Not only is the interested consumer receiving the latest research findings at the same time as the practitioner, but the consumer can also take on the role of "citizen journalist," actively engaging in the dialogue about nutrition and health issues. In short, there is a lack of clarity about who exactly are the experts, increasing the level of consumer confusion.

The proliferation of mass media channels has also led to a decline in the size of the audience captured by any individual channel. As a result, each channel now tends to focus narrowly on the interests of a specific audience,

decreasing the likelihood that a particular message will reach the intended audience with sufficient clarity and repetition to influence behavior. This shift in the nutrition communication landscape has led to a shift in Americans' sources for food and nutrition information. Two-thirds of Americans look to Internet articles, cooking shows/hosts, TV or radio news programs, magazine articles, newspapers, talk shows, public service announcements or ad campaigns on TV or radio, and blogs or social networking sites like Twitter and Facebook [8]. That Americans are increasingly connected with these media sources is both an opportunity and a challenge for communicating about nutrition. While communications campaigns can target specific populations from multiple angles, it has grown much more difficult to cut through the noise. On the other hand, it is extremely important to keep in mind that, while there has been a burgeoning of electronic resources to communicate all kinds of information, there is still a significant percentage of the population that still do not use such resources. In developing nutrition communications activities, it is critical to assess the types of channels the target population uses and the reasons why those channels are preferred, and then to tailor the intervention accordingly.

Other Challenges to Communication of Nutrition Messages for Behavior Change

While it is uncertain exactly how many nutrition-related messages the average American is exposed to each day, the number is undoubtedly extremely large, and growing given the proliferation of opportunities made available through Internet-based communications. These messages include information on food labels, in advertising, in print and electronic media of all types, and even on billboards at sporting events. The goal of much of the information that is provided is to persuade the individual to behave in way that is desired by the provider of that information. The behavior that is being advocated will depend on the agenda of those that are providing it.

In the case of the media, a chronic problem is that, more often than not, nutrition research is portrayed as revolutionary, with findings inappropriately described as breakthroughs that are ready to translate to actionable behaviors. For example, a 1995 epidemiologic study suggesting a potential inverse relationship between lycopene and prostate cancer led to widespread recommendations from mainstream media and food and supplement manufacturers to increase lycopene intakes [34]. By 2007, however, the media exposed the limitations of research on lycopene's protective effects: a headline in the *New York Times*, for example, read, "Lycopene as Cancer Blocker? Review Says Evidence Is Scant." That same year, new reports posited another nutritional panacea for prostate cancer prevention: an article in *Science Daily* asked, "Worried about prostate cancer? Tomato-broccoli combo shown to be effective." It went on to report that rats who had been implanted with prostate cancer cells and fed a combination of 10% of their diet as tomato powder and another 10% as broccoli powder had less growth of prostate tumors than rats fed one or the other, lycopene powder, or a drug given to men with enlarged prostates. Translating that advice to humans (an extrapolation, given that the effect was seen in rats who consumed 20% of their diet from two vegetables), a 55-year-old man concerned about prostate health should consume 1.4 cups of raw broccoli and 1 cup of tomato sauce or a half cup of tomato paste every day! Because new findings are so often framed as absolute truth rather within the context of a specific issue, it is understandable that consumers say they are confused when conflicting results appear.

Another problem that is particularly important in nutrition communication is the tendency among health professionals and the media to focus on dietary objectives that are *not* being met, rather than acknowledging progress that *is* being achieved. Such negative messaging can be discouraging. Further, even as the public falls short of meeting certain dietary guidelines, we continue to raise the bar, delivering guidance that many Americans may view as infeasible or impractical. To an individual who eats two servings of fruits and vegetables a day, for example, raising the guideline from five servings to nine may seem so lofty as to be counterproductive. Communicating achievable goals and celebrating incremental successes can enhance the success of nutrition communications.

Media Advocacy: Using Media to Get Behind Your Cause/Sway Public Opinion and Policymakers

In some cases the strategic use of media can help promote policy changes that support desired health behaviors. Advocacy is the process of using evidence to influence government-level policymakers and working with partners to elevate issues to decision-makers' agendas. (For readers interested in how to influence health policy, *Essentials of Public Health Communication* offers an excellent discussion.) If it is not possible to communicate with policymakers directly, an alternative is grassroots advocacy by a group of citizens interested in the same issue. In this situation, the key is to form an effective coalition that becomes informed about the problem and possible solutions to it, and then draws a focus to it through local events or work with the local media to frame the discussion according to the objectives of the group. Mothers Against Drunk Driving (MADD), for example, brings together individuals with a common concern and works to influence policy pertaining to that issue. At the local level, community members might use a media advocacy strategy to bring a supermarket to an underserved area. The effective use of media can raise the volume of their message to a level where it is heard by policymakers who have the power to influence environmental change. There are a number of resources available to help with the design of media advocacy campaigns, such as that published by the American Public Health Association (http://www.apha.org/advocacy).

ROLE OF NUTRITION COMMUNICATION IN CHANGING BEHAVIOR: COMMUNITY-LEVEL INTERVENTIONS

Mass media campaigns have been defined as "any planned effort that disseminates messages to produce awareness or behavior change among an intended population through channels that reach a broad audience" [33]. That definition can be readily applied to the design of nutrition communication efforts at the community level. The following two case studies illustrate the process. The first, *Sisters Together: Move More, Eat Better,* is a communications campaign that was accompanied by community-building efforts. The second, *Shape Up Somerville: Eat Smart, Play Hard,* was designed according to the principles of community-based participatory research (CBPR), and nutrition communications played a major role in many aspects of the intervention.

Sisters Together: Move More, Eat Better

Sisters Together: Move More, Eat Better was designed to prevent obesity through promotion of improved nutrition and increased physical activity in African American women between 18 and 35 years old in three inner city communities in Boston, MA. The overall framework for the campaign was drawn from the ecological model, as proposed by McLeroy et al. in 1988 [35].

People-Based Campaign Components

Defining and understanding a target population was the first step in developing *Sisters Together.* The contract from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for the development, implementation, and evaluation of the intervention mandated that the campaign focus on obesity prevention in a minority group, but did not further specify the target population. The population was defined through a series of steps. A literature review that documented higher prevalence of obesity in African American women than in the general population was confirmed by data from the behavioral risk factor surveillance study [36] in Massachusetts, which also showed that increased risk was associated with low income and living in an urban area. A search of peer-reviewed publications and popular literature, including magazines and newspapers, explored obesity treatment interventions and weight loss practices, target audience understanding of the link between disease and obesity, perceptions of body weight and image, and other cultural factors that would affect acceptance of campaign messages. In addition to helping identify a target population, this formative research uncovered insights that later informed the design of the campaign, and particularly to ensure that it addressed population-specific attributes.

The focus of the campaign was narrowed following a series of key informant interviews with nutritionists and other community health workers, who identified 18- to 35-year-old black women as an underserved population. To further understand culture, gender, social class issues, attitudes, and preferences, the campaign planning group was expanded to include experts in media, education, and nutrition who lived and/or worked in the communities and were familiar with the culture of the target population. This was a crucial step in creating a foundation for community building and community linkages.

Throughout the project, design of all new materials and activities were based on formative evaluation that addressed three fundamental questions:

- Do the materials address the themes, key information, and skills that are needed?
- Does the design reflect the culture and preferences of the target population?
- Is the language and style appropriate and understandable?

The campaign logo for *Sisters Together* (see Figure 14.2), for example, communicates the culturally relevant concept of sisterhood expressed repeatedly in lay literature. The shapes of the women reflect the acceptance of a heavier weight as ideal, hair styles and variations typical of the target population, and the sense of movement being promoted by the campaign. While the logo could be reproduced successfully in black and white, the green, red, and black used in the original design were recommended by campaign planning group members familiar with the community. The various features of the logo were tested in focus groups and, when that was not feasible, in intercept interviews to ensure that decisions were acceptable to the target population.

Beyond such campaign branding efforts, the messages and materials in *Sisters Together* were tailored to social and cultural characteristics of the target population. For example, formative research showed that one widely popular dish was macaroni and cheese, high in calories and saturated fat. The challenge was to create a version that would be significantly lower in calories and acceptable to the target population. The first step was to identify recipes that met the criteria. The second step was to show the recipes to women in the target



FIGURE 14.2 The logo for the *Sisters Together: Move More, Eat Better* campaign was developed from extensive formative research with the target population.

population to identify which ones might be acceptable, and to reject those that were not; with this population, it emerged that few of the women would prepare a recipe with cottage cheese, so the numerous calorie-reduced versions with this ingredient were removed from consideration. Once possible recipes were selected, the third step was a taste test, again with members of the target population, to determine the recipe that would be accepted most widely. This process was repeated for each of the 12 recipes used in a calendar, one of the materials designed for the communication campaign. In an evaluation of the calendar, many women reported that they liked and used the recipes, demonstrating the value of the formative research [37].

The campaign also included cooking demonstrations, which were held at as many community events as possible, with the goal of addressing key concerns for women in the community: cost, convenience, and self-efficacy with respect to preparation of food that tastes good and follows healthful criteria. Recipes used relatively less expensive ingredients and could be prepared quickly. Demonstrations emphasized basic kitchen skills, such as knife skills, frequently found to be a barrier to food preparation.

Place-Based Campaign Components

Sisters Together also incorporated place-based components, at both the local and distal levels. For example, the campaign's launch was publicized through local broadcast and print media, and promotion through these channels continued for the duration of the campaign. A coalition of community partners was also established to support and extend the campaign message. Attendance at partner events allowed not only the *Sisters* team but also its partners to cross promote their programs and events. In addition, events were used to compile a mailing list for a monthly newsletter. Each newsletter had a monthly theme, with a review of recent events held by partners, a description/promotion of partner organizations, and a detailed calendar of events for the next month.

At the distal level, *Sisters Together* remains a national initiative of the NIDDK Weight-Control Information Network, and has been and continues to be adapted to meet the needs of communities throughout the United States. The campaign workbook and other materials are available at http://win.niddk.nih.gov/publications/SisPrmGuide2.pdf. Ongoing reevaluation of the messages and materials is essential to identify adaptations that appear necessary and to ensure suitability for target populations.

Shape Up Somerville: Eat Smart, Play Hard

Shape Up Somerville: Eat Smart, Play Hard (SUS) was an intervention designed according to CBPR, a collaborative approach that combines systematic inquiry, participation, and action to address urban health problems. This approach aligns closely with the People and Places framework [3]. SUS was designed to bring the energy equation into balance by increasing physical activity options and availability of healthful foods for early elementary school children, within the before-, during-, and after-school environments, as well as the home and community. The goal was to prevent the expected weight gain in elementary school children through small changes in their diets and physical activity [38]. Nutrition communications, which grew out of formative research with the members of the target community, played a key role in virtually every aspect of the project.

People-Based Campaign Components

Similar to *Sisters Together,* the branding of SUS was developed based on formative research specific to the target population. The name for the campaign, "Shape Up Somerville: Eat Smart, Play Hard," came out of focus groups with children. (Coincidentally, "Eat Smart, Play Hard" was also adopted as the name of a national USDA campaign, so there was a logical synergy that strengthened the messaging.) A logo, designed to reflect physical activity and healthy eating behavior in both boys and girls, was derived from ideas suggested by the children in focus groups representative of the target population. Alternative designs, including different graphics and colors, were tested in formative research with the children. The final logo was a red and orange line drawing of a boy jumping rope and a girl eating a banana, with words in a font chosen and approved specifically for the project. This logo was used on all project communications, including written communications to families, promotional materials such as water bottles and T-shirts, window stickers that promoted *Shape Up Approved* restaurants in the community, and reflective tags for "Walk to School" day. This consistent branding was critical to increasing campaign recognition.

SUS also engaged families through newsletters that were developed based on information obtained in parent focus groups. In response to feedback from parents and caregivers, coupons for produce were solicited from a local vendor and included in the newsletters. Knowing that the newsletters contained coupons raised the likelihood that parents and caregivers would open and read them. In addition, newsletters provided information that would be of value to the target population, including recipes for foods that were being promoted, publicity about locations and times of farmers markets and local events, ideas for activities with their children, important food safety information, and research findings of particular relevance to the population.

Place-Based Campaign Components

Given SUS's focus on children, its place-based components logically included several school-based elements. For example, school lunches and a la carte offerings were adapted to include less energy-dense food and beverage options, with an emphasis on fruits and vegetables, whole grains, and low-fat dairy. Schools also adopted new wellness policies and were provided new play equipment to allow more active recess activities. Another program component specifically aimed to increase children's acceptance of dried beans, a nutrient-dense commodity food. Recipes were developed and tested to ensure that children would like them, and beans were promoted through a unique audio program broadcast through

the school public address system. In order to heighten interest in the program, students in the schools participated in the design and delivery of each of the 11 messages. Focus groups with children in the community informed message development, and content analysis of food advertisements to children was conducted to identify characteristics and persuasive techniques that might be used effectively [39].

Beyond the school setting, SUS also addressed issues of access to healthful foods through a program that certified restaurants as "SUS-approved" if they met specific healthy eating standards. To support physical activity in the context of an urban built environment, a "walking school bus" program was initiated, and a mandate was developed to paint crosswalks with more durable paint to make them safer for crossing. A column in the local newspaper, *The Somerville Journal*, featured regular articles to raise the visibility of the intervention and the many activities that were being conducted. For example, the *Journal* ran a series of articles titled "Where's Mayor Joe?" focusing the mayor's visits to restaurants that had adopted SUS healthy eating standards. The articles positioned Mayor Joseph Curtatone, an opinion leader in the community social network, as an individual who could promote the normative behavior being recommended in the environment. The success of this program component depended largely on the shared interests among SUS researchers and community stakeholders: SUS benefitted from the promotion of approved restaurants, the mayor gained favorable publicity, restaurants obtained a no-cost marketing opportunity, and the newspaper enhanced public relations through its promotion of community programs.

At the conclusion of the intervention, the SUS logo was signed over to the city, which has continued many aspects of the intervention. At the distal level, the success of SUS led to the development of the Balance Project, which has adapted and implemented the SUS model for other U.S. communities. National publicity, including a front-page feature of SUS in the *Wall Street Journal*, further extended the campaign's influence on nationwide policies surrounding child nutrition and physical activity.

General Nutrition Communication Recommendations

Nutrition communication, by itself, cannot be expected to influence eating behavior. Its greatest promise is as a component of a comprehensive intervention that begins with a definition and understanding of the target population, based on thorough formative research, and a clearly specified, measurable set of outcome objectives. Nutrition advice must be framed in the context of total diet and be consistent with the Dietary Guidelines for Americans. The information is complex for most consumers and is generally more effective when divided into digestible bits and actionable steps. Nutrition messages and materials should be accurate, actionable, and relevant to the target population.

Whether you are designing a nutrition communication intervention for a small group with very specific needs, or for a large, generalized group, a well-planned approach using specific strategies can help your message resonate with the target audience and drive the desired behavior change.

ACKNOWLEDGMENTS

The authors would like to acknowledge the editorial contributions by Daniel Hatfield, MS, to the preparation of this manuscript.

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Part III

Physical Activity and Fitness

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15 Physical Fitness Evaluation

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CONTENTS

Definition of Physical Fitness 199
Aerobic and Anaerobic Fitness 199
Determining Exercise Capacity: Direct Method-Open Circuit Spirometry 200
Determining Aerobic Fitness by Standardized Tests Using Indirect Methods 200
Protocols 201
Cycle Ergometer Protocols 202
Ramp Testing 202
Submaximal Testing 202
Walk Tests for Cardiorespiratory Fitness Assessment 202
Muscular Fitness 203
Muscular Strength 203
Muscular Endurance 203
Tests of Anaerobic Power 203
Body Composition 204
Definition, Assessment, and Classification of Overweight and Obesity 204
Hydrodensiometry or Underwater Weighing 204
Other Methods 204
Waist Circumference 204
Skinfold Assessment 204
References 206

DEFINITION OF PHYSICAL FITNESS

The Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) define physical fitness as, "a set of physical attributes that people have or achieve that relates to the ability to perform physical activity" [1,2]. These attributes have important implications for overall health, including one's ability to perform recreational or occupational activities, the determination of disability, injury prevention, and skeletal muscle, bone, and cardiovascular health. Moreover, higher fitness is strongly associated with better long-term health outcomes [3,4]. Engaging in proper physical training leads to an improvement in these physical attributes and physical fitness. The degree of improvement is determined by several factors, including training, diet, rest, psychological factors, and genetics.

AEROBIC AND ANAEROBIC FITNESS

The energy necessary to sustain life and perform work is extracted by the cells in one of two ways: with the use of oxygen and without oxygen. Historically, the utilization of oxygen to extract energy has been referred to as aerobic metabolism, and extracting energy without utilizing oxygen has been referred to as anaerobic metabolism. However, it is important to note that muscle cells are never entirely aerobic or anaerobic. Rather, their energy requirements are met through the harmonious interaction of the two systems, with the energy contribution of each system depending largely on the intensity of activity. In general, high-intensity activities derive their energy mainly independent of oxygen, while low-intensity activities utilize oxygen to meet their energy requirements. Therefore, aerobic fitness refers to the ability to provide the required energy for a specific task in which the body's cardiopulmonary system adequately supplies the needed oxygen to the working muscle cells. Conversely, anaerobic fitness refers to the body's ability to provide the required energy for a specific task independent of oxygen. Aerobic activities consist of repetitive, low-resistance movements (e.g., walking or cycling) that last over a relatively extended period of time (generally 5 min or more). Anaerobic activities on the other hand are characterized by bursts of intense activity lasting a comparatively short period of time (sprinting, lifting of a heavy weight, jumping, etc.). It is important to emphasize that these two energy systems (aerobic and anaerobic) are almost always working together in a harmonious way, sharing the responsibility for providing the energy requirements for the working muscles and the entire body. However, one is likely to be the predominant system to provide most of the energy for the particular activity at hand [5].

DETERMINING EXERCISE CAPACITY: DIRECT METHOD-OPEN CIRCUIT SPIROMETRY

The "true" maximum aerobic capacity is the maximum amount of oxygen (referred to as maximal oxygen uptake or VO_2 max) the body can utilize during work. This is assessed in laboratories by *open circuit spirometry.* VO_2 max is usually determined by a graded exercise test (GXT). A brief description and rationale for this procedure is as follows.

The individual breathes room air via a mouth piece (nose occluded), connected to an automated system (often termed a metabolic cart) by plastic tubes. The mouth piece is designed in such a way that it allows the measurement of the volume of expired air, while a small sample of the expired air enters the metabolic cart and is analyzed for its oxygen and carbon dioxide (CO_2) content. Oxygen uptake is determined by the product of ventilation and the difference between the O_2 content of the ambient and expired air. After resting samples are taken, the individual is subjected to a standardized exercise protocol on a treadmill or stationary bike. The exercise begins at a very low workload and increases progressively until volitional fatigue or until a clinical indication for stopping is reached. The rate of increase in external work depends on the exercise protocol used, but it is typically recommended that the test be individualized to last between 8 and 12 min.

Since the relationship between the increase in workload and oxygen consumption is linear, oxygen requirements also increase. At some point the individual reaches a volitional fatigue endpoint, and the test is terminated. This level is referred to as the maximal aerobic capacity of the individual. The oxygen utilized by the body at the point of fatigue is referred to as the VO_2 max. The measurement of VO_2 max implies that an individual's physiological limit has been reached. True VO_2 max has historically been defined by a plateau in VO_2 between the final two exercise work rates and requires that maximal effort be achieved and sustained for a specified period. Because this determination is subjective, can be difficult to define, and is rarely observed when patients with cardiovascular or pulmonary disease are tested, the term *peak* VO_2 is more commonly used clinically to express exercise capacity. Conversely, the term VO_2 *max* is more often used to describe exercise capacity in apparently healthy individuals, in whom achievement of a maximal physiological response is more likely. VO_2 max is expressed in milliliters of oxygen per minute (mL/min) or milliliters of oxygen per kilogram (kg) of body weight per minute (mL/kg/min). The latter is usually the preferred expression since it allows comparisons between subjects of different weights.

The direct measurement of VO_2 max is most often used for research purposes and has a number of important clinical applications for patients with cardiovascular or pulmonary disease. However, it is not often practical for someone who simply wishes to know the appropriate exercise intensity during his or her training. For this purpose, exercise intensity can be easily determined by the heart rate that corresponds to the appropriate percentage of oxygen consumption. Since heart rate and oxygen uptake are continuously recorded during the metabolic test, one can easily match a desired percentage of heart rate to the corresponding oxygen consumption. The advantage of the direct method is that it is highly accurate. It allows an accurate assessment of the exercise intensity of an individual based on directly measured rather than estimated aerobic capacity. However, it is an elaborate method that requires expensive equipment and trained personal and is therefore cost-prohibitive for large populations. It is mostly used in individuals with specific clinical needs and for research purposes [5].

DETERMINING AEROBIC FITNESS BY STANDARDIZED TESTS USING INDIRECT METHODS

The need for more practical methods to assess aerobic capacity for large populations led to the development of standardized exercise tests and the common practice of estimating energy requirements from different workloads. An indirect method for estimating the fitness level of an individual is based on the same principle as that for the direct assessment of VO_2 max with one exception; oxygen consumption is not directly measured. Rather, it is estimated based on treadmill speed and grade utilizing equations derived from the direct assessment of VO_2 max. The actual procedure is similar to that described for the assessment of VO_2 max with the exception that the individual is not connected to a metabolic cart (no breathing apparatus). While an ECG is monitored, the individual undergoes a standardized exercise protocol on a treadmill or stationary cycle ergometer. The most commonly used exercise protocols in the United States are described in Table 15.1, and these are discussed as follows. Exercise begins at a very low workload and increases every 2–3 min depending on the exercise protocol. The maximal workload is determined from the speed and elevation of the treadmill, or the resistance if a cycle ergometer is used. Heart rate is continuously monitored and recorded during the entire test (photo), and blood pressure is recorded every 2–3 min.

The workload is estimated for each exercise stage based on the speed and elevation of the treadmill. This estimation is based on comparison studies in which the energy requirements (oxygen consumption) were measured directly with metabolic equipment. In general, the amount of oxygen used during resting conditions is approximately 3.5 mL of oxygen per kilogram of body weight per minute (3.5 mL O_2/kg/min). This value (the resting metabolic rate) is termed 1 metabolic equivalent or 1 MET. Naturally, any increase beyond the 1-MET level represents higher total body oxygen consumption. Based on this rationale, several standardized exercise protocols have been developed to assess the MET level of individuals for clinical and other reasons. The MET level achieved upon termination of the test (the individual reaches volitional fatigue) represents the peak aerobic capacity of the individual. Because each MET is equal to approximately 3.5 mL O_2/kg/min, VO_2 max can be estimated by multiplying the MET level achieved by 3.5 [5]. It is important to note that exercise capacity assessed by such exercise tests is associated

TABLE 15.1
Commonly Used Treadmill and Bicycle Exercise Protocols

Stage	Minutes	Speed (MPH)	% Grade	METS
Bruce Protocol				
1	3	1.7	10	4.6
2	3	2.5	12	7.0
3	3	3.4	14	10.2
4	3	4.2	16	13.5
5	3	5.0	18	17.2
6	3	5.5	20	20.4
7	3	6.0	22	23.8
Modified Bruce				
1	3	1.7	0	2.3
2	3	1.7	5	3.5
3	3	1.7	10	4.6
4	3	2.5	12	7.0
5	3	3.4	14	10.2
6	3	4.2	16	13.5
7	3	5.0	18	17.2
8	3	5.5	20	20.4
9	3	6.0	22	23.8
Balke-Ware				
1	3	3.3	1	4.0
2	3	3.3	2	4.4
3	3	3.3	3	4.9
4	3	3.3	4	5.3
5	3	3.3	5	5.8
6	3	3.3	6	6.3
7	3	3.3	7	6.7
8	3	3.3	8	7.2
9	3	3.3	9	7.6
10	3	3.3	10	8.1
11	3	3.3	11	8.5
12	3	3.3	12	9.0
13	3	3.3	13	9.4
14	3	3.3	14	9.9
15	3	3.3	15	10.3
16	3	3.3	16	10.8
17	3	3.3	17	11.3
18	3	3.3	18	11.7
19	3	3.3	19	12.2
20	3	3.3	20	12.6
21	3	3.3	21	13.1
22	3	3.3	22	13.5
23	3	3.3	23	14.0
24	3	3.3	24	14.4
25	3	3.3	25	14.9
26	3	3.3	26	15.4
Balke				
1	2	3.0	2.5	4.3
2	2	3.0	5	5.4
3	2	3.0	7.5	6.4
4	2	3.0	10	7.4
5	2	3.0	12.5	8.5
6	2	3.0	15	9.5
7	2	3.0	17.5	10.5

TABLE 15.1 (continued)
Commonly Used Treadmill and Bicycle Exercise Protocols

Stage	Minutes	Speed (MPH)	% Grade	METS
Naughton				
1	2	1	0	1.8
2	2	2	0	2.5
3	2	2	3.5	3.5
4	2	2	7.0	4.5
5	2	2	10.5	5.4
6	2	2	14.0	6.4
7	2	2	17.5	7.4
8	2	2	21.0	8.3

Stage	Minutes	Revolutions per Minute	Resistance (kg m/min)	Resistance (W)	METS
Standard Bicycle Protocol					
1	2 or 3	50	150	25	3.1
2	2 or 3	50	300	50	4.2
3	2 or 3	50	450	75	5.3
4	2 or 3	50	600	100	6.4
5	2 or 3	50	750	125	7.5
6	2 or 3	50	900	150	8.6

with physical activity status of the individual. However, the ability to perform aerobic work is also determined by age and gender, as well as an important genetic component [6,7].

PROTOCOLS

The purpose of the test and the person tested are important considerations in selecting the protocol. Exercise testing may be performed for diagnostic purposes, for functional assessment, or for risk stratification. An often ignored but nevertheless consistent recommendation in the recent exercise testing guidelines is that the protocol be individualized for the patient being tested [8–10]. For example, a maximal, symptom-limited test on a relatively demanding protocol would not be appropriate (or very informative) for a severely limited patient. Likewise, a very gradual protocol might not be useful for an apparently healthy, active person. Use of submaximal testing, gas exchange techniques, the presence of a physician, and the exercise mode and protocol should be determined by considering the person being tested and the goals of the test.

Commonly used exercise protocols, their stages, and the MET level for each stage are outlined in Table 15.1. The most suitable protocols for clinical testing should include a low-intensity warm-up phase followed by progressive, continuous exercise in which the demand is elevated to a patient's maximal level within a total duration of 8–12 min [8–13]. In the absence of gas exchange techniques, it is important to report exercise capacity in METs rather than exercise time, so that exercise capacity can be compared uniformly between protocols. METs can be estimated from any protocol using standardized equations that have been put into tabular form [8,9,14]. In general, 1 MET represents an increment on the treadmill

of approximately 1.0 mph or 2.5% grade. On a cycle ergometer, 1 MET represents an increment of approximately 20 W (120 kg m/min) for a 70-kg person. The assumptions necessary for predicting MET levels from treadmill or cycle ergometer work rates (including not holding the handrails, that oxygen uptake is constant [i.e., steady-state exercise is performed], that the subject is healthy, and that all people are similar in their walking efficiency) raise uncertainties as to the accuracy of estimating the work performed for an individual patient. For example, the steady-state requirement is rarely met for most patients on most exercise protocols; most clinical testing is performed among patients with varying degrees of cardiovascular or pulmonary disease; and people vary widely in their walking efficiency [14]. It has therefore been recommended that a patient be ascribed a MET level only for stages in which all or most of a given stage duration has been completed [15].

CYCLE ERGOMETER PROTOCOLS

Although there are specific bicycle protocols named for early researchers in Europe, such as Astrand [16], bicycle ergometer protocols tend to be more generalized than for the treadmill. For example, 15–25-W increments per 2-min stage are commonly used for patients with cardiovascular disease, whereas for apparently healthy adults or athletic individuals, appropriate work rate increments might typically be between 40 and 50 W/stage. Most modern, electronically braked cycle ergometers have controllers that permit ramp testing, in which the work rate increments can be individualized in continuous fashion (see next section).

RAMP TESTING

An approach to exercise testing that has gained interest in recent years is the ramp protocol, in which work increases constantly and continuously. In 1981, Whipp et al. [17] first described cardiopulmonary responses to a ramp test on a cycle ergometer, and many of the gas exchange equipment manufacturers now include ramp software. Treadmills have also been adapted to conduct ramp tests [13,18,19]. The ramp protocol uses a constant and continuous increase in metabolic demand that replaces the "staging" used in conventional exercise tests. The uniform increase in work allows for a steady increase in cardiopulmonary responses and permits a more accurate estimation of oxygen uptake [13]. The recent call for "optimizing" exercise testing [8,10,12,15] would appear to be facilitated by the ramp approach, because large work increments are avoided and increases in work are individualized, permitting test duration to be targeted. Because there are no stages per se, the errors associated with predicting exercise capacity alluded to previously are lessened [8,9,13].

SUBMAXIMAL TESTING

In general, maximal, symptom-limited tests are not considered appropriate until 1 month after myocardial infarction (MI) or cardiac surgery. Thus, submaximal exercise testing has an important role clinically for predischarge, post-MI, or postbypass surgery evaluations. Submaximal tests have been shown to be important in risk stratification [19–22] for making appropriate activity recommendations, for recognizing the need for modification of the medical regimen, or for further interventions in patients who have sustained a cardiac event. A submaximal, predischarge test appears to be as predictive for future events as a symptom-limited test among patients less than 1 month after MI. Submaximal testing is also appropriate for patients with a high probability of serious arrhythmias. The testing endpoints for submaximal testing have traditionally been arbitrary but should always be based on clinical judgment. A heart rate limit of 140 beats/min and a MET level of 7 are often used for patients younger than age 40 years, and limits of 130 beats/min and a MET level of 5 are often used for patients older than 40 years. For those using beta-blockers, a Borg perceived exertion level in the range of 7–8 (1–10 scale) or 15–16 (6–20 scale) are conservative endpoints. The initial onset of symptoms including fatigue, shortness of breath, or angina, is also indications to stop the test. A low-level protocol should be used, that is, one that uses no more than 1-MET increments per stage. The Naughton protocol [23] is commonly used for submaximal testing. Ramp testing is also ideal for this purpose because the ramp rate (such as 5 METs achieved over 10-min duration) can be individualized depending on the patient tested [13].

Submaximal testing can also be used to assess the capacity of apparently healthy individuals to exercise safely or to estimate VO_2 max by extrapolation. The premise of estimating VO_2 max from a submaximal test is based on the linear relationship between heart rate and oxygen consumption, provided that the work is aerobic in nature. In submaximal test protocols, the HR at each workload is plotted against the workload and extrapolated to VO_2 max at an age-predicted maximal heart rate (typically 220-age). VO_2 max can be calculated using prediction equations [2] or estimated from values obtained by commonly used exercise protocols if the following assumptions are met: (1) the workload is reproducible; (2) a steady-state heart rate is obtained during each stage; and (3) a linear relationship exists between heart rate and oxygen consumption over a wide range of values. Examples of submaximal tests used to estimate peak VO_2 include the YMCA test, the Astrand test, and others [16,24,25].

WALK TESTS FOR CARDIORESPIRATORY FITNESS ASSESSMENT

A number of walking tests have also been developed for estimating cardiorespiratory fitness or assessing functional status of patients with cardiovascular or pulmonary disease in clinical settings. Advantages of walk tests include the fact that they are easy to perform and are relatively inexpensive, and thus can be applied to large populations. These include (1) the 6-min walk test, (2) the Cooper 12-min test, (3) the 1.5 mile test, and the Rockport one-mile fitness walking test [2].

The 6-min walk test is popular for assessing functional status in clinical settings, and is mostly used among diseased populations such as patients with heart failure, stroke, and peripheral vascular disease. The objective of the test is to cover the greatest distance by walking in 6 min. Its obvious advantages are that it requires practically no equipment (other than a stop watch) and little time.

Although the association between the 6-min walk performance and exercise capacity is only modest, peak VO_2 can be estimated from the 6-min walk distance by the following multivariate equation along with other readily available information:

$$\begin{aligned} Peak\ VO_2 = {} & [0.02 * distance(\mathrm{m})] - [0.191 * age(\mathrm{yr})] \\ & - [0.07 * weight(\mathrm{kg})] + [0.09 * height(\mathrm{cm})] \\ & + [0.26 * RPP(*10^{-3})] \end{aligned}$$

where
- m is meter
- kg is kilogram
- cm is centimeters
- yr is year
- RPP is rate pressure product (systolic blood pressure [mm Hg]* heart rate)

The Cooper 12-min test is based on a similar concept (covering the greatest distance in 12 min), while the objective of the 1.5 mile test is to run the distance (1.5 miles) in the shortest period of time. Unlike the 6-min walk test, both of these tests are more suitable for healthy, younger individuals. They also require little or no additional equipment and can be administered to large populations.

The Rockport one-mile fitness walking test involves covering a 1-mile distance in the shortest period of time. However, in addition to the time required to cover the 1-mile distance, the test utilizes peak heart rate achieved during the last minute of the walk, and an estimate of peak VO_2 is derived. If heart rate monitoring is not an option during the test, a 10-s heart rate obtained immediately after the completion of the test can be used as an alternative. However, this is likely to overestimate peak VO_2 compared to that calculated when heart rate is obtained during the last minute of the walk.

MUSCULAR FITNESS

The ACSM defines *muscular fitness* as the ability of the muscle to perform tasks that require muscular strength or muscular endurance. Strength is an important component of fitness assessment since it has implications for an individual's functional capabilities, disability, bone health, and insulin resistance and has been shown to have a strong association with long-term outcomes [26].

MUSCULAR STRENGTH

Muscular strength is defined as the ability of the muscle or muscle groups to exert force during a voluntary contraction [1]. The maximal force a muscle or group of muscles can exert is traditionally assessed by tests that require maximum effort against the greatest resistance one can move through the full range of motion once. This is known as the 1-repetition maximum (1-RM). A percentage of the 1-RM is then used to determine the number of repetitions one should perform to enhance the strength for a specific muscle. Generally, 8–12 repetitions at 40%–60% of 1-RM are sufficient to enhance muscular strength. An appropriate resistance training regimen involves performing these 8–12 repetitions 1–3 times, 2–3 times per week. While intensities as much as 80% and relatively low repetitions (such as 3–5) have been shown to be quite effective for rapid strength gains, this approach is generally limited to athletes whose performance requires great amounts of force.

It is important to note that intensity for resistance exercise is not always easy to determine and the 1RM does not depict a true intensity. The number of repetitions and the percentage of resistance based on 1RM differ significantly between individuals and muscle groups. Thus, the 1RM should only be used as a general guideline [2].

MUSCULAR ENDURANCE

Muscular endurance is defined as the ability of the muscle or muscle groups to perform repetitive contractions over a period of time against resistance, such as lifting a set amount of weight several times [2]. Muscular endurance is assessed by tests requiring more than 12 repetitions. A simple test of muscular endurance is the maximum number of push-ups or sit-ups one can execute without rest [2].

TESTS OF ANAEROBIC POWER

Because *anaerobic* power is an important determinant of athletic performance requiring high levels of exertion over short periods, tests have been developed to measure the capacity of the anaerobic energy systems. One of the more common tests of this type is the *Wingate* test, which involves 30–120 s of high-intensity effort on a cycle ergometer. The resistance is based on body mass (originally 0.075 kp per kg body mass, though this may vary) and is applied after initial inertia and unloaded resistance are overcome. *Peak power* is considered to represent the highest mechanical power generated during any 3–5 s period during the test; *average power* is the average of the total power generated during the test. An underlying assumption of the Wingate test is that peak power reflects the energy-generating capacity of the oxygen-independent high-energy phosphates, whereas average power is a representation of one's glycolytic capacity [27,28]. In studies comparing the Wingate test results to athletic performance and laboratory findings, it has been demonstrated to be a good index of these energy systems, although studies are mixed in terms of its ability to predict success in events requiring high exercise intensity [28].

BODY COMPOSITION

In the United States and most of the industrialized world, obesity has reached epidemic proportions [29]. Overweight and obesity are not simply cosmetic problems, but serious health conditions. They are both considered to be leading risk factors for a number of chronic health conditions including diabetes, hypertension, coronary heart disease, and premature mortality in developed countries. Although the mechanisms and causes of obesity are poorly understood, experts agree that obesity is largely the result of a chronic imbalance between caloric intake and caloric expenditure. This imbalance is likely the outcome of a complex interaction between genetic and environmental factors [30].

DEFINITION, ASSESSMENT, AND CLASSIFICATION OF OVERWEIGHT AND OBESITY

Body composition is comprised of three major structural components: muscle, bone, and fat. Obesity is defined as the accumulation of excess body fat, usually ≥25% of the total body weight for men and ≥33% for women [31]. Assessing body fat is not a simple task. Several methods have been developed with mixed success. The most commonly used methods, the strengths and weaknesses are presented as follows.

HYDRODENSIOMETRY OR UNDERWATER WEIGHING

One of the most accurate assessments of body composition is hydrodensiometry or underwater weighing. This method is based on Archimedes' principle, which states that the weight an object loses when immersed in water is equal to the weight of the displaced water resulting from that immersion. Percent body fat is estimated from body density, knowing that lean mass (bone and muscle) is heavier than body fat. The following equations for estimating body composition from underwater weighing were developed in the late 1950s and early 1960s [32,33] and are still in common use:

$$\% \text{ Body fat} = (457/\text{Body density}) - 414.2 \text{ [34]}$$

$$\% \text{ Body fat} = (495/\text{Body density}) - 450 \text{ [35]}$$

A number of equations have also been developed over the years to address specific populations, gender, and different races.

OTHER METHODS

Direct assessment of body fat by densitometry is one of the most accurate methods, but it is generally not practical for large populations. Thus, several indirect techniques have been developed over the years to assess body composition. The most commonly used methods for estimating or assessing body composition, their advantages and disadvantages are described in Table 15.2 [5].

Because direct body fat assessment is impractical for large populations, the American Heart Association (AHA) and other health organizations have adopted body mass index (BMI) as a practical clinical indicator of adiposity [30]. BMI, calculated as weight [kg] divided by height [m] squared (kg/m^2), correlates well with total body fat and is related to cardiovascular and all-cause mortality [34–36]. The estimated BMI for different weights and heights is presented in Table 15.3.

A set of cut-points at five BMI intervals to classify overweight and obesity have been adapted by the National Heart, Lung, and Blood Institute and World Health Organization [31]. Based on this classification, men and women with a BMI ≥30 kg/m^2 are considered obese (Table 15.4). However, it is important to keep in mind that BMI may not accurately reflect true adiposity for some populations. For example, a relatively muscular male weighing 100 kg, 1.80 m in height and approximately 20% actual body fat, has a BMI of 30.86 (BMI = 100/1.8^2). Conversely, a male 1.80 m tall, weighing 80 kg, with 30% actual body fat, has a BMI of 24.7. According to the classification system commonly used (Table 15.4), these individuals will be misclassified as obese and not obese, respectively [5].

WAIST CIRCUMFERENCE

Evidence supports the concept that excess accumulation of adipose tissue in the abdomen, characteristic of male-type fat distribution (android, abdominal, or central obesity) is associated with a higher risk for mortality than peripheral distribution of body fat [38]. This is because fat that surrounds the internal organs, known as *visceral fat*, is most closely associated with metabolic disorders that increase cardiovascular risk, including insulin resistance, lipid abnormalities, and heightened markers of inflammation. Since BMI also fails to take body fat distribution into account, waist circumference provides a practical method for assessing mortality risk associated with central distribution of fat, if a direct body fat assessment is not available. Waist circumference correlates more strongly with abdominal fat than BMI. Waist circumferences >102 cm for men and >88 cm for women are associated with increased cardiovascular risk [39,40].

SKINFOLD ASSESSMENT

Body composition estimated by skinfold measurements is based on the premise that approximately one-third of the total body fat is subcutaneous fat and the remaining is visceral fat. Thus, skinfold thickness parallels total body fat and is another method often use to estimate body composition. Because proportionally more fat is deposited viscerally with advancing age, age-adjusted equations should be

TABLE 15.2
Various Methods of Assessing Body Composition

Method/ Techniques	Method of Assessment	Advantages	Disadvantages
Densitometry from underwater weighing	Subject exhales fully all air. Then he/she submersed in water for only a few seconds. Weight is assessed under water	It is based on Archimedes principle. This method computes percentage body fat from body density (body mass/body volume)	Expensive and time consuming. Requires a laboratory equipped with a water tank trained personnel. It also requires that individuals exhale forcefully to reduce all possible all air from lungs. Then they are submersed in water for several trials, each lasting several seconds. This may not be tolerated well by some subjects who will either not undergo the procedure or make it difficult to obtain an accurate reading
Dual-energy x-ray absorptiometry (DXA)	Uses two low-energy distinct x-ray beams that penetrate bone and soft tissue areas to the depth of 30 cm. Computer software reconstructs the attenuated beams and produces an image of the tissues and quantify muscle, and fat mass	Quick, takes approximately 12 min to complete and correlates very highly with densitometry. Total body mass or regional tissue mass can be assessed	Expensive, requires trained personnel
Bod-pod	Relatively new procedure that uses an elliptical-shaped box that the subject sits in. It is based on air displacement plethysmography	Quick, takes approximately 3–5 min and has high reproducibility. Does not require any special skills by technician	Expensive. Claustrophobia may be an issue with some participants
Magnetic resonance imaging (MRI)		Can distinguish between changes in muscle mass and fat. Good for studies designed to assess changes in muscle mass (i.e. resistance [weight] training)	Very expensive, requires highly trained technicians. Cost prohibitive for large cohort studies.
Bioelectrical impedance	A light current is introduced to the individual. Body fat is estimated by opposition to current flow	Quick, relatively inexpensive	Tends to over predict body fat. Requires trained personnel and standardized conditions (hydration, environmental temperature) that may not be possible in all situations
Skinfolds	Requires a caliper that measures body fat at standardized anatomical body sites	Relatively easy and inexpensive to perform (requires a caliper). No special laboratory required other than a room for some privacy. Time requirements are only a few minutes per subject, thus allowing large numbers of individuals to be processed	Skilled and experienced personnel are required
BMI	Weight and height are needed	The simplest and least expensive method, requiring only the weight (kg) and height (m) of the individual	It is only an index of body dimensions. It does not measure body fat, but only assumes that higher BMI translates to higher body fat content. This may or may not be true and can vary greatly for different populations
Waist circumference and waist–hip ratio	Measurements of waist and hip circumference	Simple, inexpensive and relatively quick to perform	Both waist circumference and the waist-to-hip ratio are indices of body composition. They do not measure body fat. However, they both provide an index of fat distribution

TABLE 15.3
BMI Based on Weight and Height

HT (in.)	120	130	140	150	160	170	180	190	200	210	220	230	240	250
Body Weight (lb)														
58	25	27	29	31	33	36	38	40	42	44	46	48	50	52
59	24	26	28	30	32	34	36	38	40	42	44	46	48	50
60	23	25	27	29	31	33	35	37	39	41	43	45	47	49
61	23	25	26	28	30	32	34	36	38	40	42	43	45	47
62	22	24	26	27	29	31	33	35	37	38	40	42	44	46
63	21	23	25	27	28	30	32	34	35	37	39	41	43	44
64	21	22	24	26	27	29	31	33	34	36	38	39	41	43
65	20	22	23	25	27	28	30	32	33	35	37	38	40	42
66	19	21	23	24	26	27	29	31	32	34	36	37	39	40
67	19	20	22	23	25	27	28	30	31	33	34	36	38	39
68	18	20	21	23	24	26	27	29	30	32	33	35	36	38
69	18	19	21	22	24	25	27	28	30	31	32	34	35	37
70		19	20	22	23	24	26	27	29	30	32	33	34	36
71		18	20	21	22	24	25	26	28	29	31	32	33	35
72		18	19	20	22	23	24	26	27	28	30	31	33	34
73			18	20	21	22	24	25	26	28	29	30	32	33
74			18	19	21	22	23	24	26	27	28	30	31	32
75				19	20	21	22	24	25	26	27	29	30	31
76				18	19	21	22	23	24	26	27	28	29	30
77				18	19	20	21	23	24	25	26	27	28	30

Source: Jakicic, J.M. et al., *Med. Sci. Sports Exerc*., 33(12), 2145, 2001.
Note: Body mass index <18 is not recommended, and therefore these values are not represented in this table.

TABLE 15.4
Classification of Body Weight and Obesity Based on BMI and Waist Circumference

	Obesity Class	BMI (kg/m²)	Waist Circumference	Associated Health Risk
Underweight		<18.5		
Normal		18.5–24.9		Average
Overweight		25.0–29.9	Men: ≥94 cm Women: ≥80 cm	Increased
Obesity class	I	30.0–34.9	Men: ≥102 cm Women: ≥102 cm	Moderate
Moderate obesity	II	35.0–39.9		High
Severe obesity	III	≥40		Very high

used in older men and women. Assuming that the appropriate technique is used and factors that contribute to measurement error are controlled, the technique correlates fairly well with hydrodensiometry (r = 0.70–0.90). Accuracy is also compromised with extremely obese or extremely lean individuals.

Over the years, several sites and techniques have been identified and used to assess body composition via skinfolds. A thorough review of anthropometric assessments related to skinfolds is recommended for those interested in a more detailed description of this methodology [41]. These techniques are also reviewed in the *ACSM Guidelines for Exercise Testing and Prescription* [2].

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16 Exercise Prescription for Apparently Healthy Individuals and for Special Populations

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CONTENTS

Physical Activity Recommendations 210
Exercise Prescription 210
- Physical Fitness Parameters 210
- Exercise Training Principles 210
  - Progressive Overload 210
  - Specificity 211
  - Reversibility 211
- Cardiorespiratory Endurance Training 211
  - Type (Mode) of Exercise 211
  - Intensity of Exercise 211
  - Time (Duration) of Exercise 213
  - Frequency of Exercise 213
  - Overall Exercise Volume 213
  - Rate of Progression 213
- Resistance Training 214
  - Type of Resistance 214
  - Amount of Resistance, Repetitions, and Sets 214
  - Frequency of Training 214
  - Rate of Progression 214
- Flexibility Training 215
- Warm-Up and Cooldown 215
- Physical Activity Adherence 215

Exercise Prescription for Special Populations 215
- Children and Adolescents 215
- Older Adults 216
- Pregnancy and Postpartum 216
- Diabetes Mellitus 217
- Cancer 218
- Arthritis 219
- Disabilities 219

Summary 220
References 220

More now than ever, increasing one's physical activity is recognized as an important means of improving one's health. Table 16.1 lists the currently documented health benefits of physical activity [1]. *Physical activity* is defined as "bodily movement that is produced by the contraction of skeletal muscle and that substantially increases energy expenditure" [2]. *Exercise*, on the other hand, is a more strictly defined subset of physical activity that is "planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness" (e.g., cardiorespiratory endurance, muscular strength) [2]. Increases in both exercise and overall physical activity can maintain and improve health. Accordingly, this chapter will (1) review the current recommendations for physical activity, (2) discuss prescription of both formal exercise and overall physical activity, and (3) discuss prudent alterations to the normal exercise prescription in some of the more prevalent clinical populations.

TABLE 16.1
Health Benefits of Physical Activity: A Review of the Strength of Scientific Evidence

Adults and Older Adults

Strong Evidence

Lower risk of:
- Early death
- Heart disease
- Stroke
- Type 2 diabetes
- High blood pressure
- Adverse blood lipid profile
- Metabolic syndrome
- Colon and breast cancers

Prevention of weight gain

Weight loss when combined with diet

Improved cardiorespiratory and muscular fitness

Prevention of falls

Reduced depression

Better cognitive function (older adults)

Moderate to Strong Evidence

Better functional health (older adults)

Reduced abdominal obesity

Moderate Evidence

Weight management after weight loss

Lower risk of hip fracture

Increased bone density

Improved sleep quality

Lower risk of lung and endometrial cancers

Children and Adolescents

Strong Evidence

Improved cardiorespiratory endurance and muscular fitness

Favorable body composition

Improved bone health

Improved cardiovascular and metabolic health biomarkers

Moderate Evidence

Reduced symptoms of anxiety and depression

PHYSICAL ACTIVITY RECOMMENDATIONS

In 2008, the U.S. Department of Health and Human Services released its Physical Activity Guidelines for Americans [1]. The purpose of this document was both to summarize the scientific data related to physical activity published since the release of the 1996 Surgeon General's Report, Physical Activity and Health [2] and to resolve any confusion created through differing recommendations released after the Surgeon General's Report. For adults aged 18–64 years, the Guidelines recommend a minimum of 150 weekly minutes of moderate-intensity aerobic activity and recognize that increasing benefits are likely to accrue through at least 300 min/week. Alternatively, 75–150 min of vigorous-intensity aerobic activity can be performed to amass similar benefits (*moderate-* and *vigorous-intensity* aerobic activities are defined and discussed later). A combination of moderate- and vigorous-intensity activity may also be employed. In addition, resistance training involving all major muscle groups is recommended at least twice weekly. Additional recommendations for children, the elderly, and other special populations are discussed later in this chapter.

EXERCISE PRESCRIPTION

Physical Fitness Parameters

Physical fitness is "the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies" [3]. Elements of physical fitness have traditionally been categorized as either health related (cardiorespiratory endurance, muscular endurance, muscular strength, body composition, flexibility) or skill related (agility, balance, coordination, speed, power, reaction time) [4]. Definitions of the various physical fitness elements are listed in Table 16.2. The health-related fitness components are certainly important in chronic disease prevention and rehabilitation. However, particularly among the elderly and those with certain musculoskeletal diseases, maintenance of a certain level of skill-related fitness is also critical to independent function and quality of life. For example, the ability to drive a car or cross a busy street safely depends as much on *skill*-related and *health*-related fitness. Conversely, all of the health-related fitness parameters are key elements of various athletic and recreational activities. Therefore, while categorization of these elements may be helpful in developing fitness goals and an exercise plan, one should realize that training toward elements of *both* health-related and skill-related fitness may be prudent with some clients.

Exercise Training Principles

Although goals and responses to physical activity and exercise training can vary considerably from person to person, three general principles should be considered when developing an exercise plan: *progressive overload*, *specificity*, and *reversibility.*

Progressive Overload

Adaptations only occur in physiological systems when the systems are stressed at levels to which they are unaccustomed. In other words, for any physical fitness or health parameter, a *threshold* of physical activity exists that a person must exceed in order to experience improvement. This minimal amount of training needed depends upon both the baseline level of the variable to be changed and a person's genetic capacity to experience positive changes in the targeted physiological system(s).

Given a steady overload, physiological improvement will level off or plateau after a given period of time. The term *progressive* overload indicates that the training stimulus must continue to increase in order for further improvement to be recognized. The overall training stimulus can

TABLE 16.2
Health-Related and Skill-Related Physical Fitness Parameters[a]

Health Related	Skill Related
Cardiorespiratory endurance—The ability of the circulatory and respiratory systems to supply fuel during sustained physical activity and to eliminate fatigue products after supplying fuel	*Agility*—The ability to rapidly change the position of the entire body in space with speed and accuracy
Muscular endurance—The ability of muscle groups to exert external force for many repetitions or successive exertions	*Balance*—The maintenance of equilibrium while stationary or moving
Muscular strength—The amount of external force that a muscle can exert	*Coordination*—The ability to use the senses, such as sight and hearing, together with body parts in performing motor tasks smoothly and accurately
Body composition—The relative amounts of muscle, fat, bone, and other vital parts of the body	*Speed*—The ability to perform a movement within a short period of time
Flexibility—The range of motion available at a joint	*Power*—The rate at which one can perform work
	Reaction time—The time elapsed between stimulation and the beginning of the reaction to it

Source: Corbin, C.B. and Lindsey, R., *Concepts in Physical Education with Laboratories*, 8th edn., Times Mirror Higher Education Group, Dubuque, IA, 1994.

[a] Although physical fitness is dichotomized into health- and skill-related categories, overlap exists between the two (see text).

usually be augmented by increasing the *intensity*, *duration*, and/or *frequency* of physical activity.

Specificity

Overload will only result in an adaptation to the muscle groups and physiological systems that are stressed in training. Specificity of training applies to the motor units involved (e.g., muscles used, joint angle), speed of contraction, and the energy systems and primary substrates used (e.g., aerobic versus anaerobic metabolism, fat versus carbohydrate). Unless a person is severely untrained (e.g., frail elderly), strength training will do little to improve cardiorespiratory endurance and vice versa. Furthermore, although distance cycling and running are both aerobic activities using the legs, the carryover from training in one mode to performance improvement in the other is limited. Similarly, while squat training mainly improves quadriceps strength, this improvement may not be recognized when testing with another exercise (e.g., leg extension) that uses different motor unit recruitment and accessory muscles. Therefore, in addition to training specifically toward a person's goals, assessment of improvement should involve testing that is congruent with the training that has been employed. The more specific a person's training goals (e.g., athletic performance), the more important these issues become.

Reversibility

Just as the body adapts positively to increases in physical activity, it adapts negatively to inactivity. The rate of deconditioning varies depending on the previous training level and how much it is curtailed. For example, casting or extended bed rest can result in sharp rapid declines in strength and endurance performance. In a more practical sense, fitness levels tend to decline significantly after about 2 weeks of exercise cessation. Endurance training of 2–3 days/week and resistance training of at least once per week are generally necessary to maintain previously attained fitness levels.

Cardiorespiratory Endurance Training

Maximal oxygen consumption (VO_{2max}) is the most accurate measure of cardiorespiratory fitness. Although some health benefits may be recognized with the practice of moderate-intensity physical activity that is less likely to improve VO_{2max} [5], strong inverse relationship exists between VO_{2max} and overall mortality and most major chronic diseases [6]. As such, the American College of Sports Medicine has traditionally recommended the following frequency, intensity, time, and type (FITT) of exercise for the improvement of cardiorespiratory fitness [7].

Type (Mode) of Exercise

Activities that overload the cardiorespiratory system are repetitive (rhythmic) in nature and involve larger muscle groups. Examples include brisk walking, running, cycling, rowing, and exercising on an elliptical machine. Sports that constantly require intermittent bouts of vigorous body movement, such as basketball, soccer, and tennis, can also contribute to improved cardiorespiratory fitness. Unless medical conditions dictate otherwise, the majority of exercise should be weight-bearing in order to help prevent osteoporosis.

While specificity of training is very important for athletes, persons training more for overall health and fitness purposes will likely benefit from practicing a variety of exercise modes. Such practice will likely lead to fewer overuse injuries and will also add variety to the training regimen, possibly leading to better program compliance. For beginning exercisers, walking is generally a very good activity to include since it requires little skill and results in fewer overuse injuries than most other modalities.

Intensity of Exercise

Improvement in VO_{2max} can usually be attained by exercising regularly at 50%–85% of $VO_{2reserve}$ ($VO_{2reserve} = VO_{2max} - VO_{2rest}$). Obviously, this range is wide; the most effective

TABLE 16.3
Calculation of Target Oxygen Consumption ($VO_{2target}$) and Target Heart Rate (HR_{target}) by Reserve Method

$VO_{2target}$[a]	HR_{target}
Step 1: Calculate $VO_{2reserve}$ $VO_{2reserve} = VO_{2max} - VO_{2rest}$ *Step 2*: Multiply $VO_{2reserve}$ by the desired percentage $VO_{2fraction} = VO_{2reserve} \times$ target percentage *Step 3*: Calculate $VO_{2target}$ by adding VO_{2rest} to $VO_{2fraction}$ $VO_{2target} = VO_{2fraction} + VO_{2rest}$	*Step 1*: Estimate HR_{max}[b] $HR_{max} = 220 - age$[c] *Step 2*: Calculate $HR_{reserve}$ $HR_{reserve} = HR_{max} - HR_{rest}$ *Step 3*: Multiply $HR_{reserve}$ by the desired percentage $HR_{fraction} = HR_{reserve} \times$ target percentage *Step 4*: Calculate HR_{target} by adding HR_{rest} to $HR_{fraction}$ $HR_{target} = HR_{fraction} + HR_{rest}$
Example: You want a person with a VO_{2max} of 35 mL/kg/min to exercise at 65% $VO_{2reserve}$: *Step 1*: Calculate $VO_{2reserve}$ $VO_{2reserve} = 35.0 - 3.5 = 31.5$ mL/kg/min *Step 2*: Multiply $VO_{2reserve}$ by the desired percentage $VO_{2fraction} = 31.5 \times 0.65 = 20.5$ mL/kg/min *Step 3*: Calculate $VO_{2target}$ by adding VO_{2rest} to $VO_{2fraction}$ $VO_{2target} = 20.5 + 3.5 = 24.0$ mL/kg/min	**Example:** You want a 50-year-old person with a HR_{rest} of 70 bpm to exercise at 65% $HR_{reserve}$: *Step 1*: Estimate HR_{max}[b] $HR_{max} = 220 - 50 = 170$ bpm[c] *Step 2*: Calculate $HR_{reserve}$ $HR_{reserve} = 170 - 70 = 100$ bpm *Step 3*: Multiply $HR_{reserve}$ by the desired percentage $HR_{fraction} = 100 \times 0.65 = 65$ bpm *Step 4*: Calculate HR_{target} by adding HR_{rest} to $HR_{fraction}$ $HR_{target} = 65 + 70 = 135$ bpm

[a] MET values may be substituted for VO_2 (1 MET = 3.5 mL/kg/min).
[b] When possible, use HR_{max} from maximal graded exercise test instead of estimation.
[c] Alternatively, the formula "$HR_{max} = 206.9 - (0.67 \times age)$" may be used.

intensity will depend in part upon the duration and frequency of exercise. Nevertheless, larger improvements in VO_{2max} typically occur with higher intensities. However, higher volumes of exercise (to include intensity, duration, and frequency) are more likely to result in overtraining symptoms (e.g., fatigue, injury, decreased performance, suppressed immune function). Exercise training at 60%–80% $VO_{2reserve}$ generally results in improved VO_{2max}. Although intensities above this range may benefit certain athletic performances, they should be practiced sparingly.

As stated in this chapter's introduction, the Physical Activity Guidelines for Americans give recommendations for both moderate- and vigorous-intensity physical activity. In relative terms, *moderate-intensity* physical activity is defined as activity requiring 40%–60% of $VO_{2reserve}$ while *vigorous-intensity* physical activity is anything that requires above 60% $VO_{2reserve}$. While moderate-intensity physical activity may result in some fitness improvement for those starting at a low fitness level, the progressive overload necessary to elicit and maintain improvement lies in the vigorous-intensity range for many people, especially those who are younger and/or more fit.

If a person's VO_{2max} has been measured or estimated through exercise testing [7], exercise intensity may be prescribed as a given percentage of $VO_{2reserve}$. $VO_{2reserve}$ is calculated by subtracting the estimated value for VO_{2rest} (1 MET = 3.5 mL/kg/min) from VO_{2max}. $VO_{2reserve}$ is then multiplied by the target percentage and VO_{2rest} is then added back to the product to yield the target VO_2. An example of this procedure is presented in Table 16.3.

Knowing the MET ("metabolic equivalent") levels of various activities can be useful in prescribing physical activity after a target VO_2 range has been determined. One MET is an estimation of a person's energy expenditure when seated at rest (3.5 mL/kg/min). As an example, if a person performs an activity that requires six times the energy requirement of sitting at rest, that activity would carry a MET level of 6, requiring a VO_2 of approximately 21 mL/kg/min ($6 \times 3.5 = 21$). The Compendium of Physical Activities (http://sites.google.com/site/compendiumofphysicalactivities/) has been published to provide the MET requirements of more than 800 leisure-time and occupational activities [8]. Table 16.4 includes examples of MET levels for some more common activities. If a target MET range has been determined ($MET_{target} = VO_{2target}/3.5$), the Compendium can be used to identify activities of appropriate intensity.

Many professionals find it more practical to prescribe exercise intensity by heart rate rather than VO_2. Since heart rate and VO_2 have a linear relationship during graded exercise, a given percentage of heart rate reserve ($HR_{reserve}$) parallels the same percentage of $VO_{2reserve}$ and, therefore, may be used in its place. When available, it is preferable to use the maximal heart rate (HR_{max}) attained from a maximal graded exercise test. If a true HR_{max} is not available, an age-predicted value may be used. Just as with the $VO_{2reserve}$ method, HR_{rest} is subtracted from HR_{max} to obtain $HR_{reserve}$.

TABLE 16.4
Sample Metabolic Equivalent (MET) Levels of Common Physical Activities

Activity	METs	Activity	METs
Walking, 2 miles/h	2.8	Aerobic dancing	5.0–9.5
Walking, 3 miles/h	3.5	Golf, using power cart	3.5
Walking, 4 miles/h	5.0	Golf, walking, pulling/ carrying clubs	4.3–5.3
Running, 6 miles/h	9.8	Tennis	4.5–8.0
Running, 7.5 miles/h	11.5	Soccer	7.0–10.0
Running, 9 miles/h	12.8	Washing and waxing car	2.0
Bicycling, 5.5 miles/h	3.5	Most housecleaning activities	2.5–3.5
Bicycling, 9.4 miles/h	5.8	Gardening	2.3–5.8
Bicycling, 15 miles/h	10.0	Mowing lawn, riding mower	2.5
Swimming, sidestroke	7.0	Mowing lawn, walk, power mower	4.5–5.0
Swimming, crawl, ~50 yards/min	8.3	Mowing lawn, walk, hand mower	6.0
Swimming, crawl, ~75 yards/min	10.0	Shoveling dirt or snow	5.3–7.8

Source: Ainsworth, B.E. et al., *The Compendium of Physical Activities Tracking Guide*, Healthy Lifestyles Research Center, College of Nursing and Health Innovation, Arizona State University, Tempe, AZ, http://sites.google.com/site/compendiumofphysicalactivities/.

The target heart rate is then derived by multiplying $HR_{reserve}$ by the desired percentage and adding HR_{rest} to the product (Table 16.3).

The most common formula for estimating HR_{max} in adults is "HR_{max} = 220 − age." It is most accurate at the age of 40 years and over- and underestimates HR_{max} in younger and older people, respectively. A more accurate formula, "HR_{max} = 206.9 − (0.67 × age)," has recently been introduced [9]. While this formula is slightly more complicated, it may result in a more appropriate intensity prescription, particularly among the elderly. Regardless of the formula used, it is important to realize that HR_{max} has a standard deviation of 10–12 beats per minute (bpm) across the adult age span. This can obviously limit the value of using age-predicted HR_{max} in determining a target heart rate. As such, many professionals prescribe HR_{target} as a range of 10% $HR_{reserve}$ or so. A person's subjective feeling of effort should also be taken into account during exercise. On a scale of 0–10, where sitting is 0 and maximal effort is 10, moderate-intensity activity should yield a rating of 5 or 6 and vigorous-intensity activity of 7 or 8 [1]. Such ratings are particularly useful for people who have clinical conditions or take medications that affect the heart rate response to exercise.

Alternative to the $HR_{reserve}$ method, exercise intensity may be prescribed using a straight percentage of HR_{max} (65%–90% HR_{max} is approximately equivalent to 50%–85% $HR_{reserve}$). However, many professionals prefer the $HR_{reserve}$ method, as it is more individualized by taking HR_{rest} into account.

Time (Duration) of Exercise

For improvement in cardiorespiratory fitness, 20–60 min per session is recommended, with duration and intensity interacting with one another. For example, 20–30 min of exercise at a higher intensity can yield similar benefits to 50–60 min of exercise at a lower intensity. Similar health and fitness benefits are recognized regardless of whether exercise is performed continuously or intermittently throughout the day in bouts of 10 min or more.

Frequency of Exercise

Three to five days of exercise have traditionally been recommended for the improvement of cardiorespiratory fitness. While 6 or 7 days/week may be practiced to accumulate the moderate-intensity guidelines of 150–300 min/week, such a frequency of vigorous-intensity exercise will likely increase one's chance of injury while yielding few additional health or fitness benefits. Therefore, as with other exercise prescription parameters, exercise frequency should vary with goals. For example, daily or near-daily physical activity is advocated for weight loss or maintenance while "recovery days" of rest or lighter activity are usually necessary between more intense workouts.

Overall Exercise Volume

The 1996 Report of the Surgeon General recommended 1000 kcal as the minimum weekly energy expenditure necessary to accrue health benefits [2]. This recommendation is congruent with the 150 weekly minutes of moderate-intensity or 75 min of vigorous-intensity physical activity recommended in the Physical Activity Guidelines for Americans [1]. The concept of a dose–response relationship is more evident in the more recent recommendations, that is, a greater amount of physical activity will yield greater health and fitness benefits. Therefore, the Guidelines recognize that 300 weekly minutes of moderate-intensity physical activity is superior to 150 min for most people (and 150 weekly minutes of vigorous-intensity physical activity may be superior to 75 min). Further health benefits from physical activity quantities above those recommended in the Guidelines are not well documented. In addition, while greater fitness benefits may result from higher volumes of exercise, the risk of overtraining symptoms also increases.

On the other end of the continuum, some people may be deconditioned to the extent that they have difficulty in attaining the minimal physical activity recommendations. Such people should do as much physical activity as they can without undue fatigue, with the goal of progressing into the range recommended in the Guidelines, which state "For all individuals, some activity is better than none" [1].

Rate of Progression

Training volume can be increased through alteration of exercise frequency, intensity, and/or duration. Many professionals first choose to implement small changes in exercise duration (5–10 min per session), as they are usually well tolerated

and may be less likely to negatively affect exercise adherence. Depending upon a person's beginning exercise volume and his/her goals, frequency and/or intensity may then be increased. Although somewhat anecdotal, the "ten percent rule" is a good rule of thumb; exercise volume (usually quantified by distance or time) should not be increased by more than 10% per week. In addition, overtraining symptoms (e.g., upper respiratory infection, muscle/joint pain) should be recognized and a reduction of training volume and/or a change of exercise modality should be implemented.

Resistance Training

The Physical Activity Guidelines for Americans recommend that muscle-strengthening (resistance) activities that involve all major muscle groups be performed on two or more days per week [1]. Benefits of resistance training include maintenance or increases in bone mass, insulin sensitivity, and skeletal muscle mass, the latter being important for those attempting to lose weight. Maintenance or gain in strength can also be important in preserving physical function in the elderly and persons with certain disabilities.

Type of Resistance

Dynamic resistance exercises alternately overcome (*concentric* contractions) and accommodate (*eccentric* contractions) a given force. This force is often in the form of weights (either "free" weights or stacked weights on various machines), but can also exist in other forms, such as elastic bands or one's own body weight. The type of resistance to be used in training depends largely upon the goals of the participant and a combination of resistance modes is often employed. More "controlled" modes (e.g., weight machines, resistance bands) are generally safer and less likely to require a spotter, while less controlled modes (e.g., free weights) require more balance and tend to mimic real-life movement more. For the purposes of safety and effectiveness (i.e., specificity), proper technique (e.g., keeping back straight, controlling eccentric portion of exercise) should be stressed with any type of exercise. In addition, unless the development of isometric (static) strength is a specific training goal, resistance exercises should be dynamic, generally taking the involved joints through the fullest range of motion possible. This allows a greater number of motors units to be trained, creating more functional benefits.

Regardless of the mode(s) of resistance used, all major muscle groups should be exercised. At least 8–10 different exercises are generally required to target all of the major muscle groups. Accordingly, to encompass the entire body and lessen the chances of strength imbalances, opposing (antagonistic) muscles groups should be exercised. For example, if the abdominal muscles are focused upon in one exercise, another exercise should target the lower back muscles; both the biceps and triceps should be targeted in separate exercises, etc. For practical purposes, multi-joint exercises (e.g., bench press, squat) that simultaneously train more than one muscle group are preferred over single-joint exercises (e.g., triceps extension, leg extension) because they are more time efficient and tend to represent real-life movements more. However, single-joint exercises can still serve as useful adjuncts, particularly if they mimic a particular movement in a sport or other activity for which a person is training.

Amount of Resistance, Repetitions, and Sets

To achieve improvements in both muscular endurance and strength, completion of 8–12 repetitions of each exercise to a point of *fatigue* (not necessarily *failure*) is recommended. Lifting to fatigue infers that an additional repetition would be difficult to perform without help [1]. Performing 8–12 repetitions to fatigue generally requires a resistance of 60%–80% of a person's 1-repetition maximum (1RM; the maximum amount of weight that can be lifted in a single effort in that same exercise) [7]. Performing fewer than 8–12 repetitions to fatigue (which would employ a greater resistance) will result in more strength gain than gain in endurance, while performing more than 8–12 repetitions (requiring less resistance) will result in more improvement in muscular endurance.

The compilation of repetitions of an exercise performed at one time (e.g., 8–12) is termed a *set*. Multiple sets of an exercise may be performed with 2–3 min rest in between being recommended. For beginners, performing a single set of an exercise for 8–12 repetitions to fatigue on a regular basis will almost always result in strength gains. In time, additional sets will likely be necessary for further improvement [1]. ACSM recommends that —two to four sets be performed with each muscle group. However, more than one exercise may be employed for a given muscle group. For example both the bench press and dips involve the pectoralis and triceps muscles, but require different movement patterns. Therefore, completing a single set of both of these exercises would satisfy this recommendation for these muscle groups [7]. In short, the number of sets to be performed depends upon the goals of the participant. Health and functional benefits can be recognized with a minimum number of sets while athletes commonly exceed the number of sets recommended by health organizations.

Frequency of Training

To allow sufficient recovery, resistance training sessions should be spaced at least 48 h apart from one another [7]. Therefore, 2–3 days/week of resistance training is recommended. If time constraints do not permit all exercises to be performed in a given day, then the same muscle groups should not be exercised on consecutive days (e.g., train the upper body one day and the lower body the next).

Rate of Progression

As mentioned earlier, resistance training sets should be performed to fatigue in order for muscular fitness gains to be achieved. A person should increase the resistance of an exercise when he or she can perform one or two extra repetitions with good form. To remain in the desired repetition range (e.g., 8–12), increases of 2.5–5 lb are generally appropriate for smaller muscle groups and increases of 5–10 lb are generally appropriate for larger ones.

Even when the earlier criteria are followed, people training for larger gains in muscle size and strength often *plateau* or fail to experience continued improvement after many months. In this case, *periodization*, the frequent alteration of training intensity, repetitions, sets, and/or resistance mode, can be useful. While beyond the scope of this chapter, ACSM has published a position stand addressing this topic [10].

Flexibility Training

Maintenance of flexibility, the range of motion around a joint, can be important for the prevention of low back pain and for the maintenance of activities of daily living. While stretching might help prevent injury in activities where one's range of motion is taken to its limits (e.g., gymnastics), there is no conclusive evidence that stretching prevents injury in activities requiring less range of motion (e.g., jogging) or that it prevents muscle soreness [11,12].

Nevertheless, since flexibility decreases with aging, stretching is an important component of a well-rounded fitness program. Unless ballistic (bouncing) movement is part of an activity for which a person is training, static stretching, where a person holds a stretch for an extended period (15 s or more), is recommended. Stretching is more effective, and possibly safer, after a person has gone through a warm-up period. In fact, unless a person is getting ready to perform activities that challenge their range of motion, stretching is usually most effective at the end of an exercise session rather than at the beginning. If stretching before exercise, a person should still warm up first (see next section). ACSM recommends that stretching exercises be performed at least four repetitions per stretch for at least 15 s each on at least 2–3 days weekly [7].

Warm-Up and Cooldown

Both before (*warm-up*) and after (*cooldown*) the conditioning phase of an exercise session, at least 5–10 min of low-intensity physical activity should be performed. The increased blood flow and body temperature resulting from the warm-up period allows the muscle and connective tissue to become more pliable, reducing the chance of injury during vigorous activities. It also allows a more gradual cardiovascular adaptation to the stress of exercise, which is particularly important for people who are more likely to experience cardiac events. Similarly, a proper cooldown period helps prevent venous pooling in the lower extremities, thereby facilitating venous return to the heart and brain. Muscular endurance activities, such as abdominal exercises, and stretching may also be better performed during the cooldown phase.

Physical Activity Adherence

Specific strategies for enhancing physical activity participation are detailed elsewhere in this book. In general terms, the clinician should recognize that a good bit of flexibility exists in how a person can choose to meet physical activity guidelines (i.e., wide ranges exist in the components of FITT) and that physical activity may be practiced in a variety of settings (at home, outside, in a fitness facility, etc.). In addition, leisure-time physical activity may be practiced alone, with a partner, or in a group setting. Everyone should be encouraged to experiment with a variety of exercise regimens and to continue to practice the one(s) they enjoy the most.

Approximately 56% of American adults fail to meet current physical activity recommendations [13]. As patients are more likely to be physically active when such behavior is endorsed by their physicians, an initiative of Healthy People 2020 is to "increase the proportion of physician office visits that include counseling or education related to physical activity" [14]. However, most physicians have received little education on physical activity counseling as part of their medical training. Appropriately, in order to facilitate delivery of prudent physical activity information by health care providers, ACSM and the American Medical Association launched an educational website, Exercise is Medicine, in 2007 (http://exerciseismedicine.org) [15].

EXERCISE PRESCRIPTION FOR SPECIAL POPULATIONS

With rare exception, everyone should be physically active. However, physical limitations and safety issues sometimes necessitate that the "normal" exercise prescription described earlier be altered. As such, this next section discusses recommendations for children and older adults, pregnant women, and people with some of the more prevalent chronic diseases. This discussion is only introductory in nature; other sources dedicated to the subject of clinical exercise physiology are available and cover a wider variety of chronic conditions in greater detail [16–18]. Exercise prescription for individuals with cardiovascular disease (CVD) and obesity is detailed elsewhere in this book.

Children and Adolescents

Proper physical activity can help develop and maintain a healthy body weight and cardiometabolic risk profile, can reduce symptoms of anxiety and depression, and can instill positive habits that may carry over into adulthood. The Physical Activity Guidelines for Americans recommend that youth accumulate at least 60 min of moderate- and vigorous-intensity physical activity daily [1]. These 60 min should include a combination of aerobic activities (e.g., bicycling, dancing) and short bursts of activity (e.g., playing tag, soccer) as well as activities that promote muscular fitness (e.g., climbing trees or playground equipment) and bone health (impact activities such as running or jumping rope). The Guidelines can be met through structured sports, games, and exercise classes and/or unstructured play.

Adults can facilitate physical activity among youth by providing ample opportunity for participation. Two examples of how to do this are by limiting screen time (television, video games, and computers) and increasing the amount of

time dedicated to physical activity during the school day. Academic performance is not sacrificed when students are provided with opportunities for daily physical activity in school, such as daily recess, physical education classes, or implementation of physically active learning opportunities in other classes [19]. Many youth will choose to be active when given ample opportunity. However, some cohorts that tend to be less active (adolescent girls, obese) may benefit from structured exercise programs that include like peers and focus on a variety of activities that are popular within a given gender and age group (e.g., dance for adolescent girls).

Compared to adults, a couple of physiological differences in children are worth noting. First of all, children sweat less than adults and do not acclimatize to heat exposure as quickly. They also possess a delayed thirst response. Therefore, it is important to gradually expose children to exercise in warmer environments and to emphasize frequent fluid intake (every 15–20 min). Second, adult formulas for maximal heart rate do not apply to children and adolescents, who typically have maximal heart rates of approximately 200–205 bpm. For exercise prescription purposes, however, RPE scales tend to work well with older children (>8 years old) [20].

Older Adults

Among older adults, proper physical activity can increase and maintain physical function, improve and maintain body composition, promote psychological and cognitive well-being, and assist in primary and secondary prevention of chronic diseases. Keeping in mind that exercise intensity is relative (e.g., a given walking speed may be considered light for one person and vigorous for another), the physical activity guidelines are essentially the same for adults over the age of 65 years as they are for middle-aged and younger adults [1]. Frail persons, who may have difficulty meeting the guidelines, should practice as much physical activity as they can tolerate with the goal of safely advancing their physical activity into the range recommended for the general population.

In addition to the same endurance and resistance exercise advocated for the general population, older adults at risk for falling should add exercises 2–3 days/week that focus on balance. While a wide variety of such activities exist, the ones performed should focus on a person's particular needs. Examples include walking sideways and backward, repetitively standing and sitting, standing with eyes closed, tai chi, etc. Previously inactive seniors, in particular, may benefit from the services of a properly credentialed personal trainer or exercise class in the beginning stages of an exercise program.

Pregnancy and Postpartum

Proper physical activity during pregnancy may help prevent excessive weight gain, gestational diabetes, and pregnancy-induced hypertension. When proper precautions are followed, very little risk is associated with exercise. On average, women who exercise throughout pregnancy may deliver a few days earlier and have babies that are a few ounces lighter. However, there is no evidence that properly practiced exercise leads to preterm deliveries or low-birth-weight babies. Absolute (exercise under no circumstances) and relative (exercise only when benefits outweigh risks) contraindications and warning signs to terminate exercise as published by the American College of Obstetricians and Gynecologists (ACOG) are listed in Tables 16.5 and 16.6, respectively [21].

TABLE 16.5
Absolute and Relative Contraindications to Aerobic Exercise during Pregnancy

Absolute Contraindications

- Hemodynamically significant heart disease
- Restrictive lung disease
- Incompetent cervix/cerclage
- Multiple gestation at risk for premature labor
- Persistent second- or third-trimester bleeding
- Placenta previa after 26 week gestation
- Premature labor during the current pregnancy
- Ruptured membranes
- Preeclampsia/pregnancy-induced hypertension

Relative Contraindications

- Severe anemia
- Unevaluated maternal cardiac dysrhythmia
- Chronic bronchitis
- Poorly controlled type 1 diabetes
- Extreme morbid obesity
- Extreme underweight (BMI < 12)
- History of extremely sedentary lifestyle
- Intrauterine growth restriction in current pregnancy
- Poorly controlled hypertension
- Orthopedic limitations
- Poorly controlled seizure disorder
- Poorly controlled hyperthyroidism
- Heavy smoker

Source: Reprinted with permission from the American College of Obstetricians and Gynecologists, *Int. J. Gynecol. Obstet*., 77, 79, 2002.

TABLE 16.6
Warning Signs to Terminate Exercise while Pregnant

- Vaginal bleeding
- Dyspnea prior to exertion
- Dizziness
- Headache
- Chest pain
- Muscle weakness
- Calf pain or swelling (need to rule out thrombophlebitis)
- Preterm labor
- Decreased fetal movement
- Amniotic fluid leakage

Source: Reprinted with permission from the American College of Obstetricians and Gynecologists, *Int. J. Gynecol. Obstet*., 77, 79, 2002.

The Physical Activity Guidelines for Americans [1] recommend that previously inactive women progress to at least 150 weekly minutes of moderate-intensity physical activity. In addition, within reason and in consultation with their physician, women who are already practicing vigorous-intensity aerobic activity may continue to do so during pregnancy as long as no warning signs occur (e.g., vaginal spotting). Although vigorous-intensity physical activity is safe for most previously active women, fetal effects of severe hyperthermia or repeated bouts of hypoglycemia that may result from more prolonged or competitive exercise are unknown. Hence, competitive training during pregnancy requires more precaution and close physician supervision [21].

Due to potential decompression sickness, ACOG recommends that scuba diving not be practiced during pregnancy. In addition, women who plan to expose themselves to higher altitudes (>6000 ft) should be made aware of the signs of altitude sickness at which they should terminate exercise, descend from the altitude, and seek medical attention. Sports and other activities with the potential for contact or falling should be avoided, especially as the pregnancy progresses. Also, supine exercise can inhibit venous return and is contraindicated after the first trimester. Women at risk or with a history of preterm delivery should reduce their physical activity during the third trimester [21].

The American College of Sports Medicine advocates resistance training during pregnancy to a point of moderate fatigue [7]. Such training has been shown to reduce insulin requirements in women with gestational diabetes [22,23]. However, little research has been performed to determine the effects of more intense resistance exercise, particularly practicing of the Valsalva maneuver (holding one's breath during exertion) or prolonged or intense contractions involving the abdominal muscles. ACSM recommends avoidance of the Valsalva maneuver after the first trimester [7].

During the postpartum period, regularly practiced physical activity may reduce excessive weight gain and/or lessen depressive symptoms. In lactating mothers, moderate-intensity exercise does not significantly affect breast milk content or volume or their infants' weight gain [24]. In addition, a combined aerobic and resistance training program was shown to decrease bone mineral loss in lactating mothers [25].

Nearly all women without postpartum complications are able to resume leisure-time physical activity by 6 weeks following delivery, if not much sooner. However, earlier physical activity should begin at a low intensity and duration and should progress gradually, particularly in women who deliver via caesarian section.

Diabetes Mellitus

Both type 1 and type 2 diabetes mellitus are characterized by abnormally high blood glucose levels. Since physical activity facilitates glucose uptake by skeletal muscle, it can serve as an important mechanism of managing glucose concentration in either disease. In addition, through its effect on weight management, an adequate amount of physical activity (combined with a prudent diet) may assist in partial or, more rarely, full reversal of type 2 diabetes. Proper physical activity can also improve one's CVD risk profile. Exercise can also be an effective means of preventing diabetes onset in people with impaired glucose tolerance [26].

TABLE 16.7
Criteria for Electrocardiographic Stress Testing before Exercise Training Participation in Diabetes Patients

1. Age >40 years, with or without cardiovascular disease risk factors other than diabetes
2. Age >30 years and
   a. Type 1 or 2 diabetes of >10 years in duration
   b. Hypertension
   c. Cigarette Smoking
   d. Dyslipidemia
   e. Proliferative or preproliferative retinopathy
   f. Nephropathy including microalbuminuria
3. Any of the following, regardless of age
   a. Known or suspected coronary artery disease, cerebrovascular disease, and/or peripheral artery disease
   b. Autonomic neuropathy
   c. Advanced nephropathy with renal failure

Source: Reprinted with permission from Colberg, S.R. et al., *Med. Sci. Sports Exerc*., 42, 2282, 2010.

Since diabetics are at increased risk for CVD, they should undergo a physical examination before engaging in vigorous-intensity exercise. Recommended criteria for electrocardiographic stress testing before exercise training [27] are listed in Table 16.7. Although many type 1 and 2 diabetics participate independently in exercise and sports, it is recommended that novices begin training with a qualified exercise specialist, particularly when resistance training is involved, in order to avoid injury and blood glucose abnormalities that are more likely to occur in persons with diabetes [27].

Chronic hyperglycemia can lead to neural, retinal, and circulatory damage that can present special problems during and as a result of exercise in persons with more advanced diabetes. Silent ischemia may be present in persons with underlying CVD. In addition to having proper screening for CVD, such patients need to be aware of other warning signs of CVD (e.g., dizziness, unusual shortness of breath). In addition, advanced neuropathy may cause a diabetic patient to be oblivious to foot ulcerations, which are more common due to microcirculatory damage. Therefore, diabetic patients should always exercise with clean, dry socks and proper fitting footwear. In addition, they should check their feet daily for blisters and ulcerations. Non-weight-bearing exercises should be practiced in persons with foot injuries or open sores [27]. Thermoregulation can also be impaired in persons with advanced diabetes, so particular precaution (e.g., keeping extremities warm, proper hydration) should be practiced in cold and hot weather.

Due to the risk of intraocular hemorrhage, diabetic patients with retinopathies should be carefully screened before participating in exercise. High impact activities (including running)

and high-intensity activities are not recommended. In addition, although it can be very beneficial in helping manage blood glucose, higher intensity resistance training that causes straining on the participant's part is contraindicated due to high increases in blood pressure [27].

Maintenance of a proper blood glucose concentration is important during and following exercise. As long as they are feeling well, type 2 diabetics may exercise with elevated glucose levels (>300 mg/dL) [27]. However, type 1 diabetics should not exercise in this condition (or with glucose >250 mg/dL and presence of ketone bodies), as this represents insulin deficiency and exercise will likely exacerbate the hyperglycemia.

Hypoglycemia is a more common incident during and following exercise. As such, proper balance and timing of exercise, diet, and medication is important. Due to increased glucose uptake during exercise, insulin or insulin secretagogue doses may need to be decreased in both type 1 and 2 diabetes patients, particularly in the hours preceding exercise. Exercise should not be practiced during times of peak insulin uptake and insulin injections during the hours before exercise should not be in the vicinity of the exercising muscles. To avoid nocturnal hypoglycemia, it is best not to exercise within a few hours before bedtime. However, if this must be done, a carbohydrate snack should be ingested before going to sleep. In addition, carbohydrates (5–30 g) should be consumed following intense or prolonged exercise. Persons taking insulin or insulin secretagogue should consume a carbohydrate snack before participating in physical activity if their glucose level is <100 mg/dL [27]. Regardless of medication type, all diabetic patients should be aware of hypoglycemic symptoms (weakness, nervousness, etc.).

With some important alterations, the exercise prescription for persons with diabetes should be very similar to that for healthy adults. Overall volume of physical activity should be 150 min/week or greater, recognizing the importance of a dose–response relationship, especially as far as weight management is concerned. Although previous inactive persons should begin exercise at a moderate intensity, progression to mostly vigorous-intensity exercise may lead to a greater improvement in blood glucose concentration [28]. Since exercise-induced alterations in insulin sensitivity can begin to reverse within a few days on inactivity, it is recommended that no more than 2 days of inactivity be allowed between exercise bouts [27]. In fact, daily, or near-daily, physical activity of similar intensity and duration can be useful in maintaining a balance among the glycemic effects of physical activity, diet, and medications. Due to beneficial effects on insulin sensitivity, resistance training is recommended at least 2, and preferably 3, days/week in patients without retinopathies [27]. With both aerobic and resistance training, increases in exercise volume should occur gradually to avoid disruptions in glycemic control.

Finally, although cardiac reactivity to physical activity should be normal in most diabetics, autonomic neuropathy may result in a blunted heart rate response in some patients. Unless a maximal heart rate has been obtained through graded exercise testing, calculation of a target heart rate using an age-predicted maximum is inappropriate in patients with known or suspected neuropathy. Use of subjective feelings of exertion should be employed instead.

Cancer

Whether currently undergoing treatment or in remission, regular physical activity can yield both physiological and psychological benefits for most cancer patients. Physical activity can help reduce the decline of functional capacity during treatment. Even during palliative care, properly practiced physical activity may prolong independent function and can reduce depressive symptoms and generate a greater sense of control. During recovery, in addition to contributing to a faster and more complete restoration of physical function, proper physical activity can reduce the chances of the reoccurrence of certain cancers, particularly those of the breast and colon. Additionally, since some cancer treatments increase the likelihood of future CVD and diabetes, the practice of physical activity is important in the management of cardiometabolic risk.

Exercise prescription should vary based on the type and severity of cancer. Since the side effects of cancer treatments can in some cases be nearly as severe as the disease itself, the type and time course of treatment should be taken into account as well. Similarly, during recovery, a person's capacity to exercise will be affected by any tissue damage they encountered due to the cancer and treatments and how far they are into remission.

McNeely et al. have published a list of suggested contraindications to exercise testing and training that has been adopted by ACSM [7,29]. In summary, these contraindications include platelet counts <50,000, white blood cells <3000, hemoglobin <10 g/dL, fever >100°F (38°C), resting heart rate >100 or <50 bpm, resting systolic blood pressure >145 or <85 mm Hg, and resting diastolic blood pressure >95 mm Hg. Also included as contraindications are more severe subjective side effects of cancer and its treatments, including severe cachexia, bone/joint pain (particularly in spinal region), declines in functional status (strength, balance, etc.), gastrointestinal disorders (vomiting, diarrhea, severe nausea, etc.), and cardiovascular and pulmonary symptoms (chest pain, severe dyspnea, etc.). Exercise should also be avoided on the day of intravenous chemotherapy and within 24 h after treatment. A more complete list of these contraindications appears in the referenced sources [7,29].

Due to a wide variety of cancers and treatments, there are numerous potential precautions to take when prescribing exercise. In general terms, exercise prescription and progression needs to be highly individualized and should vary day-to-day as the patient deals with the side effects of their treatments and the disease itself. Fatigue will commonly persist for days, and often for weeks or more, following chemotherapy and radiation. Although exercise is generally good for bone health, bone of cancer patients may be more susceptible to fracture due to radiation therapy and/or cancer metastases.

As such, higher impact activities should be avoided during cancer treatment and, if desired, should be introduced very gradually during recovery. Due to the risk of contamination, bone-transplant patients and patients with low white blood cell counts should take care to exercise in a clean environment. Also, although water exercise can be very beneficial to some patients, it should be avoided in those with indwelling catheters or central lines and feeding tubes and for those receiving radiation. In addition, patients undergoing radiation therapy may develop severe skin irritations. Therefore, comfortable clothing should be worn and the skin should be kept dry and clean during and after exercise [7].

ACSM recommends that cancer patients perform aerobic physical activity at 3–5 days/week for 20–60 min. Although a moderate-intensity of 40%–60% $VO_{2reserve}$ or $HR_{reserve}$ is recommended, some patients will find this difficult and should adjust their intensity accordingly. One to three sets of 10–15 repetitions of resistance exercise at 40%–60% 1RM are recommended on two to three nonconsecutive days per week. Flexibility training, which can be particularly beneficial following some surgeries, is recommended 2–7 days/week. Four repetitions of 10–30 s are suggested [7]. With the exception of high-impact activities, a wide range of exercise types can be used to meet a patient's goals. In addition, some exercise modalities, such as tai chi, offer the opportunity to complete moderate-intensity exercise in a supportive group atmosphere.

Arthritis

Both osteoarthritis and rheumatoid arthritis result in pain with movement. This often sets up a vicious cycle in which a person moves less due to pain. In turn, stamina and neuromuscular conditioning decline, which can eventually result in a decreased ability to perform activities of daily living. As functional tolerance deteriorates and arthritic pain increases, physical activity levels will most likely decline further, making the individual less functionally tolerant and more susceptible to hypokinetic diseases. As such, a major objective of exercise in individuals with arthritis is to increase and preserve physical function. Although physical activity may acutely cause pain, chronically practiced physical activity can actually reduce joint pain and stiffness, resulting in a higher quality of life. Also, as arthritis is common in overweight and obese individuals, physical activity can also serve as a means of weight control and cardiometabolic disease risk factor management.

Exercise levels recommended for the general population also increase physical fitness and produce health benefits in persons with arthritis [7]. However, certain adaptations may make physical activity more tolerable and increase compliance. While adequate warm-up is important in all cases, it is particularly important with arthritis as the increased blood flow warms the joints and makes movement easier and less painful. Since many arthritic patients experience more stiffness and pain in the morning, exercise later in the day is often wise, especially after morning medications have had time to reach their peak effects. In addition, many patients find warm water (83°F–88°F, 28°C–31°C) exercise to be more comfortable than other environments. Out of the water, proper fitting shoes with adequate stability and cushioning may help prevent excessive knee, hip, and/or back pain. Custom-made orthotics may be beneficial for persons with biomechanical abnormalities.

To increase and maintain functional ranges of motion, flexibility exercises are particularly important for patients with arthritis. Although resistance training can increase strength and stability around affected joints, maximal isometric contractions, practiced at a few angles per joint, may be preferable to dynamic contractions in persons who experience higher levels of joint pain. As this becomes less painful, patients can then advance to dynamic exercise with lighter resistance, increasing the resistance as tolerated. With aerobic training, people with more pain and/or less functional tolerance may need to exercise intermittently in the beginning, but should be able to progress to more continuous activity.

Some pain during exercise is to be expected with arthritis. However, if joint pain persists more than 2 h following exercise, the volume of training should be reduced [7]. Pain makes physical activity less enjoyable and is likely to negatively affect exercise compliance. Therefore, patients should not be pushed to a point where they are less likely to continue to stay active.

Disabilities

Depending on the type and extent of disability, proper physical activity may improve physical fitness and functional abilities and may reduce a person's risk for cardiometabolic diseases. The range of disabilities (cerebral palsy, spinal cord injury, stroke, etc.) is too wide to permit a thorough discussion of exercise prescription for each in this chapter. However, a few points are important to remember across many conditions. For example, disabilities resulting in autonomic impairment will yield abnormal cardiovascular responses to exercise and impaired thermoregulation. Therefore, perceived exertion may be a better gauge of exercise intensity and special precaution should be taken to prevent hyper- or hypothermia. In addition, adaptions in equipment or clothing may be needed to help persons with particular disabilities perform common exercises. For example, persons with impaired gripping ability may benefit from Velcro gloves when performing resistance exercises or arm ergometry. Shorter bouts of physical activity spread throughout the day may be necessary for persons with very low physical tolerance.

When possible, persons with disabilities should perform the same physical activity recommended for more able-bodied adults [1]. When this is not possible, they should perform as much physical activity as they are able to accomplish without undue fatigue. Aerobic, resistance, and flexibility exercise should all be practiced. Even when exercise tolerance is very low, physical inactivity should be avoided to maintain as much functional independence as possible and to avoid hypokinetic diseases.

SUMMARY

Current physical activity guidelines advocate a well-balanced exercise program to include aerobic, resistance, and flexibility training. To allow for individual preferences and abilities, these guidelines allow a good bit of flexibility among frequency, intensity, and duration of physical activity, as long as a critical overall volume is met. Health and fitness-related benefits can also be obtained with a variety of exercise modalities. The chosen modalities should be safe for a given individual and should be enjoyable to enhance program adherence.

In addition, disease or disability should not inhibit anyone from being physically active. Individuals who are not able to meet the physical activity levels recommended for the general public should still strive to be as active as possible within the confines of any disease or disability. *Everyone* can benefit from physical activity.

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Part IV

Behavioral Psychology

Bess Marcus, PhD

17 Applying Psychological Theories to Promote Healthy Lifestyles

Sarah E. Linke, PhD, MPH and Dori Pekmezi, PhD

CONTENTS

Individual Level 223
Health Belief Model 223
Theory of Reasoned Action and Theory of Planned Behavior 224
Interpersonal Level 225
Social Cognitive Theory 225
Transtheoretical Model 226
Ecological Level 227
Socioecological Model 227
Summary 228
References 228

The application of psychological theories and models to health behavior change research, program development, and policy has soared in popularity over the past few decades. Desired outcomes are most likely achieved within the context of health behavior change programs that are based on an objective understanding of the target health behaviors and the variables that influence them; theories and models enable researchers and other program developers to organize these variables to achieve these outcomes [1]. Theories and models provide structures for identifying and examining problems, choosing or developing appropriate interventions, and assessing results. They fall within the parameters of the current emphasis on employing evidence-based interventions in the public health, behavioral medicine, and medicine fields [1].

Comprehensive lists and descriptions of theories and models that have been utilized to guide health behavior research have been described extensively elsewhere (refs). We focus here on a select few that have consistently received attention in the health behavior literature, including the following: Health Belief Model (HBM), Theory of Reasoned Action (TRA)/Planned Behavior (TBP), Social Cognitive Theory (SCT), Transtheoretical Model (TTM), and Socioecological Model (SEM). The main components and structures of these theories and models, along with examples of their use in the literature, are described in the sections later.

Many of these theories share some similar or even identical constructs, including the widely adopted concept of self-efficacy, which was coined by the famous psychologist Albert Bandura [2,3]. This construct refers to confidence in one's abilities to successfully perform a particular behavior (i.e., walk 1 mile) despite barriers such as bad weather or a busy schedule. Most incorporate static individual differences (e.g., demographic variables), dynamic individual differences (e.g., mood/affect), and interpersonal factors (e.g., social support), but the degree to which each of these variables is highlighted varies widely from one theory or model to another. Although similarities among the models and theories are clearly apparent, their differences set them apart from one another and make them more or less useful as frameworks through which to understand and/or modify different types of health behaviors. For example, some are more applicable to one-time or short-term health behaviors (e.g., HBM), while others are better suited for longer-term ones (e.g., TTM). An overarching characteristic that differentiates models and theories is their relative focus on the primary force(s) influencing behavior change. Thus, we organize the selected models and theories into three broader levels: individual, interpersonal, and ecological.

INDIVIDUAL LEVEL

Health Belief Model

The HBM [4–6], depicted in Figure 17.1, was initially developed in the 1950s in attempt to understand and explain why many individuals were not participating in preventive health services, even when they were offered at no cost. The HBM proposes that the likelihood that individuals will engage in any given health behavior largely depends on their *perceptions* of the following variables: severity of the illness(es) it helps prevent, their susceptibility to the illness(es), benefits of engaging in the behavior, and barriers to engaging in the behavior. According to the HBM, individuals are more likely to adopt the target health behavior if they believe the potential illness is serious, that they are highly susceptible to it, and that the benefits of engaging in the behavior outweigh

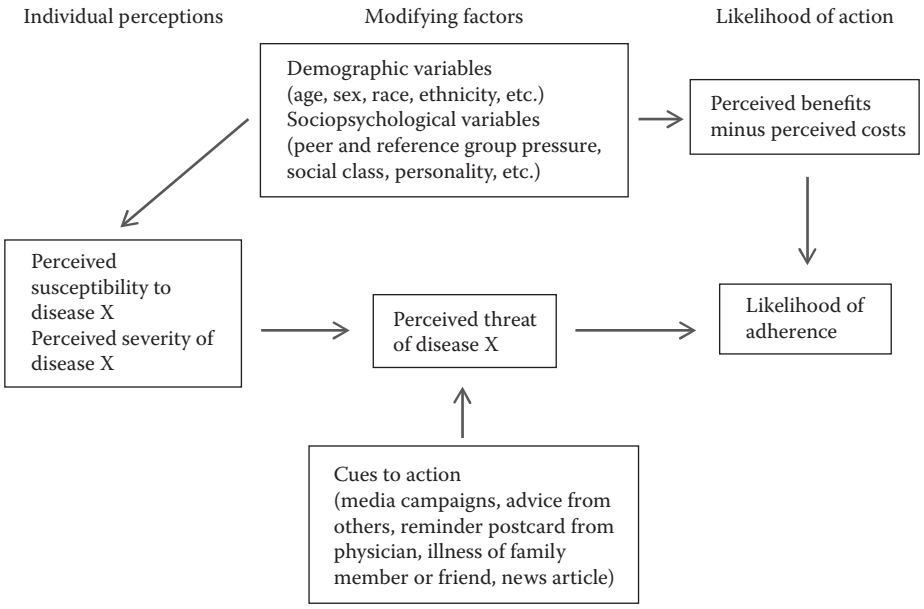


FIGURE 17.1 Health Belief Model.

the associated barriers. The construct "cues to action," which are factors that prompt action (e.g., media campaigns, physician reminders), was later added to the model to increase its explanatory power. Other factors, such as demographic characteristics (e.g., age, race, ethnicity, gender) and psychosocial variables (e.g., peer influence, mood/affect) also exert considerable influence over individuals' decisions to engage in a specific health behavior according to the HBM. Self-efficacy, described as behavior-specific self-confidence [2,3], was also later added to the HBM in attempt to increase its ability to accurately predict health behavior [7]. Self-efficacy was not initially included as an HBM construct because the model was primarily used to predict one-time or short-term health behaviors, such as getting a vaccination or health screening, for which self-efficacy is not particularly relevant. Nevertheless, these modified or extended versions of the HBM have been utilized in relatively recent research examining the model's ability to predict short-term behaviors such as breast self-examination among women with a family history of breast cancer [8] and HPV vaccination initiation among adolescent girls in high risk communities [9].

The HBM has since been applied to longer-term health behaviors and habits, such as exercise, smoking cessation, and dieting, with some success, but it has received significant criticism and has not held up to rigorous scientific examination in these contexts. Indeed, a recent meta-analysis of studies using HBM constructs to longitudinally predict health behavior concluded that utilizing the direct effects model may not be useful because the two primary constructs (perceived severity and perceived susceptibility) only weakly predicted behavior [10].

Although the HBM has been one of the most utilized models in health behavior research [11], many concerns about the model remain. For example, the relationships among the model's constructs are not clearly delineated; measurements of some HBM constructs are not standardized; and some of its constructs (especially "cues to action") are difficult to empirically test [10,12]. Furthermore, other models have exhibited stronger predictive ability of health behavior than the HBM [13]. Thus, although some HBM constructs may be helpful to consider in the prediction of health behavior, the model as a whole may not be particularly useful except in the context of single or short-term behaviors [10].

Theory of Reasoned Action and Theory of Planned Behavior

The TRA, developed by Ajzen and Fishbein [14,15], stems from premises of cognitive and social psychology. The TRA posits that individuals' likelihood of engaging in a particular health behavior can be predicted by the strength of their *intentions* to engage in that behavior. Intentions represent a combination of their own attitudes toward the behavior and their "subjective norms." According to the TRA, attitudes are formed by individuals' beliefs about the consequences of the health behavior and the weight they place on those consequences. Likewise, subjective norms are products of individuals' beliefs about others' expectations of them regarding the behavior and their motivation to comply with those expectations. The TRA is depicted in Figure 17.2.

Research examining the TRA has demonstrated that it is most useful at predicting behaviors under volitional control; however, most behaviors are not completely within an individual's control. Therefore, Ajzen [16] proposed an extension of the TRA called the TPB in attempt to better predict health behaviors. The TPB incorporates TRA constructs and adds a construct called perceived behavioral control, which is defined as individuals' perceptions of their ability to perform a given behavior [16]. The TPB's perceived behavioral control construct is similar to the concept of self-efficacy

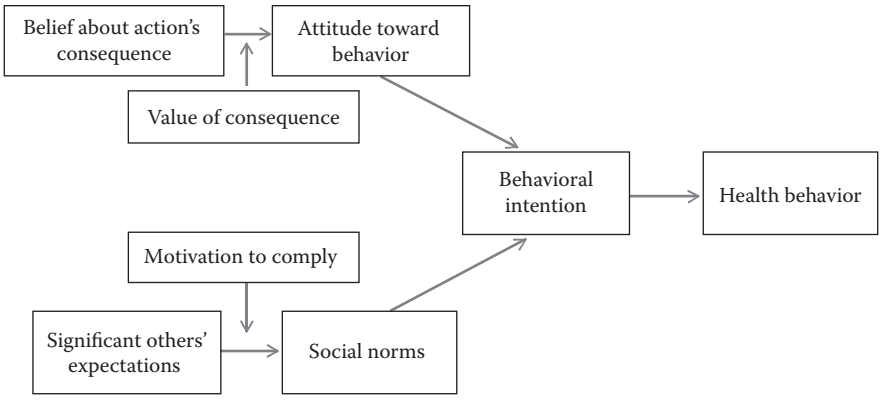


FIGURE 17.2 Theory of Reasoned Action.

[2,3] and defined in terms of control beliefs (the presence or absence of perceived facilitators and barriers associated with a given behavior) and perceived power (the impact of these facilitators and barriers).

Unlike the HBM, the TRA and TPB models clearly delineate the relationships between their individual constructs. As a result, research examining the predictive abilities of these models has generally supported each of them as a whole [13]. However, a major concern about the models is that they do not incorporate any constructs that allow for affective/emotional or psychosocial variability [17], which has also been a noted concern with the HBM [18]. Some have proposed extended version of the TPB to more thoroughly account for the components that are missing from the model, including past behavior, self-identity, and the additional social influence variables of group norms, family social support, friends' social support, and social provisions, without much greater success in the results [19]. Furthermore, the models do not take into account the fact that some behaviors are so habitual that they are not subject to planning or reasoning; in these cases, even the strongest of intentions are not likely powerful enough to overcome the automatic nature of well-established habits [17].

Although the TRA and TPB have received less attention in health behavior research than some of the newer models in recent years, they consistently rank among the most utilized theories in the field and demonstrate considerable predictive value [20]. The TRA and/or TPB have been used as guiding frameworks for assessing, understanding, and influencing behavior change in diverse populations with a variety of health behaviors, such as female condom use among Chinese sex workers [21], safer sex intentions and protected sex among heterosexual, HIV-negative methamphetamine users [22], family meal frequency among adolescents [23], fruit and vegetable consumption [24], and physical activity maintenance [25], among others.

INTERPERSONAL LEVEL

Social Cognitive Theory

SCT is one of the most robust health behavior change theories [26,27]. It evolved from Social Learning Theory [26,28], and originally focused on observational learning, or learning by watching others' behavior (also called modeling) and the reinforcements (both positive and negative, internal and external) that help determine whether or not one will repeat the behavior. Updated by Bandura and colleagues, SCT posits that behavior change is influenced by internal individual factors (e.g., cognitive, affective, biological) as well as the social and physical environment. The model is reciprocal in that each of these factors affects the others in a continuous, dynamic feedback loop (Figure 17.3) [26].

Self-efficacy is the main construct of SCT [29] and, as mentioned previously in this chapter, a powerful predictor of behavior change that has been incorporated into numerous social and behavior science theories [26,27]. Self-efficacy beliefs have been strongly associated with actual performance of a diverse range of health behaviors [30,31]. According to Bandura, self-efficacy can be increased through mastery experiences, social modeling, improving physical and emotional states, and verbal persuasion [27]. Mastery experience is gained through succeeding in attainable, yet increasingly challenging health behavior change goals and is considered to have the strongest influence on self-efficacy beliefs [26,27,32]. Modeling, as previously discussed, can be

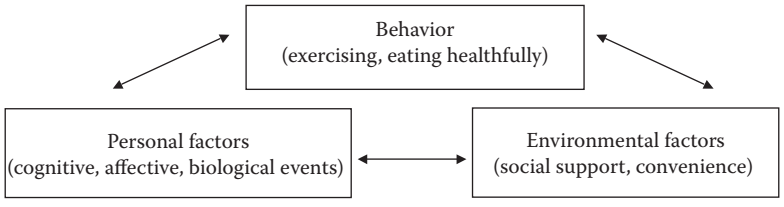


FIGURE 17.3 Reciprocal determinism.

accomplished by watching others perform the desired behavior; it is especially effective when relatable peer(s) perform the behavior. Finally, maintaining an optimal level of physiological intensity (i.e., excited but not too anxious) for performing the behavior, which can be accomplished by using relaxation techniques and positive self-talk as well as receiving encouragement from others, can increase self-efficacy [26,27,32].

Self-regulation strategies are also used to enhance confidence for behavior change and typically begin with self-monitoring, or systematically observing, one's current health behaviors [27]. Data are collected with pedometers, food diaries, smoking logs, or other tools, depending on the health behavior(s) being targeted. These objective data can then be reviewed to determine how specific health behaviors might be improved and to identify incremental and long-term behavior change goals. Overlapping to a degree with the concept of mastery experience, self-regulation can also include establishing rewards for meeting behavior change goals and enlisting social support from family and friends for performing target behaviors [27].

Another important determinant of behavior according to the SCT is outcome expectancies [26]. This construct, defined as the influence that the outcomes anticipated from a health behavior exert on one's willingness to perform this behavior, makes intuitive sense and has been supported in numerous research studies [33]. SCT posits that a health behavior is more likely to be performed if positive outcome expectancies are present, whereas negative outcome expectancies reduce the likelihood of the health behavior. For example, individuals will be much more inclined to run a mile if they anticipate that doing so will energize them rather than cause them to feel sore. The relative value of the anticipated outcome also plays an important role in this decision-making process. For example, an individual may view a positive anticipated outcome of smoking a cigarette (feeling more relaxed) as less important than a negative anticipated outcome (smelling like smoke) and thus decide accordingly to forgo the cigarette.

SCT offers a comprehensive model of the behavior change process. Some critics suggest that this model is overly broad and has not been tested as a whole in the way other theories are routinely examined [27]. Rather, studies have shown that specific SCT concepts (e.g., self-efficacy) are associated with behaviors, but such research does not confirm the entire theory. Nevertheless, the SCT provides a strong foundation for health promotion research and practice, using numerous strategies to address diverse public health issues. Furthermore, SCT has been successfully applied to a variety of health behaviors (e.g., cardiovascular disease [34–38], cancer screening [39], tobacco use [40–43], alcohol use [28,44–46], diet [47,48], obesity [49], physical activity [33,47,48,50,51], diabetes prevention [52], condom use [53,54]) in a wide range of ages (including children [48], teens [45], and elderly [51]) and underserved populations (e.g., African Americans [41], Latinas [49,52], low-income individuals [48,49]), and in several different countries (mostly in the United States, but also in China [53], Sweden [48], and Australia [51]).

Transtheoretical Model

The TTM is an integrative model of behavior change developed from many different psychological theories, such as SCT [55] and Learning Theory [28,56]. Prochaska and colleagues first described this model after noting that people vary in terms of motivational readiness to quit smoking [57] and move through specific stages of motivational readiness along the path to behavior change [58]. The five stages of change that form the core of the TTM are

- Precontemplation, in which change is not being considered
- Contemplation, in which change is being considered
- Preparation, in which an individual takes small steps toward change
- Action, in which the health habit has been recently adopted
- Maintenance, in which the change has been sustained for ≥6 months

This model is considered cyclical, accounting for people's tendency to move back and forth through these stages of change. Individuals may lose resolve and abandon new behavior patterns, feel guilty, lose confidence, and revert to their previous routines, with probable recycling through the earlier stages of precontemplation or contemplation. Thus, numerous cycles through the stages often happen before an adopted health behavior becomes a habit [59,60].

The cognitive and behavioral strategies and techniques that people use to advance through these stages of change are described as processes of change (see Table 17.1). The TTM posits that people use different processes of change at different stages in the change process and are likely to benefit from interventions developed specifically for their level of motivational readiness and most relevant to their current information needs [26,60]. For example, to help move individuals from precontemplation to contemplation, processes such as consciousness raising and dramatic relief should be attempted, whereas people in the action stage are more likely to find contingency management, counterconditioning, and stimulus control helpful [59].

TABLE 17.1
Pros (Advantages) and Cons (Disadvantages) of a Health-Related Behavior: The Example of Exercise

Pros

- I would be healthier if I exercised more regularly.
- I would feel better about myself if I exercised more regularly.
- Other people would respect me more if I exercised more regularly.

Cons

- I would probably be sore and uncomfortable if I exercised more regularly.
- If I exercised more regularly, my family and friends would get to spend less time with me.
- I would feel that I was wasting my time if I exercised more regularly.

TABLE 17.2
Processes of Change within the Transtheoretical Model

Process	Definition
Consciousness raising	Increasing information about self and problem
Self-reevaluation	Assessing how one feels and thinks about oneself with respect to a problem
Self-liberation	Choosing and commitment to act or belief in ability to change
Counterconditioning	Substituting alternatives for problem behaviors
Stimulus control	Avoiding or countering stimuli that elicit problem behaviors
Reinforcement management	Rewarding oneself or being rewarded by others for making changes
Helping relationships	Being open and trusting about problems with someone who cares
Dramatic relief	Experiencing and expressing feelings about one's problems and solutions
Environmental reevaluation	Assessing how one's problem affects physical environment
Social liberation	Increasing alternatives for nonproblem behaviors available in society

Theoretical constructs, such as self-efficacy and decisional balance, also play important roles in the adoption and maintenance of health behaviors according to the TTM [26,59,60]. The decisional balance construct comes from Janis and Mann's Decision-Making Theory [61] and involves weighing the perceived advantages and disadvantages of behavior change when deciding whether to adopt a new health behavior. Table 17.2 lists examples of perceived benefits (the "pros") and perceived costs (the "cons") of physical activity. A standardized "decisional balance" score may be derived by subtracting total standardized cons scores from total standardized pros scores [62]. Decisional balance has been shown to vary as a function of stage [58,62,63]. Early stages (precontemplation and contemplation) are associated with higher ratings of disadvantages (cons) and lower ratings of advantages (pros) of change, whereas later stages (action and maintenance) are associated with lower ratings of disadvantages (cons) and higher ratings of advantages (pros) of change [59].

Although the TTM originated in the addictions research field, it has since been applied to numerous health behaviors (e.g., fruit and vegetable consumption [64], weight control [65], condom and oral contraceptive use [66,67], sunscreen use [68], medical compliance [69], cervical cancer and mammography screening [70,71], stress management [72], intimate partner violence [73,74], and exercise [75,76]), in diverse populations (e.g., college students [77], African American adolescents [64], and patients with severe mental illness [78], tuberculosis [79], HIV [80], and multiple sclerosis [69]), and in many countries (e.g., Taiwan [71], Nepal [80], Malaysia [79]).

However, several criticisms of this model have been raised [81,82]. For example, the complexity of health behaviors is an issue when considering stage-based behavior change theories. Staging algorithms typically ask about physical activity or diet in general, but motivational readiness for change may vary for subcategories not fully captured by these algorithms (e.g., interested in walking and vegetable consumption but not strength training or reducing fat intake). The TTM also focuses on stage progression as a significant outcome but this is not always associated with actual behavior change [83,84]. Nevertheless, the TTM has been a highly influential theoretical framework comprised of a number of useful organizing constructs that have been shown to be meaningfully related in empirical data and psychometric studies.

ECOLOGICAL LEVEL

Socioecological Model

In more recent years, psychological theories and models have increasingly incorporated the broader contexts that affect health behaviors, recognizing that these external factors are often as influential as internal factors [85–87]. Social ecological models are based on four fundamental principles that are critical to understanding their application to health behavior change [88–90]: (1) the environmental and personal factors that influence health behavior dynamically interact with each other; (2) environments are multidimensional and complex; (3) people are multidimensional and complex, and intervention designs should consider both the individual and the groups with which the individual is affiliated; and (4) people–environment interactions exert multiple levels of influence, such that individuals often modify their settings, and social features of settings influence individuals. The social ecological framework suggests that both person-focused and environment-focused strategies can be applied to health behavior change [89]. For example, person-focused strategies may include preventive screening programs, individual counseling, or participation in lifestyle interventions. Environmental strategies include both geographic (e.g., mixed use communities) and sociocultural (e.g., integrating target health behaviors into organizational structures/cultures) aspects.

The SEM has recently grown tremendously in popularity, particularly in the public health realm. The SEM differs from more traditional psychological models in that it explicitly incorporates not only the individual's immediate external influences (e.g., interpersonal relationships) but also more peripheral factors (e.g., community, environment). Furthermore, rather than predicting a specific order or direction in which influences exert themselves, the SEM depicts the individual in the center of increasingly broader circles of influence, which interact with one another in an ongoing process (see Figure 17.4).

The SEM has been applied in assessment and intervention research on a variety of health behaviors and/or in diverse populations, including fruit and vegetable consumption among low-income African Americans [91], church-based health promotion interventions [92], physical activity

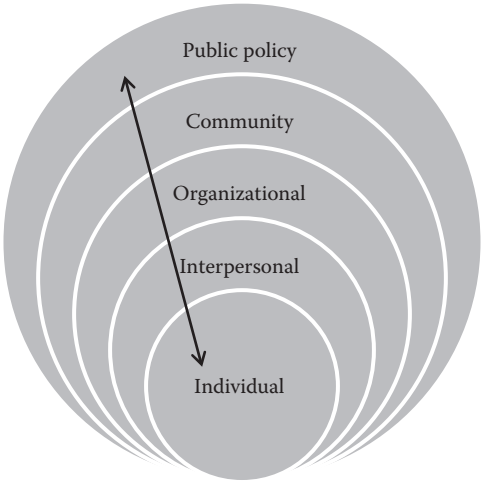


FIGURE 17.4 Socioecological Model.

promotion and fruit and vegetable intake [93], and physical activity assessment within a variety of different populations [94–96], among others.

As with all of the aforementioned models and theories, some challenges arise in the application of the SEM to health behavior change interventions. Because the model is exceptionally comprehensive, its application is inherently complex. For example, addressing the SEM's multiple levels of influence, including regional (e.g., neighborhoods), structural (e.g., the physical environment), and institutional (e.g., government, worksite, family) factors, on health behaviors is challenging due in large part to limitations on control over these external variables. In addition, additional research is required to help determine which of the model's multiple components are critical in the behavior change process. Despite its complexity, the SEM appears to be a promising model for an increasingly multidisciplinary scientific community.

SUMMARY

In this chapter, we summarized only a few of the numerous psychological models and theories that guide health behavior change interventions. We chose to focus on some of the most frequently utilized models and theories in the literature as well as to represent the range of general categories by which they are organized (i.e., individual, interpersonal, ecological). Over the past few decades, the fields of behavioral medicine, public health, and medicine (among others) have been gradually shifting from a sole focus on the individual to a progressively greater focus on the local and, to a growing extent, global environment in which the individual resides [1,88]. Although this shift recognizes and better accounts for the increasingly globalized world that undoubtedly influences individuals' behavior more than ever before, these new ecological models and theories are quite complex and somewhat generic [88–90]. Their numerous and relatively broadly defined variables are often difficult to measure, rendering these models as a whole difficult to assess. However, they relieve individuals of at least some of the overwhelming amount of personal responsibility placed on them by the individual and, to a somewhat lesser but still significant extent, interpersonal models and theories, which explicitly or implicitly assert that individuals should engage in target health behaviors regardless of the external barriers they may face. Moreover, the health problems and challenges for which health behavior change interventions are designed have also shifted from primarily acute and/or short-term illnesses (e.g., deadly viruses and infections) to predominantly chronic diseases (e.g., cardiovascular disease and diabetes). As mentioned previously, one-time or short-term problems appear to be adequately addressed by the individual-focused theories and models, whereas interventions for longer-term problems are more appropriately designed using interpersonal (and presumably ecological) ones.

Many other theories not included in this chapter also incorporate key concepts that help explain and predict health behaviors. Perhaps the two biggest challenges facing the various disciplines involved in health behavior change research are (1) to match specific goal health behaviors with the models and theories that incorporate the most relevant and appropriate constructs in order to design and implement effective interventions and (2) to systematically incorporate and account for the wide range of ecological factors that clearly influence health behavior to an increasingly greater extent in the modern, global world.

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18 Cognitive and Behavioral Approaches to Enhancing Exercise Participation

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CONTENTS

Overview of Empirically Supported Behavioral and Cognitive Interventions for Promoting Physical Activity 234
Extending Work on Behavioral Approaches to Physical Activity Promotion 234
Expanding Self-Monitoring to Include Imagery and Motivation 234
Including Sedentary Behavior as an Intervention Target 234
New Approaches to Enhancing Behavioral Assessment and Intervention 235
Using Emerging Technology to Enhance Self-Monitoring 235
Coupling Behavioral and Cognitive Interventions with Technology Using Ecological Momentary Assessment 236
Advances in Physical Activity Interventions through Varied Channels of Communication 236
Phone- and Print-Based Interventions 236
Peer Support Telephone Calls 236
Computer- and Web-Based Interventions 237
Advances in Channels of Activity Intervention and Implications for Promotion of Community-Wide Physical Activity 237
Community-Wide Physical Activity and the Role of Built Environment 238
Physical Activity Interventions in Racial/Ethnic Underserved Samples 239
Translating Behavioral and Cognitive Approaches into Real-World Interventions to Promote Physical Activity Intervention Outreach 240
Maintenance of Physical Activity Following Intervention 241
Advancing Understanding of Activity Maintenance by Examining Exercise Lapse 241
Conclusion 241
References 242

Physical activity research has led to many developments in the understanding of the benefits of activity in prevention, risk reduction, and improvements in health. By the end of the twentieth century, progress had been made in understanding correlates of regular activity; numerous randomized clinical trials (RCTs) had compared theoretically based interventions, particularly those based on cognitive and behavioral approaches with control conditions; and programmatic and lifestyle-based activity had been integrated into public health guidelines. Despite this compelling evidence for the benefits of physical activity and progress in research approaches, physical activity levels typically remained low in most population subgroups [1,2].

Over the past decade, much work has been done to extend the understanding of optimal approaches to physical activity promotion. Numerous reviews [3–6], meta-analyses [7,8], and well-controlled individual studies have enhanced understanding of intervention components that appear to be consistently effective in promoting physical activity participation. Since the publication of the previous version of this chapter, nearly 40 reviews and multiple meta-analyses related to exercise interventions have been published. Randomized trials have been extended to clinical populations and real-world community settings.

In this chapter, we will provide an overview of the findings reflected in these reviews and seminal studies. The aim of this chapter is to describe the domains of exercise intervention that have emerged in the past 10 years and describe their translation in real-world settings. When conclusions may be reached from the existing literature, we will highlight for whom the approaches work and in what circumstances. Novel and emerging approaches will also be described, including the use of technology, expanding approaches to conceptualizing physical activity evaluation, dissemination of interventions by peer leaders, and recent applications of newer frameworks to enhance outreach. Our purpose is to illustrate the intervention approaches that have had demonstrated efficacy in promoting exercise and physical activity in clinical and health-promoting settings and summarize the conclusions of key quantitative and qualitative reviews. We focus on interventions that are based on scientific studies of behavior and cognition. These interventions emphasize the manipulation of observable environmental and person characteristics, but they also include internal states and

cognitions that, although not directly measureable, can be inferred from observations and self-reported by individuals. We do not attempt to provide another critical review of the literature, since timely reviews are already available for the interested reader.

OVERVIEW OF EMPIRICALLY SUPPORTED BEHAVIORAL AND COGNITIVE INTERVENTIONS FOR PROMOTING PHYSICAL ACTIVITY

A 2011 systematic review was conducted of existing reviews of intervention components associated with increased effectiveness in diet and physical activity interventions [5]. Of several thousand articles identified, 30 met the stringent criteria for detailed review. In this review, outcome measures included weight, weight loss, and diet in addition to physical activity. Evidence grades were assigned to each reported analysis, using the Scottish Intercollegiate Guidelines Network (SIGN) system to take methodological quality into account. The physical activity outcomes examined were quantified changes, as measured by objective means such as accelerometer or by self-report or by changes in cardiorespiratory fitness. Consistent with previous reviews [2] and with behavioral theory [9], *self-monitoring*, *specific goal setting*, *feedback on performance*, and *goal review* were found to be associated with greater intervention effectiveness. *Prompting* practice of activity and *individual tailoring* via provision of information or counseling on intervention content were supported as specific intervention behavior change techniques resulting in increased activity.

An additional recent review of physical activity interventions [7] utilized meta-analysis with a focus on activity outcomes in healthy adults. This review was unique because it was not limited to randomized trials and thereby avoided publication bias (some limitations of this approach are evident in our later discussion). Thus, this meta-analysis included diverse interventions, ranging from group education focused sessions to supervised activity sessions, and inclusion of a variety of experimental designs and both published and nonpublished studies. Notably, nearly 100,000 activity intervention study participants' data were examined. The vast majority of participants were middle-aged (median of the mean age was 44 years), were predominantly women (74%), and were rarely ethnic minority (14% among studies that reported this information). The inclusive nature of this review highlighted the wide array of intervention approaches being undertaken—interventions ranged from very brief (a single motivational contact) to intensive supervised activity sessions spanning many weeks. Examination of effect sizes generally supported the conclusions of the previously described review [5], that is, behavioral strategies such as *goal setting*, *contracting*, *self-monitoring*, and *using cues or rewards* were effective in increasing physical activity. Contrary to other study summaries, the review concluded that use of the Social Cognitive Theory [10,11] and Transtheoretical Model [12] and cognitive strategies were ineffective in promoting activity. However, it should be noted that the authors' approach to grouping cognitive interventions probably differed from the cognitive approaches subsumed under this category by including basic health education and provision of information. Health education did not increase effect size. *Face-to-face delivery* of interventions had better effect size than did *mail and phone delivery*. The presence of *supervised exercise* in the intervention was associated with better physical activity outcomes in dichotomous moderator analyses, but this finding was not supported in supplemental analyses that examined multiple moderators. Interventions delivered by *dedicated project staff* (vs. *train-the-trainer* models), *modeling of the activity* by research staff, and *standardized interventions* (vs. individually tailored interventions) were also supported.

EXTENDING WORK ON BEHAVIORAL APPROACHES TO PHYSICAL ACTIVITY PROMOTION

Expanding Self-Monitoring to Include Imagery and Motivation

Studies have consistently documented the important role that goal setting and self-monitoring can play in physical activity interventions. A challenge to current studies utilizing this and related behavioral strategies is to learn how to further optimize the process of self-regulation in order to maximize intervention approaches. A recent study provides an example of using theory to create novel monitoring intervention approaches. Using self-regulation theory as a guide, Chan and Cameron used mental imagery related to physical activity to promote physical activity goal-directed behaviors in 182 sedentary adults [13]. In this RCT, participants received training in one of two types of activity-related imagery or neutral imagery over a 4 week period and were assigned daily practice. The physical activity imagery consisted of approach imagery (attainment of desired goal states) or process imagery (steps for enacting behavior). Approach imagery was associated with increased approach motivations for physical activity at Week 4 as well as greater intentions for activity and more action planning and facilitated more physical activity at Week 4 via action planning. These findings offer promise for novel low-cost approaches to enhancing self-monitoring and goal setting.

Including Sedentary Behavior as an Intervention Target

An additional behavioral approach to physical activity intervention that has emerged is a focus on reduction of sedentary behavior as a target outcome. Time watching television (TV), time sitting in cars, and general sitting have all been found to be associated with premature mortality and compromised metabolic function, even in physically active

adults [14]. It has been recommended that interventions target breaking-up periods of sedentary time in order to reduce health risks [14]. An intervention study aimed at reducing sedentary time was conducted with older adults since this age group has the highest level of sedentary behaviors and exhibited associations between overall sitting and television time and metabolic syndrome in previous research [15]. Participants were 59 men and women age 60 years and older, who reported watching TV for at least 2 h/day, were not currently employed for pay, and were ambulatory. A pre/post-experimental design was used. The intervention had a key message to stand up and move after 30 min of uninterrupted sitting. Intervention approaches included aspects of Behavioral and Social Cognitive Theory [10,11] (goal setting to reduce sedentary time and increase the number of breaks in prolonged sedentary time, self-monitoring of sedentary time and goals, enhancing self-efficacy and outcome expectancies, formulation of a behaviorally specific action plan, rewards for behavior change) as well as identifying alternative preferred nonsedentary activities. Participants used an activity workbook and sedentary time was assessed with accelerometers and sedentary time feedback provided along with comparison to a normative sample of similar age and gender. Results indicated that reach was 87.5% of those screened and met inclusion criteria. Participants reported high satisfaction with the intervention on a single-item rating. Findings highlight the feasibility of this brief approach and the compatibility of integrating behavioral and cognitive strategies into interventions targeting sedentary behavior.

NEW APPROACHES TO ENHANCING BEHAVIORAL ASSESSMENT AND INTERVENTION

Using Emerging Technology to Enhance Self-Monitoring

Self-monitoring theory has developed alongside various techniques to facilitate its implementation in physical activity assessment and intervention. The traditional use of activity self-management techniques such as activity session diary keeping has given way to electronic monitors. Pedometers, accelerometers, and handheld (palmtop) computers have been widely used to assess physical activity levels in research and clinical interventions, often to assess the feasibility of the now-heuristic recommended exercise dose of 10,000 steps/day. A review by Choi et al. noted that it is often difficult to accrue this level of activity with routine daily activity and that pre-intervention deficits of approximately 4000 steps/day (typical range of 3000–6000) are observed [16]. The systematic review of existing literature reviews of intervention components referenced earlier [5] noted three reviews that examined activity interventions that incorporated pedometers. Causal evidence supported their role in increasing walking. Reviews indicated that the median weeks of study were 11, with an average increase of 2004 steps/day and median walk time increase of 54 min/week. It is noted in this systematic review that most of the interventions reviewed in meta-analysis articles also included goals related to steps and/or diaries in addition to pedometers, highlighting the self-monitoring aspect of pedometer use. A meta-analysis by Bohannon reaffirmed the utility of pedometer-based physical activity assessment, citing the immediate feedback for exercisers and readily available normative values as primary benefits [17]. Bennett et al. sought to explore the feasibility of pedometer use in a randomized controlled trial of a multiethnic sample of adults residing in public housing [18]. Participants were 433 black, Hispanic, predominantly female participants of low socioeconomic status. The study demonstrated the utility of pedometer-based methodology among lower income population-based samples. Findings were consistent with other pedometer-assessed activity levels in community samples and indicated a largely sedentary lifestyle of an average of 5300 steps/day. Studies using this approach to assessment of activity have been primarily restricted to walking and lifestyle behavior. Findings suggest that pedometers may play a role in enhancing monitoring and may also be a convenient approach that may circumvent difficulties inherent in reliance on self-reported physical activity information.

While the past decade has seen an increase in the use of activity pedometers and their efficacy has largely been supported, this methodology has limitations—most importantly, the inability to measure intensity or duration in an account of accumulated physical activity [18]. Accelerometry offers the benefits of accounting for amount, frequency, and duration of physical activity, along with estimates of energy expense and exercise schedule. This may be used to enhance exercise participation, if integrated into the interventionist's approach in a way that resembles pedometer use. However, a review by Murphy notes that the approximations made by accelerometers do not account for various walking conditions and placement [19]. In addition, the data produced by accelerometers can take more time to analyze and relay to the exerciser than that produced by pedometers. Other methodologies circumvent these limitations by coupling self-report techniques with handheld computer technologies (often called palmtop computers, or personal digital assistants). A small randomized controlled trial by King et al. demonstrated the efficacy of this technique in an 8 week intervention in which 19 participants were provided with digital physical activity monitors, as well as palmtop delivered personalized feedback, goal setting, and support [20]. Compared with 18 control participants who received written support and educational materials, the intervention participants reported significantly greater calorie expenditure and moderate to vigorous physical activity. The benefits of accelerometers and palmtop computers must be examined within the context of their comparatively high cost. Both accelerometers and pedometers may be used to enhance both assessment and intervention. Pedometer usage is feasible, particularly with population-based work; accelerometers offer detailed feedback for participants across multiple activity domains.

Coupling Behavioral and Cognitive Interventions with Technology Using Ecological Momentary Assessment

As clinicians and researchers strive to obtain a comprehensive understanding of physical activity behavior change, integrative approaches offer benefits as they span multiple methodologies. Recent strides in this approach have been made with Ecological Momentary Assessment or EMA (often referred to within clinical contexts as Ecological Momentary Intervention). The diverse techniques of EMA include diary keeping, self-monitoring systems, physiological monitoring, and behavioral observation—all within the context of the exerciser's environment. These methods can be integrated with unstructured clinical visits or with more regimented exercise prescriptions. A review by Heron and Smyth examined 27 studies that utilized the EMA framework [21]. In the small RCT by King et al., previously described [20], those participants who were provided with instructions and used a palmtop computer to facilitate activity monitoring twice a day and were provided personalized feedback and support had higher levels of physical activity and pedometer-based steps than did the control group, which received written materials.

While this study is indicative of EMA usage with limited clinician involvement, Heron and Smyth note that several of the examined weight loss intervention trials demonstrated similar efficacy and outcomes to cognitive behavior therapy treatments, and suggest that coupling behavioral and cognitive interventions with EMA has the potential to enhance positive outcomes. Another study by Pellegrini et al. separated 51 participants into three conditions: standard behavioral weight loss, a standard behavioral weight loss plus technology-based system, and technology-based system only [22]. Those in the technology-based conditions received an energy-monitoring armband and accelerometer, access to a tailored physical activity website, and telephone information sessions. When paired with standard behavioral weight loss treatment consisting of in-person sessions and paper diaries, the technology-based approach yielded significant improvements in self-reported physical activity, cardiorespiratory fitness, and body fat percentage. The statistical increase in physical activity present in this study is higher than other studies incorporating Internet-based programs within a similar methodology.

ADVANCES IN PHYSICAL ACTIVITY INTERVENTIONS THROUGH VARIED CHANNELS OF COMMUNICATION

Another additional aspect of physical activity intervention that has been evaluated in the past decade is the communication channel through which the intervention has been delivered. In order to avoid the outreach limitations and costs associated with face-to-face delivery, print materials as well as telephone outreach have been explored as modalities for activity intervention delivery.

Phone- and Print-Based Interventions

Direct comparisons of phone- and print-based physical activity intervention approaches with one another and with face-to-face intervention have yielded mixed results. Conn et al.'s meta-analysis [7] noted that both mail and phone physical activity intervention delivery approaches had smaller effect sizes relative to face-to-face delivery in single-variable analyses but these differences were not observed in supplemental analyses that examined multiple moderators.

Phone- and print-based methods are often integrated in actual physical activity interventions, as in Marcus et al.'s study of individualized and tailored physical activity promotion within Project STRIDE [23]. In this randomized controlled trial, 239 participants were assigned to either a print or telephone condition in which they received individually tailored messages drawn from Social Cognitive Theory [10,11] and the Transtheoretical Model [12]. These messages included prompts to reinforce goal-seeking behavior and a computer-generated system for assessing stages of change and motivational readiness. As measured by a 7 day Physical Activity Recall Interview, both the print- and phone-based interventions were similarly efficacious compared to the control condition. Other trials have replicated these congruent outcomes: a randomized controlled trial by van Keulen et al. distributed 1629 participants among conditions of tailored print letters, motivational telephone calls, and control interventions [24]. Tailored print communication and tailored motivational interviewing via phone were found to be equally effective in promoting self-reported physical activity compared to control groups. This finding applied to middle-aged adults, as well as participants with low education levels.

Peer Support Telephone Calls

Peer support for behavior change has been championed by those aiming to improve health outcomes by extending the outreach of available behavior change approaches beyond the reach of intervention staff [25]. The increase in studies examining the effects of peer support telephone calls led to a Cochrane review publication in 2008 [26]. At the time of this review, controlled studies were limited, and methodological issues limited the existing evidence base, leading the authors to call for well-designed trials to examine the clinical effectiveness and cost of peer supported phone contacts aimed at improving health behavior and health outcomes. The results of a well-controlled physical activity program that compared the delivery of a physical activity program delivered by program staff to delivery by trained peer volunteers using telephone contacts help to bridge the gap between understanding of the efficacy of professional interventionist phone contact and peer phone outreach. Participants were 181 sedentary adults age 50 years and older who participated in a year-long controlled activity trial. Telephone activity interventionists were 12 volunteer peer mentors and professional staff. Participants were randomly assigned to phone-based activity advice from the professional staff, peer mentors, or

a staff-delivered phone nutrition support attention control condition. This well-controlled study examined treatment fidelity for the phone interventions. Moderate intensity or vigorous activity was assessed with self-report, with accelerometry validation in a subsample. At 6 and 12 months, both physical activity phone contact arms significantly increased activity relative to the control condition. Notably, both professional and peer phone contact groups showed comparable quantity of intervention delivery in fidelity analyses, while the peer mentor interventionists demonstrated more versatility and comprehensiveness in quality of intervention content.

This study demonstrates the efficacy of peer telephone modality of physical activity intervention delivery and highlights its potential for community outreach.

Computer- and Web-Based Interventions

Computer- and web-based dissemination of physical activity-related information has vastly increased within the past decade, but is still in a state of infancy. Some work has explored the efficacy of computer-tailored interventions in comparison with other avenues of health behavior change—a meta-analysis by Krebs et al. examined the effects of 88 computer-based health interventions published between 1988 and 2009, finding no significant differences between print-, computer-, or phone-based methodologies [27]. A 2009 report on Internet-based physical activity interventions among adults [28] found more than 20 studies. Studies yielded encouraging results with response to an Internet-based physical activity intervention similar to response to other more established, effective interventions. An Australian study examined attitudes toward Internet-based physical activity behavior change content and delivery as part of a program evaluation of a randomized trial that compared face-to-face exercise intervention, Internet only, and combined Internet and face-to-face groups [29]. Face-to-face exercise delivery group participants were more satisfied with their group allocation relative to the Internet groups. Internet groups reported liking the home-based access of materials and self-paced nature of the website. Internet groups reported that time and motivation were barriers to use. No differences were found regarding acceptability or credibility of content. Website usability was high for both groups. These studies suggest that web-based formats are useful; however, they may benefit from supplementation.

A review by Bennett and Glasgow cited a variety of improvements that need to be made for the platform to be effective, as well as many signs of promise [30]. While the potential reach of web-based interventions is high—nearly 75% of adult Americas regularly use the Internet—promoting utilization, tailoring, and minimizing attrition rates are challenges that face the field. However, the authors reaffirm that the convenience and engaging anonymity of web-based interventions are strong advantages of the method. Within the context of community interventions, web-based techniques are gaining a foothold, but are underutilized: a 2011 Cochrane review by Baker et al. reported that web-based communication strategies for increasing physical activities were among six primary goals for community health interventions [4], yet very few Internet trials have been conducted with multiethnic samples.

The studies available to date indicate that computer/Internet approaches can be successfully integrated into physical activity intervention efforts. However, the advent of integrative technological approaches does not negate the relevance of more traditional phone- and print-based methodologies to increase physical activity. Within the past decade, these modalities have been just as prominent, if not more so, than their often more expensive counterparts. While these technologies are not new, the communication they enable continues to be optimized in order to facilitate the dissemination of physical activity interventions.

ADVANCES IN CHANNELS OF ACTIVITY INTERVENTION AND IMPLICATIONS FOR PROMOTION OF COMMUNITY-WIDE PHYSICAL ACTIVITY

As described in the earlier sections, print, telephone, and peer delivery modalities offer opportunities for reaching a wide variety of individuals who may benefit from these extended intervention approaches. In addition to these delivery modalities, activity interventions may be aimed at even more broad sets of participant via community-wide interventions.

A 2011 Cochrane review examined community-wide interventions aimed at increasing physical activity in order to evaluate their influence on population-level health [4]. Twenty-five studies of interventions that directed their intervention at the community level and used multiple identifiable components were identified. Of these, 19 were conducted in high-income countries; 11 of these were described as aimed to reach low, socioeconomic, or disadvantaged communities. Six studies were conducted in low-income countries. The review authors concluded that methodological issues precluded reaching clear conclusions regarding the effectiveness of community interventions; however, the methodological review offers instructive information about the types of community interventions that have been conducted and suggestions for future intervention programs and research. A major concern identified in the community-wide physical activity intervention literature was selection bias, particularly limited use of community comparisons and randomization, and the quality and validity of assessments used to measure outcomes. Despite these limitations, it is encouraging to see that the majority of interventions included establishing partnerships with local government or nongovernment local organizations. Community strategies generally involved planning initiatives with the aim of producing long-lasting benefits for the community. They also operated at a series of levels to attempt to influence activity, such as environmental changes, policy changes, and use of the media. The review also provides a description of community-level strategies for outreach to many types of disadvantaged groups: (1) social marketing

through local mass media (television, radio, newspaper); (2) other communication outreach (posters, flyers, information booklets, websites, maps) to raise awareness of the intervention program and provide specific information; (3) individual behavior change counseling by health professionals such as the use of physical activity prescriptions; (4) working with voluntary, government, and nongovernment organizations, such as sport organizations, to promote events and activities such as walking; (5) working within specific settings that may facilitate contact with individuals who have social disadvantages such as lack of transportation and might otherwise be missed by traditional outreach, for example, schools, senior centers, workplaces, community centers, homeless shelters, and shopping malls; and (6) environmental change strategies such as creation of walking trails and partnering with legislative and fiscal leaders to promote planning for outreach to the broader population.

Despite the identified methodological limitations precluding a clear understanding of the influence of community-wide interventions or the unique contributions of specific aspect of such interventions, the Cochrane review provides a useful overview of the types of approaches that have been undertaken in the last decade. Of the studies reviewed, many incorporated theory-based intervention models into their intervention methods. Of the 25 studies described, 6 focused on ecological approaches to increase activity, 4 interventions developed community interventions using the Transtheoretical Model [12] as the behavior change framework, 4 community interventions were based on Social Cognitive Theory [10,11], and 2 based their interventions on adaptations of a Community Empowerment Model [31–35]. Some community-wide interventions targeted specific social cognitive constructs such as self-efficacy or addressed the use of persuasive communications theory or emphasized principles of and community organization. In some cases, multiple models informed interventions. This highlights the challenges inherent in attempting to identify key components of effective community-based physical activity interventions.

Given the findings of previously described reviews of physical activity interventions with adult based on controlled studies indicated that the majority of participants are middle-aged, female, and nonminority, these types of community-wide intervention approaches offer tremendous potential to promote activity. More well-controlled evaluations of these approaches are needed and offer challenges for future programmatic evaluations.

Community-Wide Physical Activity and the Role of Built Environment

An additional approach to addressing the needs of the broader community when developing physical activity interventions is to consider the role of the built environment. An emerging body of studies indicates that the physical environment plays an influential role in physical activity [36,37]. Reviews have found that neighborhoods that are characterized as walkable (those with mixed land use such as having homes, schools, workplaces, and areas to shops accessible) can encourage walking to multiple destinations [36,38,39]. Reviews of the evidence to date indicate that the majority of studies of the relationship between physical activity and the built environment are cross-sectional [36,39], which limits the evidence regarding the effectiveness of changing the environment on physical activity. However, several studies have facilitated understanding of how the built environment might impact activity and how neighborhood environments might moderate the effect of activity interventions. A 2006 review of evidence to date identified several projects that evaluated the development of new walking and bicycle paths and found that this increased activity [40]. However, path use was optimized by promotional campaigns and mediated by the user's pre-existing physical activity levels, proximity of user's homes from the paths, and safety concerns, highlighting the complexity of evaluating specific effectiveness of these environmental changes. King et al. evaluated both social and built environment influences in the context of physical activity interventions across five intervention trials [37]. Features of the built environment were assessed with a Neighborhood Walkability Scale. Activity guidelines were more likely to be met by participants living in neighborhoods with more attractive scenery and ease of walking. Analyses examining within site variables also indicated that seeing others when walking and encountering dogs that impeded efforts made it more difficult to walk.

Additional analyses suggested that traffic safety was related to both facilitating and impeding activity. To explore the interactions between changes in walking over time, lifestyle physical activity intervention conditions, and the walkability of participants' neighborhoods, Kerr et al. examined data from two randomized activity intervention trials [39]. Both trials were conducted by the same researchers and used similar methodologies and geographic recruitment regions in the same county. One of the activity trials was with women with BMIs between 25 and 39 who were randomized to either a "Patient-Centered Assessment and Counseling for Exercise and Nutrition via the Internet (PACEi)" or an "enhanced" standard care comparison group. The PACEi intervention consisted of computerized assessment with a staged action plan followed by brief counseling from their primary care provider. The women were also encouraged to use a study website for activity and nutrition information, tips, and skills and to set monthly behavior change goals. They received monthly support and tailored feedback by e-mail and quarterly telephone calls. The standard care comparison group received basic print materials on the topics of physical activity and nutrition. The other activity trial was with men with BMIs between 25 and 39 who were recruited from the community through newspaper advertisements. They were randomly assigned to either the PACEi intervention with content designed for men or a general health information website. The RCT with men also provided participants with pedometers to track their daily steps. They were encouraged to access the website weekly to report goal progress, weight, and set new

goals. They also had occasional telephone and e-mail contact with project staff to assist them with the website and any technical difficulties. In examining the interactions between the built environment and interventions, it was found that men who resided in less walkable neighborhoods (as assessed with a walkability index) who were in the intervention group significantly increased their walking time (daily walking time was increased by 29 min from baseline to 1 year) while men who resided in high walkable neighborhoods decreased their walking over the course of the study (a decrease by 10 min from baseline to 1 year). Men in the control condition did not increase their walking time. For women, results showed similar trends, with women living in low walkable neighborhoods who were in the intervention group increasing their walking the most (7 min increase from baseline to 1 year), although results did not reach statistical significance. Women who perceived an unsafe volume or speed of traffic had decreased walking time (22 min daily decrease), while women who perceived that the traffic in their neighborhood was safer had increased walking time (increased by 17 min) over the course of the study. Findings of this study suggest a possible ceiling effect of living in a highly walkable neighborhood. The authors discuss the possibility of other nonwalking behaviors and focus on dietary factors. The gender differences in interactions between built environment issues and activity outcomes from the activity RCTs are intriguing and suggest that men and women may have different perceptions of and responses to changes at the built environment level. Gender difference findings may also be accounted for by the differences in frequency of goal setting and use of pedometers as a monitoring aid between the gender-specific RCTs. As reviewed in previous sections of this chapter, these basic behavioral strategies are known to enhance physical activity interventions. The study authors concluded that the pattern of results indicate that behavior change interventions can encourage walking behavior, even in less supportive and walkable neighborhood environments.

PHYSICAL ACTIVITY INTERVENTIONS IN RACIAL/ETHNIC UNDERSERVED SAMPLES

Ten years ago, reviews of physical activity intervention consistently called for additional studies that included racial and ethnic minority and underserved samples [1]. While additional studies have been conducted, the optimal approaches to providing activity interventions that reach minorities and result in the most effective level of change remain unclear.

Pekmezi et al. conducted a feasibility and efficacy study of computer- and Internet-based physical activity interventions as part of a 1-year intervention comparing three communication modalities—motivationally tailored print, motivationally tailored Internet (matched to Stage of Change), and standard Internet [41]. Participants were part of a large study sample of 249 sedentary adults in good health who had access to a computer with a modem (Step Into Motion Trial [42]). As a part of this study, these investigators were able to examine the feasibility and efficacy of the varied communication modalities in a subsample of 38 African American participants. The larger trial did not specifically include cultural tailoring [42]. Both motivationally tailored activity intervention communication conditions included provision of individualized computer expert system feedback which was delivered using either print materials (mailed to participants) or Internet. The motivationally tailored feedback was related to participant questionnaire responses and was based on constructs underlying the Transtheoretical Model [12] and Social Cognitive Theory [10,11]. The standard Internet condition provided online access to six websites about physical activity that were available at the time of the study (American Heart Association, Shape Up America, Mayo Clinic Fitness and Sports Medicine Center, American Academy of Family Physicians, American Council on Exercise, American College of Sports Medicine). Of note, participants in each of the three groups completed physical activity–monitoring logs and were provided with incentives for log completion. Findings indicated that as a group, these African American participants significantly increased their activity from baseline to 6 months post-baseline and remained more active relative to baseline and less active relative to 6 months at the 1-year follow-up. Satisfaction ratings were available for 30 participants, with 70% reporting that they read "most or all" of the activity-related information that was provided by print or Internet. The Internet and print programs were rated as "somewhat" or "very" helpful by 80% and enjoyable by 87% of those providing this post-intervention feedback. These findings suggest that computer and Internet communication approaches are acceptable to African Americans and can produce adoption and maintenance of physical activity. Additional programs and controlled studies are needed to involve larger numbers of African Americans and other minority participants in order to further evaluate the best ways to provide computer-concluded based communication and outreach in diverse populations.

Whitt-Glover and Kumanyika conducted a systematic review of interventions to increase activity and fitness in African Americans [6]. This review included studies published between 1985 and 2006. Interventions included adult and child samples. Effective programs were identified for adults; however, most of the studies conducted with children yielded null findings. Of interest, the majority of studies were conducted with women. Interventions included community-based approaches such as delivering the intervention in community settings such as the YMCA, community centers, church, worksites, and public housing projects. Cultural adaptations were included in a number of studies. For example, several physical activity interventions with African American participants were conducted in a church setting and included activity instructors from the African American community, gospel our "soul" music and incorporated prayer. Hip-hop dancing was also represented. Resnicow et al. involved African American celebrities from the local community and, in a church-based program, included video of pastors giving sermons addressing the importance and value of physical activity [43]. As highlighted in the Whitt-Glover et al. review [6], the culturally adaptive methods

of intervention were frequently paired with other behavior change approaches, including monitoring, use of pedometers, peer phone contacts, supervised exercise sessions, and social support via group walks in the local neighborhood. The multiple approaches and study design limitations make it difficult to evaluate the specific influences of these culturally tailored approaches. However, examination of findings from individual studies showing significant group differences led the authors to look for trends associated with "best practices." Common factors associated with the effectiveness of individual studies of physical activity interventions in African Americans were use of randomized controlled trial design, assessing physical activity using an objective measure, providing specific physical activity goals to participants, and including structured activity programs. These trends are consistent with other general reviews of activity intervention studies. Carefully controlled intervention studies are needed to more thoroughly examine the specific influences of culturally adapted intervention approaches.

TRANSLATING BEHAVIORAL AND COGNITIVE APPROACHES INTO REAL-WORLD INTERVENTIONS TO PROMOTE PHYSICAL ACTIVITY INTERVENTION OUTREACH

The findings of the past decade have reinforced previous research on the efficacy of behavioral and cognitive interventions to promote physical activity, but the limitations in the study designs and results highlight the need for outreach to diverse individuals and settings as well as the complexity of physical activity intervention efforts in a community context. A useful framework has been developed to enhance the impact of health interventions by addressing issues of real-world implementation of evidence-based approaches to be sure that they actually reach diverse and underserved populations and varied settings and are adopted and maintained over time. The RE-AIM framework (Reach, Effectiveness, Adoption, Implementation, Maintenance) [44] proposes five steps for translating what is known from research studies into actual intervention action in the real world [44–46]:

1. Reach the target population—Interventions reach large groups of individuals in need, including those from characteristically underserved or hard to reach settings.
2. Effective impact of the intervention (also referred to as efficacy of the intervention)—Interventions make an impact on important outcomes and consider both positive and negative influences, unanticipated outcomes, quality of life, and even economic outcomes.
3. Adoption of the intervention approach in the real-world setting—Interventions are adopted by different settings and the number, proportion, and representativeness of the settings, and people who deliver the program are representative of those who would benefit from the program.
4. Implementation of the intervention is consistent—Intervention protocol is consistently delivered as intended in the real-world setting.
5. Maintenance of the intervention at the setting and individual levels so that it is delivered and results in benefits over the long run—Intervention becomes sustainable and a part of the routine within the programs or organizations delivering it, the health-related behaviors and benefits are maintained, and when appropriate, policies are maintained.

The RE-AIM approach has been widely adopted and since its development there have been over 100 publications spanning diverse disciplines and settings [46]. King et al. have made recommendations for applying the RE-AIM approach to the built environment [45]. They argue that by using a RE-AIM approach in which the physical location of proposed interventions is considered, interventionists can greatly influence who is reached and how frequently and how environmental changes might have positive, negative, or neutral influences on the outcomes. They cite an approach called Transit Orienting Design (TOD) as an example of considering redesigning communities to promote walking, bicycling, and decreasing car dependence. In this approach, mixed-use residential and commercial areas are placed near public transportation stops to make public transportation more attractive than driving [47]. However, the economic, environmental, housing, and equity goals intended with such approaches may not always be achieved. By using a RE-AIM approach for strategic planning, the plans for built environment intervention could have the potential for impact on all aspects of the community setting, including unintended consequences such as gentrification and displacement of low-income residents [48]. The authors recommend careful strategic planning in advance of developing community interventions including interactions with varied disciplines and agencies, using relevant information already available readily from public sources such as crime, traffic, and accident data and identifying practical approaches in the community to track behavior—for example, walkability audit tools [49] to promote greater community involvement and enhance maintenance.

A 2011 review evaluated theory-based physical activity interventions from a RE-AIM perspective. Theoretically guided interventions published between 1996 and mid-2009 were included; 57 studies met criteria for review [50]. Few of the physical activity studies included in this review reported on the specific intended target population for the intervention. Most did not report on the representativeness of the study sample relative to the target population. Many studies had small sample sizes and most included motivated, healthy participants, minimizing Reach. Adoption was the least reported dimension of the intervention studies, precluding evaluation of the representativeness of sites that did adopt the intervention. Approximately one-third of the studies reported implementation information via process evaluation. It was noted that this could be a consequence of journal page limits. More than half of the studies reported information

in individual maintenance of activity levels. However, only three reported on maintenance at the organizational level. Overall, the physical activity intervention studies reviewed with the RE-AIM framework were more likely to address individual rather than organizational, level. From a practical standpoint, this impedes the translation of many of the physical activity interventions into actual practice in real-world settings with diverse populations.

MAINTENANCE OF PHYSICAL ACTIVITY FOLLOWING INTERVENTION

In this section, we turn to a problem that has been recognized since the earliest efforts to promote exercise and physical activity in clinical and community populations. Adoption of an active lifestyle for a few weeks or months is not sufficient for the health-promoting benefits of activity. We now turn to an update on approaches to the challenge of effective promotion of ongoing activity, or maintenance of the activity, over time.

A recent systematic review of maintenance of physical activity following participation in a physical activity or diet intervention (defined as at least 3 months posttreatment) found that of 157 studies reporting behavioral outcomes, 35% included follow-up data of 3 months or longer [51]. When a comparison group was also included, there were 18% reporting follow-up (29 trials). This review identified a number of behavioral strategies that were common to randomized trials that showed maintenance of physical activity behavior change for at least 3 months after an intervention. Characteristics of trials showing activity maintenance were pretrial screening based on behavioral criteria, interventions that lasted longer than 24 weeks, had face-to-face contact, used multiple intervention strategies (more than six), and used follow-up prompts. The most common strategies in trials achieving maintenance were providing instruction on how to achieve behavior change (81%), prompting to identify behaviors (71%), and providing opportunities for making social comparisons (67%). The 2011 systematic review of reviews of intervention components associated with increased effectiveness in diet and activity interventions [5] noted that maintenance in physical activity is also associated with use of time management techniques and positive, encouraging self-talk.

A recent study is informative in its use of a sophisticated approach to prospectively examining dynamic changes in data to study changes in health cognitions and physical activity following intervention. The intervention was a lifestyle change program aimed at preventing type 2 diabetes in a sample of 389 Finnish adults. Participants' cognitions and activity were measured prior to the lifestyle intervention and 3 months and 1 year post-intervention. Using growth curve modeling, the researchers were able to examine how changes in cognitions influenced exercise adoption and maintenance. They found that health-related cognitions were amenable to change and that these changes in cognitions facilitated both physical activity adoption and maintenance [52]. Use of these new approaches to examining longitudinal data offers exciting opportunities for understanding how the process of activity adoption and maintenance unfold.

Advancing Understanding of Activity Maintenance by Examining Exercise Lapse

Several studies have promoted understanding of the process of exercise behavior over time not only by examining frequency/intensity/duration of exercise accrued within a session or time frame such as weeks or longer, but also by examining missed exercise sessions or omissions of exercise over time, sometimes referred to as exercise lapses. In a study of 508 postmenopausal women ages 52–62 years, lapses in physical activity were examined over the course of a randomized trial [53]. Lapses were associated with lower levels of activity, including a relapse (inactivity) following the lapse for many women. Of interest, relapse following a lapse was greater in participants who had higher anxiety and depressive symptoms and less frequent use of behavioral exercise processes of change. Lapses were less likely to lead to a relapse in women reporting more frequent use of behavioral processes of change related to activity. This highlights the previously identified benefits of behavioral strategies in physical activity as well as the potential role of affect in activity maintenance following intervention. Lapses in exercise didn't seem to be related to decreased exercise self-efficacy and health-related quality of life, which may suggest that women can lapse and at least accrue benefits. An additional study of activity on lapse and relapse provides some additional perspective on the context of lapses and relapse. Specifically, in a study of youth activity, Shields et al. noted that contextual factors are important in determining whether lapses occur and whether these lapses spiral into unhealthy behaviors such as inactivity [54]. It was proposed that the context of activity patterns include the social influence of others. Using a prospective, longitudinal approach, the study provided some support for the suggestion that interventions may be effective at preventing an activity lapse from becoming a relapse to inactivity by increasing the social influences of the family. Findings indicated that self-efficacy for self-regulation partially mediated associations between physical activity and family social influence. Further studies of the process of activity lapses may provide useful information about the types of factors associated with lapses in physical activity behavior and how such lapses might influence the maintenance of activity over time.

CONCLUSION

At the time of the first version of this chapter, in 1999, there was growing evidence supporting the benefits of using behavior change theory to inform physical activity interventions. Evaluation of interventions utilizing approaches driven by Social Cognitive Theory [10,11], the Transtheoretical Model [12], and other frameworks supported the use of behavioral approaches, such as those that focused on specific behaviors and factors that can be manipulated to influence physical

activity behavior. Examples included using behavioral contracting and reinforcement, modeling, provision of cues and prompts. Findings highlighted the effectiveness of behavioral strategies for enhancing exercise adoption and participation. In addition, at the time of the previous version of this chapter, cognitive interventions addressing thoughts related to facilitating or hindering physical activity and incorporated methods such as guidelines and instructions aimed at enhancing motivation for behavior change and monitoring and altering self-statements were supported.

Ten years later, the earlier work in understanding the utility of cognitive and behavioral approaches to enhancing exercise participation has been extended by exciting developments in research approaches. Technology has greatly enhanced the methods available for physical activity monitoring and communications between interventionists and program participants. The use of written diaries and logs is now often accompanied by palmtop handheld computers, accelerometers, and step counters. Activity program participants may access interventions through peers, the Internet, and various types of structured telephone contact approaches in addition to—or instead of—face-to-face contacts and printed materials. Efforts to improve intervention approaches to encourage adoption of exercise are now more strongly enhanced by a renewed emphasis on the importance of interventions that promote maintenance of activity once it has been established. Recent advances in statistical methodologies have allowed for longitudinal examination of the usefulness of specific aspects of theoretically based intervention approaches, aiding in efforts to longitudinally examine the process of activity maintenance and relationship to intervention components. In addition to a focus on enhancing physical activity behaviors pre- and post-intervention, studies have examined other approaches to assessment of the exercise process, including short-term slips from planned activity. Recent intervention studies have also addressed not only activity per se but changes in the sedentary behaviors that are encouraged, if not enforced, by our modern lifestyles.

Technological changes continue to introduce new ways of replacing active living with sedentary behavior and suppress opportunities for physical activity in almost every domain of modern life. The obesity epidemic now threatens almost all population subgroups and even less technologically advanced cultures. Although these public health challenges that motivate physical activity research are undoubtedly powerful adversaries, new discoveries of the benefits of physical activity are a continuing source of inspiration to researchers, health care providers, and others committed to find more effective ways of encouraging all people to be physically active and healthy.

The advances and limitations highlighted in this review of behavioral and cognitive interventions for promoting physical activity suggest some of the directions for future work. In particular, we expect to see more studies that translate findings of efficacious interventions into a wide variety of settings and populations. New technologies are likely to make monitoring of the spectrum of activity, from complete rest to the most vigorous exertion, more accurate, and less expensive. Telecommunications and Internet communications will provide new opportunities to connect people to physical activity promotion interventions, and we need to learn how to effectively and efficiently combine the technology with the personal contacts that many people still desire. Genetic studies may help us understand why some people enjoy and get more benefit from physical activity than others, and point the way toward biological as well as behavioral and cultural tailoring of interventions to individuals. There will also be unexpected challenges, but the scientific and creative advances of the past decade suggest that there will be exciting new progress to report in future years.

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19 Behavioral Approaches to Enhancing Smoking Cessation

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CONTENTS

Health Consequences of Smoking 245
Smoking Prevalence and Epidemiology 246
Prevalence of Smoking Cessation 246
Pharmacological Aids for Smoking Cessation 246
Behavioral Smoking Cessation Strategies 247
Counseling and Therapy-Based Approaches 247
  Group Therapy 247
  Individual Counseling 247
  Telephone Counseling 247
  Motivational Interviewing 247
Smoking Cessation in Medical Settings 248
  Primary Care Visits 248
  Inpatient Hospitalization 248
Community-Based Approaches 249
  Mass Media Campaigns 249
  Worksite Programs 249
Technology-Driven Approaches 249
  Internet-Based Interventions 249
  Text Message Interventions 250
Smoking Cessation in Special Population 250
  Young Adult and Adolescent Smokers 250
  Racial and Ethnic Minority Smokers 250
  Pregnant Smokers 250
  Mentally Ill Smokers 250
Other Behavioral Approaches 251
  Exercise 251
  Abrupt Quitting and Gradual Reduction 251
Summary and Conclusions 251
References 251

In the twentieth century, tobacco killed 100 million people worldwide [1]. Unless urgent action is taken, it will kill 1 billion in the twenty-first century [1]. In the United States, significant strides have been made to reduce the smoking prevalence among certain segments of the population, but there are important areas where gains have been minimal. The purpose of this chapter is to provide a brief overview of the health consequences of smoking and to review key behavioral approaches and strategies that have been used to enhance smoking cessation. This is not a comprehensive review, but rather a summary of the most effective treatments and promising research initiatives that are currently underway.

HEALTH CONSEQUENCES OF SMOKING

Worldwide, tobacco use remains the leading preventable cause of death, and it is a risk factor for six of the eight of leading causes of death [2]. Evidence shows that any exposure to tobacco smoke, even an occasional cigarette or exposure to secondhand smoke, is harmful because it contains more than 7000 chemicals and compounds [3]. Indeed, smoking harms nearly every organ of the body and can cause cardiovascular disease, stroke, periodontitis, aneurysms, pneumonia, chronic obstructive pulmonary disease (COPD), asthma, and low bone mineral density [2]. Cigarette smoking can also cause cancer of the lung, bladder, cervix, esophagus, oral cavity, larynx, stomach, kidney, uterus, and pharynx [4].

In the United States, the negative health effects from smoking account for an estimated 443,000 deaths annually (approximately 20% of all deaths) and $193 billion in direct health care expenditures and productivity losses each year [4]. In fact, more deaths are caused by tobacco use than by all deaths from illegal drug use, alcohol use, human immunodeficiency virus (HIV), motor vehicle injuries, murders, and suicides combined [4]. Lastly, smoking has additional adverse effects on early childhood and reproductive health, including infertility, preterm delivery, stillbirth, low birth weight, and sudden infant death syndrome (SIDS) [4].

SMOKING PREVALENCE AND EPIDEMIOLOGY

It is currently estimated that more than 1 billion people smoke cigarettes worldwide, with smoking rates growing fastest in low-income countries [1]. In the United States, previous declines in smoking prevalence have stalled. For the past 3 years, the proportion of adults who were cigarette smokers did not significantly change. Specifically, 19.4% of adults aged 18 years and over [5] and 10.7% of youths aged 12–17 years [6] are current smokers. Smoking and tobacco use overall is higher in males (33.7%) than in females (21.5%) and differs by various other demographics [6]. For example, American Indians and Alaskan Natives report the highest rates of tobacco use (35.8%), followed by 29.5% of whites, 27.3% of blacks, 21.9% of Hispanics, and 12.5% of Asians [7]. Cigarette smoking is most prevalent among those who had not completed high school (34.3%), and least prevalent (12.8%) among those with a college degree. The most recent reports indicate that smoking is more common among unemployed adults than among adults who were working full time or part time (39.9% vs. 24.9% and 24.4%, respectively). Finally, smoking rates are currently highest in the Midwest (24.8%), followed by the South (21.4%), Northeast (22.2%), and the West (20.0%), and this predominately occurs in nonmetropolitan areas (26.0%), as opposed to small (23.5%) and large (21.7%) metropolitan areas [7].

PREVALENCE OF SMOKING CESSATION

Both the risk and the severity of many diseases caused by smoking are directly related to how long the smoker has smoked and the number of cigarettes smoked per day. It is beneficial to quit smoking at any age, and smokers who quit before the age of 35 years have mortality rates similar to those who never smoked [7]. More specifically, after quitting, the risk for a heart attack drops sharply after just 1 year; stroke risk can fall to about the same as a nonsmoker's after 2–5 years; risks for cancer of the mouth, throat, esophagus, and bladder are cut in half after 5 years; and the risk for dying of lung cancer drops by half after 10 years [3]. Since 2002, the number of former U.S. smokers has exceeded the number of current smokers [7]. The most recent estimates indicate that almost 70% of current smokers would like to stop smoking, but less than 5% are able to maintain abstinence for more than 12 months [7,8]. Overall, cessation rates are initially much higher among those who participate in smoking cessation programs than those who quit without assistance. However, the different rate of abstinence between these groups narrows over time, particularly after 6 months [9]. Interest in quitting and attempting to quit has been reported to be higher among certain demographic groups, such as females, non-Hispanic black smokers, those aged <65 years, and those with a post-high school education [10]. A recent report indicated that 6.2% of smokers were able to quit in the past year for ≥6 months [7]. Cessation was also found to be more likely among non-Hispanic whites, those with a higher level of education, and those with private health care plans [7].

PHARMACOLOGICAL AIDS FOR SMOKING CESSATION

The earliest studies on smoking cessation did not recognize the addictive nature of cigarette smoking. Modern day approaches now take into account that the nicotine in cigarettes is a highly addictive drug, and this has led to a wealth of research on using medication to help smokers quit. The combination of behavioral counseling and medication has been shown to be more effective than either treatment alone [11]. Therefore, prior to describing several different behavioral approaches to enhancing smoking cessation, a clarification of the medications that often accompany treatment is needed.

Currently, there are seven U.S. Food and Drug Administration (FDA) approved first-line medications shown to be helpful for increasing long-term smoking abstinence rates. These include over-the-counter (OTC) products (nicotine gum, nicotine lozenge, and the nicotine patch) and prescription-only medications (nicotine nasal spray, nicotine inhaler, sustained-release bupropion, and varenicline). When used properly, the nicotine replacement therapies (NTRs) can relieve nicotine withdrawal and have been shown to nearly double the success rate of smoking cessation when compared to a placebo [11,12]. Bupropion, an antidepressant, has also been shown to double quit rates [13]. It reduces nicotine's rewarding effects by blocking the reuptake of norepinephrine and dopamine in the mesolimbic system and nucleus accumbens, a key area for nicotine reinforcement [12]. Varenicline, the newest medication, has been shown to triple abstinence rates in smokers when compared to a placebo [11–13]. Like buproprion, varenicline attenuates the rewarding effects of nicotine. In addition, varenicline operates as a partial agonist for the $\alpha_4\beta_2$ subtype of the nicotinic acetylcholine receptors, which are associated with the addictive effects of nicotine [12]. Importantly, all of these medications can have side effects that range from dry mouth to suicidal ideation, and many of them are not appropriate or have not been studied in special population of smokers (e.g., individuals with psychiatric comorbidities, adolescents, postpartum women) [12]. Given that the combination of behavioral counseling and medication is ideal, more studies on how to best use these strategies for all smokers are urgently needed.

BEHAVIORAL SMOKING CESSATION STRATEGIES

Extensive scientific and community resources have been used to examine ways to reduce tobacco use and increase smoking cessation. Strategies that have been used range from government-based initiatives to media-based campaigns to independently run interventions targeting a wide array of smokers. The following review covers the various types of behavioral smoking cessation interventions that vary from minimal contact to intensive counseling. The programs described later can be classified based on the type of approach used, the population targeted, and the setting in which it is delivered. Regardless of their classification, all of the programs attempt to provide smokers with the information and behavioral skills thought to be necessary for achieving initial cessation and sustained abstinence.

COUNSELING AND THERAPY-BASED APPROACHES

Group Therapy

Delivering a smoking cessation intervention in a group format has been used for more than 20 years, and it remains popular [14,15]. Using a group format is particularly helpful for certain therapeutic approaches such as cognitive behavioral therapy and contingency management. Overall, the group format can provide smokers with a unique opportunity to learn about the challenges other smokers face when trying to quit, which might result in increased quit rates when compared to self-help methods [15]. While it is not yet clear whether group therapy is more effective than individual counseling, it appears that smokers motivated to quit can increase their likelihood of success if they participate in a group [15]. Given that group-based smoking cessation interventions are often less costly than other methods, group therapy may be the one of the most cost-effective behavioral approaches for smoking cessation.

Individual Counseling

Individual or face-to-face counseling is a well-established method for delivering smoking cessation treatment. The treatment can be delivered by practitioners with varying levels of education and training (e.g., smoking treatment specialists, psychologists), and it can be done in different formats, for varying lengths of time (e.g., 10–60 min sessions), and across a wide-ranging number of sessions. Individual counseling can also be combined with self-help components, medication, group counseling, and/or telephone assistance [16]. Currently, there is sufficient evidence to support using individual counseling, as it has been shown to increase the likelihood of quitting smoking when compared to less intensive treatment (e.g., self-help) [16]. Going forward, it will be important to identify the most effective and cost-effective intensity and duration of individual counseling for diverse and hard-to-reach population.

Telephone Counseling

A clear benefit of telephone counseling is that it can be used as a substitute for face-to-face contact to reach a large number of smokers at a much lower cost. There are two approaches to telephone counseling: proactive and reactive. Counselors use a proactive approach when they call smokers in attempt to support a quit attempt or prevent relapse. These calls are typically made as part of a larger effort to expand the level of support given to the smoker, which may have initially included smoking cessation counseling or the provision of self-help materials or pharmacotherapy. Reactive counseling occurs when a smoker calls a quit-line, such as 1-800- QUIT-NOW [17]. Quit-lines may be regional or national and may provide the caller with counseling at the time of the call, a future (proactive) call, mailed materials, access to pharmacotherapy, a recorded message, or a mixture of these components [18]. Recent research has shown that proactive telephone counseling can significantly increase abstinence for up to 9 months among smokers interested in quitting; however, the long-term (12 months or longer) effect is less clear [18,19]. In addition, there is some evidence for a dose–response relationship with the number of proactive calls, with three or more calls increasing the chances of quitting over other minimal interventions such as self-help materials or pharmacotherapy alone [18]. New research will need to determine how to extend the effects of proactive calls for long-term cessation and how to capitalize on reactive counseling [18,19].

Motivational Interviewing

Motivational interviewing (MI) was originally developed in the early 1980s as a treatment for substance abuse [20]. It is an individually administered, client-centered counseling approach to elicit behavior change by helping individuals explore and resolve ambivalence [21]. MI seeks to reduce resistance to change by developing a discrepancy between an individual's current behavior and his/her values and goals. Four general principles underlie this approach: (1) express empathy, (2) develop discrepancy, (3) roll with resistance, and (4) support self-efficacy. The first study to use MI for nicotine dependence was published in 1998 [22], and just over 30 trials are currently published [23,24]. Overall, MI seems to be an efficacious treatment for smoking cessation across a wide array of patients, and it is within the range of other behavioral treatments for nicotine dependence [11,23,24]. MI appears to be the most effective when delivered by trained counselors in two or more 20–60 min sessions [23,25]. In addition, MI may be more ideal for those with low levels of motivation to quit, individuals living outside the United States, adolescents, and those with medical comorbidities [23,24]. Future research will need to more rigorously test standardized MI protocols, include fidelity assessments, and determine the independent effects of MI when compared to other cessation treatments [24].

SMOKING CESSATION IN MEDICAL SETTINGS

Considering that smoking contributes to a myriad of medical problems, it is not surprising that smoking is more common in a variety of medical population. For example, smoking rates among heart disease, COPD, and stroke patients are at least 10% greater than the general population [26]. Cessation after such problems are diagnosed can still reduce morbidity and mortality. For example, patients who stop smoking after a myocardial infarction decrease risk of another MI and mortality by about one-third [27]. Likewise, cessation after being diagnosed with lung cancer reduces cancer recurrence by 46%–77% and total mortality by 46%–66% [28]. Thus, smoking cessation in medical patients can function as an important secondary prevention intervention.

The "5 As" smoking cessation framework (*Ask*, *Advise*, *Assess*, *Assist*, and *Arrange*) is specifically designed to be applicable to brief medical visits [11]. This framework calls for all clinicians to assess smoking status at each visit (i.e., *Ask*). The identification of smokers can be increased by treating smoking status as a "vital sign" [29] and building prompts into electronic medical records [30]. Having such an identification system increases the likelihood that clinicians will provide cessation interventions [11,31]. Some clinicians may worry that repeatedly bringing up smoking cessation during visits will decrease patient satisfaction; however, this does not seem to be the case [32,33].

Providing strong, personal advice to quit (i.e., *Advise*) only takes a few minutes and has clear empirical support. Specifically, physicians providing strong advice to quit can increase the likelihood of quitting even when relatively little time is spent (e.g., <3 min) [11]. Although the absolute increase in quit rates due to brief advice may only be 1%–3% [34], the cost of advice is low and the reach is high, so its potential public health impact is great.

Discussion of a patient's willingness to make a cessation attempt at this time (i.e., *Assess*) will identify patients who are currently interested in quitting and those who are not, so clinicians should be ready to use treatment techniques for both groups [35]. For those who are ready to quit, the clinician can *Assist*. Assistance strategies include developing a quit plan (including setting a quit date); recommending and/or prescribing pharmacotherapy; referring the patient to additional counseling, quit-lines, or web support; providing practical counseling (e.g., problem-solving barriers to cessation); and providing social support. It is notable that quit rates increase as time spent counseling increases [11]. Finally, following up in person or by phone (*Arrange*) provides an opportunity to reinforce cessation or encourage another quit attempt if the patient has relapsed. Ideally, a first follow-up contact would occur within a week of the quit date and a second within a month of the quit date [11].

For smokers currently uninterested in quitting, the "5 Rs" (*Relevance*, *Risks*, *Rewards*, *Roadblocks*, and *Repetition*) provide a framework for increasing motivation and are consistent with the MI approach described earlier [11]. In this framework, patients are asked (not told) about the personal *Relevance* of smoking, perceived personal *Risks* of smoking and *Rewards* of quitting, and perceived *Roadblocks* to successful cessation (for which the clinician can suggest solutions). These steps can be repeated at each visit (*Repetition*). Studies have shown that the 5 Rs approach increases the likelihood of future quit attempts in those with initially low motivation to quit smoking [36].

Integrating smoking cessation services into regular systems of medical care is ideal because when treatment is delayed or in another location, fewer patients follow through on referrals than when treatment is easily assessable [35]. Although cessation services could be integrated into almost any medical encounter (including some nontraditional contexts such as pharmacies and dental offices) [37,38], we review two of the most important in the following sections: primary care visits and inpatient hospital stays.

Primary Care Visits

In the United States, 70% of smokers see some type of a primary care provider (PCP) each year [39]. Thus, primary care–based cessation interventions can reach most smokers. In addition, PCP providers have long-standing relationships with their patients and may be in a unique position as a trusted clinician to provide influential advice that will lead to a quit attempt. It may be frustrating for the provider to repeatedly spend time discussing smoking cessation with the same patient; however, because intentions to quit can fluctuate on a week-to-week basis [40], assessing motivation to quit at every contact will catch more patients when they are ready to make an attempt. An additional advantage of conducting a smoking cessation intervention in primary care is that pharmacotherapy options can also be discussed and prescribed on the spot.

About 20% of smokers in primary care are willing to make a serious quit attempt [41]. PCPs may be concerned that intervening with smokers who are not ready to quit would be alienating. However, the opposite seems to be true; patients who receive the 5 As during primary care visits are more satisfied with their tobacco-specific and overall care, even smokers who are not ready to quit [32]. Further, there is evidence that primary care interventions that target all smokers (regardless of readiness to quit) can be effective [42].

Due to time and logistical constraints, many PCPs may be limited in the amount of follow-up support they can provide for a quit attempt. However, recent evidence suggests that referral to a proactive quit-line (e.g., service that proactively calls the patient) following brief cessation treatment during a primary care visit can approximately double quit rates [43]. Such quit-line referrals have also been successfully integrated with primary care–based pharmacological interventions [41]. Thus, referral to a quit-line may provide a viable option for follow-up care (*Arrange* in the 5 As) when primary care resources are unavailable.

Inpatient Hospitalization

Hospitalization can be considered a "Teachable Moment" when the health effects of smoking are salient and patients

are more likely to accept cessation treatment [11]. In addition, U.S. hospitals are now smoke-free, so inpatients will likely experience temporary abstinence regardless of their desire to quit [44]. Clinical guidelines [11] indicate that smoking status should be assessed upon hospital admission and documented on the problem list and discharge summary. Smokers should be offered NRT while in the hospital even if they are not considering quitting, as a positive experience with NRT relieving withdrawal symptoms may increase NRT use during future attempts [11,35].

The advice and brief counseling interventions described earlier should also be used during the inpatient stay. However, a recent meta-analysis indicates that cessation programs that do not provide cessation support for at least 1 month post-discharge are not efficacious, whereas treatments that begin during an inpatient hospitalization and continue contacts for at least 1 month after discharge increase the odds of cessation by 65% [44].

In line with these findings, starting in January 2012, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) will begin tracking the rate at which hospitals offer and provide inpatient and post-discharge cessation treatment to all hospitalized tobacco users, regardless of medical diagnosis [45].

Given that hospitalized patients are acutely ill, it is particularly important to consider possible contraindications for psychopharmacology in this setting. For example, the FDA package inserts recommend that nicotine replacement should be "used with caution" for 2 weeks following an MI [11]. The cardiac risk of varenicline has also been called into question [46]. Thus, with certain patients, inpatient providers must weigh the medical risk of prescribing pharmacological cessation aids with the benefit of an increased likelihood of cessation.

COMMUNITY-BASED APPROACHES

Mass Media Campaigns

Despite the overwhelming evidence supporting the dangers of smoking, many smokers worldwide underestimate the full extent of the risk to themselves and others [47]. Mass media, which includes television, film, the Internet, radio, newspapers, magazines, billboards, and packaging, can play a key role in shaping smoking-related knowledge, attitudes, and behaviors [47]. Mass media campaigns can be designed either to directly target individuals' behavior or to influence the social and political landscape, which can lead to a change in social norms around smoking [48]. Theoretically based campaign messages broadcasted at a sufficient intensity, frequency, and duration have been associated with an increase in the number of calls to telephone quit-lines [49], a reduction in adult and youth smoking prevalence [50–53], an increase in adult cessation rates and youth abstinence rates [54,55], and sustained positive changes in attitudes, beliefs, and intentions to smoke among youth [56]. As such, theoretically based mass media campaigns can be cost-effective when compared to other smoking cessation interventions, given that they can positively influence behavior and reach large populations quickly and efficiently [57]. Future research will need to investigate the benefits of using newer types of communication such as social media (e.g., Twitter, Facebook), as they are becoming increasingly more effective in reaching a wider cross section of the population, particularly adolescents.

Worksite Programs

Although smoking is more common among unemployed adults, nearly 25% of full- and part-time workers smoke [11]. There are numerous adverse effects associated with employees that smoke, such as increased health care costs and disability, greater absenteeism, poorer job performance, and an increased risk of injury [58]. As a result, employers may be motivated to provide support for effective worksite smoking cessation programs as a way to offset the potential costs related to the negative health consequences of smoking [59]. There are several advantages to conducting a cessation program in such an environment, including (1) access to a large, stable population; (2) the potential for high participation and compliance; (3) a socially reinforcing network and positive atmosphere; (4) an opportunity to include a diverse or hard-to-reach population; and (5) the ability to run a program that can be tailored to the interests, challenges, and needs of a particular group [60]. To date, research has shown that when individual and group counseling, pharmacological treatment, and competitions and incentives for participation in these programs are offered, employees who smoke are likely to quit at rates that are at least comparable to off-site programs [60,61]. However, more studies are needed, as participation in worksite interventions has been lower than expected, and most of the research has been conducted in traditionally stable worksites, which are becoming less common with advancing technology and increasingly mobile employees. Lastly, there is a lack of data detailing the specific costs of worksite smoking cessation programs and the relevant associated potential economic outcomes such as reduced absenteeism and increased productivity [60].

TECHNOLOGY-DRIVEN APPROACHES

Internet-Based Interventions

Almost one-third of the world's entire population (i.e., over 2 billion people) actively uses the Internet [62]. In the United States, 78% of the population uses the Internet, with rates of use equal between genders and relatively consistent across other demographic variables (e.g., age, race/ethnicity) [63]. Internet-based interventions are emerging as potential channels for smoking cessation intervention [64,65]. Internet-based services can potentially provide smokers with the option of finding information at any day or time they choose, unlike real-time counseling via telephone and individual or group counseling [64,66,67]. To date, interactive, web-based smoking cessation programs appear to be acceptable by users and more effective for cessation than control comparisons.

For example, Swartz et al. [68] used a fully automated website intervention composed of video segments and audio-targeted to users by age, sex, and race/ethnicity and found significantly higher 3 month abstinence rates (12.3%) relative to the wait-list control group (5.0%). Future research efforts need to use rigorous evaluation methods to determine the effectiveness of Internet-based components, such as e-mails, chat rooms, and other ways of engaging users and providing support during the quitting process. More information on factors, such as usability and sociability, that make people spend more time on sites or return to the sites more often is also important.

Text Message Interventions

Currently, more than two-thirds of the world's population own a mobile phone, and approximately 6.2 trillion text messages were sent in 2010 [69]. In the United States, it is estimated that 82% of the population owns a mobile phone, with 72% of adult and 87% of adolescent cell phone users sending and receiving text messages daily [70]. As such, researchers have begun examining the efficacy of using text message interventions for smoking cessation. Messages typically used during face-to-face smoking cessation support are modified for delivery via mobile phones with the content tailored to the age, sex, and ethnic group of the quitter [71]. Such an intervention allows for the smoking treatment to be delivered directly to the patient with minimal direct contact and to a large number of smokers at a low cost. Additionally, smokers can also receive messages anywhere, at the most appropriate or convenient times, and without threats to confidentiality [72]. To date, there have been just a few randomized controlled trials testing text-based smoking cessation interventions, but preliminary evidence is positive for short-term smoking outcomes (6 weeks) [72]. Future research is needed to determine if sustained effects can be achieved over longer periods of time (e.g., greater than 6 months).

SMOKING CESSATION IN SPECIAL POPULATION

Young Adult and Adolescent Smokers

More than 3000 children and adolescents become daily smokers every day [73], resulting in approximately 1.23 million new smokers under the age of 18 years each year. The prevalence of smoking among young adults aged 18–25 years remains the highest rate of all age groups [6]. To date, studies utilizing behavioral interventions with this population result in significant short-term results (7 day point-prevalence abstinence or continuous abstinence at 48 h to 3 months post-treatment). However, simply adapting adult interventions may not be effective in reducing young adult tobacco use [74]. Some of the key features of these interventions include recruiting participants through high schools and following them postgraduation as well as personalizing content to meet the specific interests of individual patients [74]. These strategies may allow for increased follow-up time and address issues related to intervention reach and effectiveness.

Racial and Ethnic Minority Smokers

Behavioral smoking cessation interventions have been shown to be effective across different racial and ethnic minorities [75]; however, treatments should be modified or tailored for the ethnic or racial population which will be used whenever possible [11]. Understanding smoking characteristics of the population is important when developing interventions for the community. Behavioral interventions alone may be more appropriate for Hispanic smokers as they consume fewer cigarettes than non-Hispanic whites [76,77] and are less likely to choose cessation aids when quit attempts are made [78]. However, given the significant heterogeneity within the nationalities in the United States, researchers should address the challenges of message framing and asking the appropriate questions for the target group [79]. In the United States, approximately 36% of Alaskan Natives and American Indians report smoking compared to about 23% of nonindigenous population [7]. Research indicates that the needs of this group are much greater given challenges including access to resources and acceptance of smoking in families and communities [80,81]. Finally, smoking in the African American community remains a major contributor to negative health consequences. Efforts to increase African Americans' participation in clinical research may aid in the development of culturally acceptable and efficacious interventions [79]. Interventions that aim to address the barriers of racial and ethnic minorities will allow researchers to develop treatments that can meet each group's specific needs.

Pregnant Smokers

Behavioral support is the most widely used smoking cessation intervention for pregnant smokers. Providing behavioral support for cessation during pregnancy increases rates of cessation by up to 6% [82]. In a review of behavior smoking cessation interventions for pregnant smokers, the authors concluded that smoking cessation programs in pregnancy are effective both in reducing the proportion of women who continue to smoke in late pregnancy and in reducing low birth weight and preterm birth [83]. Recent reviews concur that evidence regarding smoking cessation interventions are effective; few studies examine the long-term efficacy of these interventions in preventing relapse [84,85]. Approximately 75% of women who quit smoking due to pregnancy (women who quit smoking prior to becoming pregnant or during pregnancy) return to smoking by 6 months postpartum [86]. This highlights the need for continued development of interventions that address factors associated with postpartum relapse (weight concern, stress, negative affect) to increase cessation maintenance [87].

Mentally Ill Smokers

Cigarette smoking among individuals with mental illness (e.g., depression, schizophrenia) is more common than in the general population, and this can be attributed to complex neurobiological, psychological, and pharmacotherapeutic

mechanisms [88,89]. Current clinical guidelines recommend that smokers with mental health problems should be treated with the same smoking cessation strategies as those used for the general population, even though most of the research on cessation has been conducted in the general population and not in smokers with psychiatric comorbidities. Although the health risks of smoking are the same among those with mental illness, nicotine may have certain beneficial effects across a range of mental health domains, including improved concentration and cognition, relief of stress and depressive affect, and enhanced pleasurable sensations [88]. As a result, smoking cessation programs for this population should carefully consider the dynamic relationships among nicotine dependence, nicotine withdrawal symptoms, and mental illness. Current evidence suggests that flexible and individualized treatment programs (e.g., smoking reduction) may be the most successful; however, larger randomized controlled trials are needed to confirm these initial findings [90,91].

OTHER BEHAVIORAL APPROACHES

Exercise

The U.S. Department of Health and Human Services currently promotes using exercise as an aid for quitting smoking [11], and a wealth of clinical trial and acute laboratory-based research has examined the use of exercise as an adjunct to treatment. Overall, it appears that exercise is helpful for managing smoking cessation because it can reduce nicotine cravings and many of the withdrawal symptoms that often accompany quitting, such as negative affect and weight gain [92,93]. To date, however, the majority of studies conducted have only focused on females and light- or moderate-intensity aerobic exercise [93]. More recent research has begun to examine the benefits of other types of exercise such as resistance training (i.e., weight lifting) and yoga, and has included males [93–95]. Going forward, more research, with larger sample sizes, sufficiently intense interventions, equal contact control conditions, and measures of exercise adherence and change in physical activity in both exercise and comparison groups, is needed [93].

Abrupt Quitting and Gradual Reduction

The traditional behavioral method used to quit smoking is to smoke as normal until a predetermined "quit day" and then abruptly stop using all cigarettes. An alternative approach beginning to gain support is to gradually reduce the number of cigarettes smoked prior to quitting completely [96,97]. The value of this approach is somewhat controversial because there is concern that short-term decreases in smoking will not be maintained and that future quit attempts and motivation to quit will ultimately be undermined [96]. However, recent research shows that smokers using the reduction method have been able to maintain abstinence [98], and this technique may be more attractive to smokers less motivated to quit [96,99,100]. When comparing the effects of abrupt quitting versus gradual reduction, studies have found no difference in quit rates, and these effects held whether or not behavioral support, self-help materials, or NTR was used [98]. Although more studies are needed in this area, the most current research suggests that smokers should be given a choice of quitting methods, either reducing smoking before quitting or abruptly quitting [96,98].

SUMMARY AND CONCLUSIONS

Worldwide, there is an urgent need to reduce cigarette smoking. This chapter has described a range of approaches and strategies that have shown promise for changing smoking behavior in various settings and across several population. Overall, targeted behavioral interventions that build on smokers' current needs and skills are the most effective. Smokers should be matched with a cessation program based on their motivational level and previous experience with quitting. This includes strategies ranging from low intensity (brief advice) to high intensity (medication with individual counseling). Given the clear role that cultural and socioeconomic factors play in smoking status, future cessation programs need to focus on the social and contextual issues that support cigarette smoking. Ideally, smoking cessation programs will be regularly incorporated into existing community-based organizations, increasing the likelihood that these strategies will be disseminated to, and effectively used by, the population with the highest level of smoking prevalence and greatest need for help.

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20 Behavioral Approaches to Enhancing Weight Loss and Maintenance

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CONTENTS

Behavioral Strategies for Weight Loss 255
Self-Monitoring 256
Stimulus Control 257
Goal Setting, Contingency Contracting, and Reinforcement 257
Cognitive Restructuring 258
Social Support 258
Use of eHealth Technologies to Change Weight Loss Behaviors 259
Weight Maintenance Strategies 259
Maintenance Groups 260
Strategies Used by Successful Maintainers 260
Physical Activity Level 260
Cognitive Restructuring Strategies 261
Stress Management 261
Efforts to Match Treatment to a Particular Individual 262
Summary 262
References 262

The prevalence of obesity in this country has increased at an alarming rate, creating a major public health concern. The most recent National Health and Nutrition Examination Survey (NHANES) data indicate that more than two-thirds of U.S. adults are considered either obese or overweight [1]. Indeed, one-third of Americans (32.2% of men and 35.5% of women) are considered obese, defined as a body mass index of 30 or greater. The excess body fat associated with overweight and obesity is associated with a host of adverse outcomes. For example, obesity is an independent risk factor for cardiovascular disease, negatively affects cardiac function, and increases the risk factors for heart disease such as type 2 diabetes mellitus, dyslipidemia, pulmonary disease, and hypertension [2]. The entrenchment of the obesity epidemic constitutes a significant public health issue, with dramatic state-by-state increases in obesity documented over the past 20 years (see data from the Centers for Disease Control documenting these changes; [3]). This resulting pattern of increasing prevalence of obesity has led to tremendous costs to our health care system, and if it continues, "total health care costs attributable to obesity could reach $861 to $957 billion by 2030, which would account for 16%–18% of U.S. health expenditures" [4].

The factors that contribute to the prevalence of obesity in our society (a bountiful supply of inexpensive and highly appealing food, less reliance on manual labor at home and work, and sedentary leisure activities) appear rooted in our society, thus obesity levels are likely to remain at epidemic levels. Weight loss, even as modest as 5% of initial weight, can improve many of the obesity-related risk factors for heart disease [5]. Thus, effective intervention strategies designed to reduce body weight have never been more important.

BEHAVIORAL STRATEGIES FOR WEIGHT LOSS

Behavior modification approaches to obesity have been applied and researched for more than 40 years. Consisting of a set of approaches drawn from the principles of social learning theory, behavioral modification emphasizes alteration of eating and activity habits by manipulation of eating-related environmental cues. It postulates that maladaptive behaviors are learned through classical conditioning, instrumental conditioning, or modeling, and emphasizes (1) the contribution of environmental factors that precede behavior (antecedents), through intervention strategies such as stimulus control, as well as (2) the consequences of eating and exercise behaviors, through intervention tactics such as contingency management and incentives [6]. Individuals who successfully utilize these strategies often reduce their initial body weight by 8%–10% within 4–6 months of treatment [7]. It should be noted that behavior modification is currently the most widely used formal treatment for those with mild to moderate obesity and

has led to improvements in the magnitude and stability of weight loss maintenance [8]. Even with the advent of other medical or dietary treatments for obesity, including various low- and very-low-calorie diets, pharmacotherapy, or surgical approaches, the majority of these are commonly implemented in combination with behavioral approaches, thus improving the effectiveness of these interventions for weight loss success [9–11].

The purpose of this chapter is to review several key behavioral approaches to weight loss and maintenance. For each approach, we describe how the intervention was developed; that is, we present the behavioral principles that guided its conceptualization, describe how the strategy is utilized, and review research on its effectiveness. It should be noted that most of the research examining the effectiveness of these strategies for weight loss has focused on altering eating habits, rather than exercise behaviors. Exercise by itself is not a particularly effective weight loss strategy with typical weight losses less than 3% of initial body weight [12]. However, it is clear that greater weight loss occurs when weight loss treatment includes both dietary and exercise components.

SELF-MONITORING

Self-monitoring, defined as the systematic observation and recording of one's own specific target behaviors [13], is a critical component of any behavioral treatment for obesity [14]. Self-monitoring for weight management most often focuses on dietary intake, but is also used to observe physical activity patterns, and changes in body weight. Through daily recording of dietary intake, and the circumstances under which eating occurs, critical information is obtained that allows the health care provider to tailor more accurate, specific intervention strategies [8,15]. Additionally, self-monitoring not only has been found useful in both assessment and treatment phases of weight management, but several studies have documented spontaneous reduction in caloric intake upon initiation of self-monitoring, presumably due to the increased awareness of food intake [16,17]. Studies consistently show that individuals who self-monitor eating and exercise behaviors more consistency and completely (e.g., all food consumed, time of eating, quantity of food eaten, or grams of fat consumed) have the greatest weight loss [18,19]. Sperduto et al. [20] found that behavioral weight loss groups that incorporated self-monitoring experienced greater weight reduction, as well as better attendance, than control groups not monitoring their eating and activity levels. Burke et al. recently published a systematic literature review on self-monitoring of food intake, physical activity, and body weight in behavioral weight loss studies [21]. They concluded that there is a consistent finding between adherence to self-monitoring and greater weight loss. While the studies reviewed covered a wide array of self-monitoring methods, the paper diary was used most often. Adherence to self-monitoring was reported most frequently as the number of diaries completed. The authors noted that the most significant limitations of the research in this area are the reliance on self-report for measuring self-monitoring and a lack of diversity in the samples [21]. The use of technological devices, such as smartphone applications, to aid in self-monitoring has improved the convenience of self-monitoring and perhaps the reliability of data gathered in real time. Whether this leads to improved weight loss outcomes remains unclear.

While most research on self-monitoring and weight loss has examined the monitoring of food intake or the monitoring of food intake with physical activity, there is some evidence to suggest that monitoring exercise alone increases physical activity levels and can result in modest weight loss even without a dietary intervention. In a study conducted by Carels et al., participants recorded daily the type and duration of their physical activity. Individuals who were the most consistent monitors of physical activity (turned in the most exercise diaries) exercised more often, experienced fewer difficulties with exercise, and achieved significantly greater weight loss [22]. In a review of the literature examining the effectiveness of pedometers, Bravata et al. found that using a pedometer increased physical activity by 27% and reduced BMI by 0.38 [23]. A recent meta-analysis of pedometer-based walking studies without a dietary intervention found that pedometer usage resulted in an average weight loss of about 0.05 kg/week and that longer interventions were associated with greater weight change [24]. Consistent with this, Polzien et al. [25] found that continuous use of an energy expenditure armband body monitor (Sensewear Pro Armband; Bodymedia, Pittsburgh, PA) during a 12 week behavioral weight control program led to a slightly better weight loss than either standard behavioral weight loss or using the armband body monitor only intermittently. Given that pedometers are quite inexpensive, easy to use, and lead to increased physical activity and weight loss (albeit modest), pedometer usage combined with self-monitoring is a useful tool for the weight loss interventionist.

Frequency of self-monitoring of body weight has recently been called into question. Previously, weekly weigh-ins were widely held to be most effective for optimal weight loss, providing weekly feedback on weight loss success, while not allowing success to be entirely defined by the number on a scale. However, this assumption has been challenged recently, given the argument that more frequent self-monitoring of body weight serves to increase awareness of weight and its relation to recent behaviors engaged in (e.g., food intake and lifestyle activity). Recent research suggests that more frequent weighing (daily) is associated with greater weight loss and less frequent weighing is associated with weight gain [21]. For example, Butryn et al. [26] investigated self-weighing and weight loss maintenance in individuals who had successfully maintained a weight loss, and found that more frequent weighing (once per day) was associated with lower BMI. Weight gain at 1 year follow-up was significantly greater for participants whose self-weighing frequency decreased compared with those whose frequency increased or remained the same. Consistent daily self-weighing may help individuals maintain their weight loss by alerting them to small increases in body weight so that they can

make the appropriate adjustments in their behaviors to prevent additional weight gain. Nevertheless, among those few individuals who weigh themselves multiple times a day, it is our clinical impression that this frequency may become anxiety provoking and may lead to weight regain. In sum, these findings suggest that daily self-weighing should be stressed in clinical practice.

Research confirms the need for consistent self-monitoring in behavioral weight reduction programs, not only to produce benefits such as increased awareness of eating behaviors, physical activity patterns, and greater weight loss, but also to prevent failure in self-awareness and self-regulation [19,27]. Although there is no doubt that self-monitoring is an effective strategy, adherence can be a problem. Research is needed to uncover effective strategies for maintaining this self-monitoring. One strategy may be to reduce the level of detail required for the self-monitoring record as participants may find detailed self-monitoring to be too time-consuming to maintain over the long run. Helsel et al. found that transitioning to a simplified approach to self-monitoring did not negatively affect short-term weight loss in overweight adults [28]. Advances in technology can also offer suggestions that may ease the burden of dietary self-monitoring. For example, a study by Burak and King compared traditional paper diaries to digital photos and found that the individuals using photos to record intake were more successful at losing weight [29]. Given that so many cell phones are equipped with cameras, taking a photo of the food consumed may be an easier and more accurate way of recording intake than writing in a paper diary. Yon et al. compared traditional paper diaries to personal digital assistants (PDA) for dietary self-monitoring in overweight adults enrolled in a behavioral weight control program for overweight adults [30]. This study found no significant differences in weight loss or dietary self-monitoring. Both methods were effective at producing weight loss suggesting that matching individuals to a mode of self-monitoring that is fitting to their lifestyle and skills may lead to greater adherence. In summary, overweight individuals should be encouraged to self-monitor their food intake and physical activity using the mode (paper diary, photos, PDA, pedometer, smartphone) they find most acceptable and to weigh themselves daily.

STIMULUS CONTROL

Stimulus control is a term used to describe a set of procedures that seek to alter the antecedent stimuli that control behavior [31]. Stimulus control applied to weight management is directed toward modifying factors that serve as cues for inappropriate eating [32] or physical inactivity. Cues are often environmental (e.g., driving by a favorite fast food restaurant on the way home from work), but can be derived from internal factors as well, including cognitive (e.g., conveniently placed reminders to exercise) or physiological (e.g., cravings to eat when under stress) cues [33]. Indeed, obese individuals are more likely to be distracted by food-related cues than are normal weight individuals or those who have lost and maintained their weight [34]. Consistent with this, research utilizing functional brain imaging has shown overweight to be related to a hyperresponsivity of dopamine-based reward circuitry in the brain and a greater attentional bias to food cues among adolescents, leading to an increased risk for weight gain [35]. Targeting and altering an individual's triggers for eating, as well as the consequences of eating, remain integral components of most behavioral weight loss programs for adults, as well as for children [8,32,36].

Stimulus control strategies may be divided into several categories: limiting the times and places associated with eating, reducing exposure to food by storing it out of sight, limiting activities associated with eating, and reducing the purchase of problematic foods, thereby breaking "automatic" eating responses [8,16,37]. In one study [38], participants were randomly assigned to one of several behavioral interventions. Importantly, the stimulus control strategies taught—and used by participants (specifically, eating in one place only, shopping from a list, storing food out of sight, and deciding ahead what to eat)—were the only variables that predicted weight loss. Additionally, when combined with positive eating behaviors, such as making healthy food choices and limiting portion sizes, stimulus control strategies were the only factors that predicted weight loss and successful maintenance. Stimulus control strategies incorporated within standard behavioral weight loss treatments have also been shown to facilitate weight loss [39]. In a brief, 8 week weight loss study, those who received the active intervention, consisting of a "Ten Top Tips" brochure of 10 stimulus control strategies for reducing calorie consumption, promoting healthy routines, and increasing self-monitoring, were more likely to have lost 5% or more of their body weight than those in the no-treatment control condition [40]. By encouraging basic changes in these daily behaviors, new healthier behaviors may be learned and substituted for previously entrenched, unhealthy behavior chains.

GOAL SETTING, CONTINGENCY CONTRACTING, AND REINFORCEMENT

The process of setting small, realistic goals allows the complex task of losing weight to be broken down into meaningful, simple steps that are achievable [33]. Contingency contracting builds upon the notion of goal setting, asking an individual to identify the target behavior needed to be changed, the consequences for meeting—and not meeting—the target behavior goal, the time frame for completion of goals, and the proposed reinforcement for achieving the goal. Based upon the learning principle of shaping [41], goal setting and contingency management can be useful and powerful tools in delineating specific target behaviors for change, as well as establishing criteria for success and consequences for both desirable and undesirable outcomes [42,43]. Weight loss programs incorporating behavioral contracting have resulted in greater weight loss and lower attrition rates than programs not incorporating these elements [42,44]. Inherent in the use of contingency management are the processes of self-monitoring, self-evaluation, and reward for goals obtained.

Several methods of direct reinforcement of weight loss have been investigated in the literature, including monetary contracts for weight loss, dietary compliance, or physical activity; refundable deposit contracts; or lottery incentive programs. Early research by Mahoney [14] investigated the contribution of self-reward for short-term weight loss, comparing treatment conditions of self-reward for weight loss, self-reward for habit improvement, self-monitoring without specific instruction in self-reward, and a delayed treatment control group. Results suggested that when self-reward, in the form of a refundable deposit, was added to the process of self-monitoring and self-evaluation, greater weight loss was obtained.

More recently, there is mixed support for the use of economic incentives, in the form of deposit contracts or lottery incentive programs, in producing significant short-term weight loss, with some studies yielding significantly improved weight losses in those receiving economic incentives [45,46], and other studies finding incentives yield no differences in weight loss program enrollment or weight loss [47]. Interestingly, one study investigating a behavioral intervention with direct reinforcement (monetary compensation) as compared with a behavioral intervention combined with free prepackaged, portion-controlled meals found that adding this food provision, but not the monetary compensation, was associated with significantly improved weight loss, as well as improved treatment attendance and quality of diet [6]. The authors speculate that, in addition to the economic incentive of free meals being offered, the packaging of food and portion-controlled meals may have also significantly affected antecedent eating cues. Similarly, Rock et al. found that those receiving a structured weight loss program that included free prepared meals lost significantly more weight than those assigned to a usual care group (two visits with a study dietician), with these weight losses largely maintained through 2 year follow-up [48].

At the present time, there is great variation in the types of direct reinforcement incentive programs being utilized in behavioral weight management programs, as well as variability in the behaviors targeted for change. While results are mixed, it is clear that contingency management and the role of direct reinforcement will continue to be explored for their effectiveness in improving weight loss outcomes. Most studies of direct reinforcement have included incentives within the active treatment phase (average 12–20 weeks), although have yet to explore the longer-term use of economic incentives. This research may have significant implications for managed health care programs in the future.

COGNITIVE RESTRUCTURING

Cognitive restructuring techniques focus on changing the errors in thinking that contribute to maladaptive, unhealthy behaviors [49]. Behavioral treatment programs for obesity have long incorporated cognitive strategies for changing the maladaptive thought processes that are likely to hinder weight loss success [8,50,51]. Based upon Mahoney and Mahoney's [52] early work describing maladaptive cognitions frequently experienced by dieters, common irrational beliefs are identified and modified in order to improve success at weight loss and long-term maintenance. Common irrational beliefs held by overweight individuals include: self-doubt over weight loss ("I've never been able to do it, why would I succeed now?"), establishment of unrealistic goals ("I'll never overeat again"), and punitive self-statements ("I'm a failure because I can't lose weight"). Individuals that hold more of these maladaptive cognitions and disparaging views of self are more likely to experience greater emotional distress and unhealthy eating patterns, which contributes to difficulty losing weight and maintaining weight loss [16,52,53].

Research suggests that cognitive factors play a critical role in weight regulation [54], with alteration of maladaptive cognitions particularly important in developing greater control overeating, preventing relapse, and thus, improving long-term success. Although cognitive distortions may be commonly experienced among overweight and obese individuals, research supporting the utility-specific cognitive restructuring techniques in weight management interventions has been mixed. In a comparison of cognitive-behavioral treatment (CBT) for obesity, behavioral therapy, and minimally guided self-help, Cooper et al. found that the CBT and behavior therapy conditions resulted in average weight losses of 10% of initial body weight [55]. However, at 3 year follow-up, the large majority of participants in all three conditions had regained nearly all of the weight lost, leading the authors to suggest that the long-term management of obesity is resistant to psychological methods of treatment [55]. However, Werrij et al. found that the addition of cognitive therapy to a group dietary intervention led to a greater weight loss at end of 10 week intervention, which was sustained at 1 year follow-up [56]. Although research to date highlights the importance of cognitive factors in obesity and weight control, identification of specific, clinically effective cognitive techniques is needed. Focusing on development of appropriate cognitive outcome measures that shed light on the specific cognitive processes involved in weight loss treatment may be worthwhile.

SOCIAL SUPPORT

Social support is commonly included in behavioral weight management protocols in one of three capacities: (1) teaching skills to participants in order to elicit and further enhance their social support networks, (2) actively involving significant family members in the weight loss process with the participant, or (3) eliciting social support as part of the group process. While there are many instances in the scientific literature of increased social support leading to improved weight loss and maintenance [57], questions remain about the amount of support needed in order to maximize success, the type of support most effective at eliciting weight loss, and whether supports also need to lose weight in order to be an effective source of support. While it has been well documented that having social support is associated with

successful weight loss, how to enhance an individual's support for healthy living is not well understood.

The presence of a cooperative spouse, or family member, does not guarantee improved weight loss [58]. Brownell et al. [59] found that participants whose spouses attended weight loss sessions and were trained in the specific techniques of modeling, self-monitoring, and reinforcement lost significantly more weight than either participants with a cooperative spouse who did not attend sessions or participants with a noncooperative spouse who refused to participate in sessions. These results are consistent with a study by Gorin et al., which found that participants who had at least one successful partner (defined as at least 10% weight loss) lost significantly more weight at all follow-up time points through 18 months, as compared with those with no successful partners or those without participating partners [60]. As would be expected, weight loss behaviors of participants and their partners were highly related, such as completion of food diaries. Thus, support partners appear to be beneficial in obesity treatment when the partners themselves lose weight, perhaps due to increased instrumental support offered during the process of weight loss.

Further research is needed to discover which types of social support are most helpful for successful weight loss. Recent research has explored the role of autonomy support and autonomous self-regulation on short-term weight loss [61], which suggests that receiving autonomy support (e.g., "My family and friends listened to how I would like to do things regarding my weight") in the naturally existing social environment of family and friends is more effective at yielding weight loss, as opposed to well-meaning, directive support. Qualitative interviews examining the social support needs of overweight/obese African American women are consistent with the earlier text, with women interested in receiving support through co-participation in exercise, using positive reinforcement and incentives, and avoiding criticism [62].

With the increased use of technology-driven weight loss interventions, the issue of how social support fits into these interventions is raised. A review of the literature on technology-based weight loss interventions finds that social support remains a critical aspect of successful Internet-delivered weight loss programs [63]. Indeed, use of online supportive counseling, whether via chat rooms or e-coaches, may be an alternative to face-to-face meetings [64]. A recent study conducted by Gabriele et al. [65] evaluated three different forms of support included in a 12 week Internet-delivered weight loss intervention: minimal e-coach support (involving a weekly lesson e-mail and no individualized support), nondirective e-coach support (individualized feedback, with goals selected by participant), and directive e-coach support (specific advice on weight loss provided, with goals and topics of discussion chosen by e-coach). Females in the directive support condition lost more weight than females in the nondirective and minimal support conditions, suggesting that a directive support approach for weight loss may be particularly useful for those participants who are motivated to lose weight, but perhaps feel they lack the skills necessary to overcome obstacles. Research such as this illustrates how the various dimensions of social support (e.g., directive and nondirective) can be manipulated in order to explore how to best incorporate support into a weight loss program for a given individual, whether delivered face-to-face or over the Internet.

USE OF eHEALTH TECHNOLOGIES TO CHANGE WEIGHT LOSS BEHAVIORS

The past decade has seen tremendous growth in the area of eHealth technology, defined as "the use of emerging information and communication technology, especially the internet, to improve or enable health and health care" [66]. While initial eHealth technology facilitated tailoring of intervention print materials, the current generation of eHealth technology, such as smartphones, digital cameras, personal data assistants (PDA), and tablets, continues to expand what is possible in receiving timely, tailored psych-educational information; reporting on physical activity and dietary behavior goals and tracking daily progress; and providing and receiving individualized social support via synchronous chat rooms or e-coaches [67]. Smartphones, now carried by over 80% of U.S. adults, have become pervasive in our society [68]. There are countless smartphone software applications (apps) available for calorie counting, meal planning, exercise tracking, calorie expenditure, etc. These include such apps as *myfitnesspal.com*, which allows a person to track their eating and exercise behaviors on their smartphone and automatically synchronize this information to the web, or *mealsnap.com*, which allows a person to use their smartphone to take a picture of any food or drink, with the system automatically identifying and providing estimated calories. Indeed, it is estimated that nearly one-third of the 1.4 billion smartphone users in 2015 will be using mobile health care apps [69]. Needless to say, there is a growing literature on the use of smartphones in improving health behaviors [70]. Indeed, the concept of ecological momentary assessment (EMA), or the use of personal computing devices to enhance accurate reporting of real-time, self-reported data, can now also be applied to an ecological momentary intervention paradigm [67]. Future empirical studies and clinical applications will need to consider how to best marry the convenience of eHealth technologies with further improving the quality and outcomes of the interventions provided.

WEIGHT MAINTENANCE STRATEGIES

It has been well documented that recidivism following weight loss is a serious problem [71]. Some estimate that most patients regain all of their weight within 3–5 years [72]. Although numerous studies have documented high relapse rates for weight control, few investigations have identified effective maintenance strategies. This section reviews the relevant research on behavioral strategies for weight maintenance.

MAINTENANCE GROUPS

In the 1980s, Perri et al. established the foundation of current knowledge of effective maintenance strategies. In a series of studies [73–75], the effects of professional contact, telephone contact, relapse prevention training, social support, exercise, and problem-solving skills were investigated. Perri et al. [75] examined 26 men and 97 women who were 20%–100% overweight and who participated in a 20 week group behavior therapy weight management program. During the 20 week program, participants were taught numerous behavioral strategies: self-monitoring, stimulus control, self-reinforcement, cognitive restructuring, and slowing the rate of eating. After 20 weeks, subjects were randomly assigned to follow-up only or to four different 6 month biweekly maintenance programs:

1. A posttreatment contact condition that included weigh-ins, self-monitoring, and therapist-led problem solving of difficulties in maintaining habit changes in eating and exercise behavior. The problem-solving training included four steps: problem identification, brainstorming, decision making, and solution implementation and verification.
2. Posttreatment contact and a social influence program. The social influence program included monetary group contingencies for adherence, participation in lectures, and instructions in peer telephone contact.
3. A posttreatment contact and an aerobic exercise program that combined a new set of exercise goals and therapist-led exercise sessions.
4. A posttreatment contact and a social influence and an aerobic exercise program.

Participation in these behavioral maintenance groups proved highly beneficial. At the 18 month follow-up, the participants in the four posttreatment programs maintained 82.7% of their weight loss compared to an average sustained weight loss of only 33.3% for the participants in the no-posttreatment contact condition. Participants in the combined maintenance condition maintained 99% of their weight loss, suggesting that the combination of high-frequency exercise, coupled with support and problem solving, holds great promise in improving the long-term management of obesity. With increase use of telemedicine, these results have been applied to a telephone-based maintenance program. The researchers found that extended care, delivered either by telephone or in face-to-face sessions, was equally effective in preventing weight regain [76]. Since the Internet has the potential to reach a greater percent of the population than face-to-face clinic visits, this technology has recently been examined. However, investigators found that monthly personal contact was more beneficial in maintaining weight loss compared to a web-based intervention [77]. Finally, in terms of maintenance innovations, motivational interviewing counseling techniques have been widely used in the addictions field for many years. Recent research has applied these techniques in a weight loss maintenance program, finding them to be as effective as an approach focused on weight loss skill building [78].

STRATEGIES USED BY SUCCESSFUL MAINTAINERS

In a national survey, researchers at the University of Pittsburgh School of Medicine [79] created a National Weight Control Registry (NWCR) of 629 women and 155 men who lost an average of 30 kg and had maintained a weight loss of at least 13.6 kg for 5 years. The researchers were interested in learning more about the participants' weight loss and weight maintenance strategies and about what types of behavioral approaches people used. Fifty-five percent of the sample used a formal weight loss program, and 45% lost weight on their own. Most of the individuals (89%) modified both their dietary intake and their physical activity level to lose weight. The three most commonly used strategies to change diet were to limit the intake of certain foods, limit the quantities of food, and count calories.

During their 5 years of maintenance, most individuals (92%) reported limiting their intake of certain foods. Many also reported relying on self-monitoring techniques for limiting quantities of foods (49%), restricting fat intake (38%), counting calories (36%), or counting fat grams (30%). Participants also reported using stimulus control techniques. They ate most of their meals at home where food choices are more restricted. Subjects reported engaging in a high level of physical activity, averaging an equivalent of walking 28 miles/week. Participants engaged in cycling, aerobics, walking, running, and hiking. Thus, these maintainers participated in the type of physical activity that is recommended for weight loss, but the amount of time they reported exercising is more than double what is typically recommended.

A great deal continues to be learned from participants in the ongoing NWCR. Nevertheless, it is possible that this group of highly successful weight loss maintainers may not be representative of all individuals who have worked to maintain their weight losses. Later, we outline some of the key characteristics of weight loss maintenance that are consistent across the majority of research conducted.

PHYSICAL ACTIVITY LEVEL

While self-monitoring is the cornerstone of successful weight loss, exercise is the key to maintenance. As discussed earlier, successful maintainers tend to engage in a high level of physical activity [79]. Kayman et al. [80] found that maintainers were far more likely than regainers to exercise at least three times per week for 30 min or more. Maintainers also engaged in more lifestyle activity than relapsers.

Since exercise clearly facilitates weight maintenance, research is now focused on how to facilitate the adoption and maintenance of an active lifestyle. One promising approach is home-based exercise programs. Researchers have found that instructing patients in home-based exercise rather than in

group-based exercise over a 12 month intervention facilitated weight maintenance at a 3 month follow-up [81]. According to the authors, the greater convenience and flexibility of home-based exercise probably contributed to higher exercise adherence. During months 7 through 12, subjects in the home-based condition completed 78% of their exercise sessions compared to 48% in the group condition. Interestingly, participants in the home-based conditions attended more weight loss group sessions and were more likely to complete food records. A subsequent 4 year weight loss study yielded similar results—physical activity level related to weight loss maintenance and maintainers attended more treatment sessions and reported more favorable food intake [82]. Thus, the investigators speculate that exercise adherence may promote adherence to other strategies such as group attendance and self-monitoring of eating behavior, both of which facilitate maintenance.

More recently, clinicians and investigators have been closely examining lifestyle activities. Sedentary behaviors, such as watching television, are associated with elevated risk for obesity and type 2 diabetes [83]. Others researchers have found that obese individuals sit 2 h longer per day compared to lean individuals, thus leading to a difference of about 350 kcal/day, which could contribute to a weight gain of over 10 kg/year [84]. These findings have led some practitioners to focus on increasing physical activity level, both aerobic and strength training, and on decreasing sedentary behaviors, such as screen time [85].

COGNITIVE RESTRUCTURING STRATEGIES

As in active weight loss efforts, cognitive restructuring strategies also appear important during the maintenance phase of weight loss. For example, it has been proposed that unrealistic weight loss expectations may contribute to relapse [86]. If individuals are disappointed in their ability to reach their goal weight or discouraged with their rate of weight loss, these negative cognitions and emotions may reduce motivation and/or trigger overeating episodes. Research examining outcome expectations reveals the importance of challenging unrealistic outcome expectations [87]. In a study of 60 obese women, participants were asked prior to weight loss to identify their goal weight and four other weights: "dream weight" ("a weight you would choose if you could weigh whatever you wanted"); "happy weight" ("this weight is not as ideal as the first one; it is a weight, however, that you would be happy to achieve"); "acceptable weight" ("a weight that you would not be particularly happy with, but one that you could accept, since it is less than your current weight"); and "disappointed weight" ("a weight that is less than your current weight, but one that you could not view as successful in any way; you would be disappointed if this were your final weight"). Participants' goal weight averaged a 32% reduction in body weight. Despite a 16 kg weight loss during a 48 week treatment program, only 9% of subjects achieved a "happy weight." Furthermore, although they reported achieving numerous positive physical and psychological effects of weight loss, 47% still had not yet even reached their "disappointed" weight. Cognitive strategies to promote the adoption of a reasonable weight goal need to be identified by future research.

More evidence for the importance of cognitive strategies during the maintenance phase is provided by a study conducted by Kayman et al. [80]. These investigators found that maintainers incorporated a new eating style but to avoid feelings of deprivation did not completely restrict their intake of problem foods. In contrast, regainers also dieted but did not permit themselves any of their favorite foods, and they viewed their weight loss foods as special foods, different from the foods their family would have and different from the foods they wanted. Thus, classifying foods as "good" and "bad" probably promoted dichotomous thinking and may have contributed to relapse.

Confidence and attributions of success are other important cognitions to address in maintenance treatment. A recent study examining the relation between method of weight loss (VLCD, commercial program, self-guided approach) and weight loss maintenance found that the individuals who had used a self-guided approach were the most successful at maintaining their weight loss, leading the authors to speculate that confidence in one's ability to lose weight may have affected the choice of weight loss method [88]. In other words, individuals who chose to lose weight without outside assistance may have greater confidence in their ability to lose weight than those who selected a very intensive treatment such as a VLCD. Additionally, individuals who lose weight on their own may be more likely to attribute their success to their own efforts rather than attribute their success to a weight loss program.

STRESS MANAGEMENT

Having a high stress level is associated with health problems and unhealthy behaviors. Adults with high stress are more likely to be overweight and sedentary and have low confidence [89]. Therefore, stress reduction strategies continue to be important as individuals move from the weight loss phase to the weight maintenance phase of weight control. Kayman et al. [80] found that regainers and maintainers reported experiencing stressful events at the same rate; however, the two groups differed in how they responded to stress. Maintainers used problem-solving skills or confrontive ways of coping with stress. In contrast, relapsers used emotion-focused or escape-avoidance strategies such as eating, sleeping, or just hoping the problem would go away. A basic component of most stress management interventions is training in problem-solving skills, in which individuals are taught to identify problems, generate solutions, evaluate solutions, implement a solution, and then evaluate the results. More recently stress reduction programs have incorporated yoga, tai chi, and mediation, and how these interventions may impact weight maintenance should be examined [90]. Research continues to identify that problem-solving skills are important for weight loss outcomes [91]. Thus stress management strategies, in particular problem-solving skills, may be important for weight maintenance.

Social support has also been identified as a weight maintenance facilitator [59]. A support system can help one to solve problems, offer emotional support, or be available for practical assistance. Maintainers identify more support systems [92] and are more likely than regainers to seek support when dealing with stress [80]. This finding was recently replicated in a study of 1869 overweight and obese younger adults that determined increased emotional support to be a key predictor of weight loss maintenance [93].

In summary, continued contact with a professional, consistent physical activity, social support, and maintaining dietary intake changes all facilitate weight maintenance. Behavioral strategies that have garnered support for their role in weight maintenance include self-monitoring, stress management and problem solving, stimulus control, and cognitive restructuring. Although it is clear that there is a relationship between physical activity level and weight maintenance, we need to discover more effective intervention strategies for adoption of a more active lifestyle. Preparing participants and practitioners for adopting a continuous care model of obesity should also be beneficial.

EFFORTS TO MATCH TREATMENT TO A PARTICULAR INDIVIDUAL

There remains movement within the field of obesity treatment to consider individual characteristics when recommending treatments. Thus, rather than using a single approach with all obese individuals, effort is made to tailor or match treatments to individuals. For example, individuals may be matched to treatment based upon their percentage overweight. Treatment recommendations are determined by their likely effectiveness and a risk-benefit analysis [94]. Clark et al. [95] found greater attrition from a low-intensity weight loss program among individuals with higher levels of obesity. Factors other than level of obesity are also considered important when making treatment decisions. Schwartz et al. [96] surveyed experts in weight loss treatment to identify client characteristics important for treatment matching. Five factors were identified by a majority of the experts as important when making treatment decisions: weight, weight loss history, medical condition, eating disorders, and psychiatric comorbidity. Additional matching characteristics worth considering include a history of being the victim of sexual trauma [97], in particular, being the victim of childhood sexual abuse [98], and a negative body image [99] since both of these factors have been shown to impact obesity treatment outcome. Intuitively, the idea of treatment matching makes sense; however, there has been very little empirical validation of treatment matching models. Future research is needed that examines the validity and utility of treatment matching models for obesity.

SUMMARY

It is clear that the United States is experiencing an obesity epidemic, with a critical need for the development of effective strategies for weight loss and maintenance. Fortunately, the research literature provides empirical support for the effectiveness of several behavioral approaches for weight management (see Table 20.1). There is clear support for the effectiveness of self-monitoring dietary intake, physical activity levels, and body weight. Advances in technology, such as smart phones and their applications, as well as use of pedometers and accelerometers, have made monitoring these behaviors simpler and more accurate. It is also important to target and alter triggers for eating. Goal setting and contingency management have proven to be valuable tools in improving monitoring and altering overeating triggers. Recent research suggests that meal provision may be a particularly effective incentive for weight loss. Cognitive factors play a critical role in weight management, with alteration of maladaptive cognitions particularly important in developing more control over eating, preventing relapse and, improving long-term success. Social support can also be beneficial, particularly when provided in an empathic versus critical manner. Consistently engaging in high levels of physical activity appears key to maintaining a weight loss. Further research is warranted that examines the adoption and maintenance of an active lifestyle in an obese population. Although self-control procedures are still an integral part of most weight management programs, the focus has begun to shift to a lifestyle modification approach that recognizes that in order to successfully lose weight, the obese individual needs to establish a new—and improved—lifestyle that supports the maintenance of a healthier and thinner physique [92,100].

TABLE 20.1
Weight Management Strategies

Weight Loss	Maintenance
Decrease caloric intake	Physical activity
Increase caloric expenditure	Low-fat diet
Self-monitoring	Coping skills
Weigh daily	Extended treatment
Stimulus control	Social support
Cognitive restructuring	Reasonable goal weight
Social support	Self-monitoring

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Part V

Women's Health

Pamela M. Peeke, MD, MPH, FACP

21 Women's Health
Challenges and Opportunities

Pamela M. Peeke, MD, MPH, FACP

There is a picture that frequently appears in PowerPoint presentations when gender differences are to be discussed. It's entitled "the gender-specific control panel." The top part of the panel shows a single on-and-off switch humorously depicting the stereotypic male view of life. Below, the panel is densely populated by countless, colorful knobs and switches reflecting the broad spectrum of influences over a woman's well-being. Despite the witty tongue in cheek pictorial, there is wisdom to be shared. In their comprehensive role as caregivers, women more often than not neglect their own self-care. Wading through the "knobs" of responsibilities, obligations, and deference to the welfare of others, women are prone to lose focus on their own health maintenance needs. However, even in the face of this age-old feminine challenge, the status of women's health care is changing for the better. Women can now access more credible information about the critical importance of health prevention. And they're feeling more free to discuss these issues with their medical provider. This includes establishing rituals of breast checks, monitoring bone mineral density, consuming a nutrient-rich diet of whole foods, and incorporating aerobic activities and strength training into daily life routines. This chapter will provide clinicians with the knowledge, tools, and tips to help them better communicate with and guide their female patients to optimal health and wellness.

With a projected doubling in the overall incidence of breast cancer by 2040, including an alarming rise in young women, there is an important need for prevention as well as treatment strategies. Beth Dupree outlines the epidemiology of breast cancer with particular focus on the history and controversy surrounding the role of hormonal replacement therapy (HRT). Clinicians will also enjoy an illuminating discussion of breast development through the hormonal milestones of a woman's life. Clarifying the roles of genetics and screening as it relates to breast cancer are kernel elements of this chapter. The protective effect of healthy lifestyle choices for both pre- and postmenopausal women is covered in depth, including the ability to prevent breast disease through positive behaviors beginning in youth. Acknowledging that 75%–80% of breast cancers occur in women with no family history, clinicians are tasked to help their patients decrease personal risk through healthy lifestyle behaviors.

Sobia Khan and Holly Thacker outline the medical as well as socioeconomic costs born by the diagnosis of osteoporosis. Worldwide osteoporosis affects over 75 million people, and causes more than 8.9 million fractures annually. The National Osteoporosis Foundation notes that currently over 10 million Americans carry the diagnosis of osteoporosis with another 34 million at risk, all occurring at a cost of $20 billion. With over half of all women over 50 years predicted to incur an osteoporosis-related fracture, the need for prevention is imperative. What is often overlooked is the level of serious disability associated with fractures, as well as life-threatening complications related to treatment and immobility. Of paramount importance is an understanding of the risk factors for bone loss and fracture, including age, genetics, lifestyle choices, menopausal status, prior incidence of a low trauma fracture, parental history of hip fracture, present tobacco smoking history, and long-term glucocorticoid use. In this chapter, clinicians will become familiar with the state of the art of screening for osteoporosis, noting that current evidence suggests that it is most effective in determining which postmenopausal women have low bone mineral density and how to prevent fractures in this population in particular. First detailing a host of therapeutic pharmacological options once a diagnosis of osteoporosis is confirmed, a strong case is then made for the incorporation of critical lifestyle elements including diet, vitamin D, and calcium supplementation as well as weight-bearing and strength training exercise. Clinicians will find the case studies useful models for their own daily decision making in patient care.

Inherent to any discussion about women's health is the issue of menopause. As close to 50 million women transition through this milestone stage of life, there are a constellation of challenges and endless questions about how to navigate the often stormy waters of hormonal fluctuations. Margery Gass provides the blueprint for comprehending the often complex physiology behind these endocrine fluxes, from causation to genetics. Clinicians are provided with a look into the psychosocial and cultural influences that shape a woman's perception of aging, beauty, and self-esteem during this watershed period. Menopause provides women a unique opportunity to stop and reassess their life goals and whether their current lifestyle habits support the achievement of these objectives. From weight control to sexual function, strategies are detailed to optimize quality of life from pre- to postmenopause. Clinicians are shown how to help a woman make the connection between her mental and physical fitness and how menopausal symptoms may manifest themselves. Complementary and alternative modalities are a constant source of inquiry

by women seeking options to traditional pharmacological modalities, to include nonhormonal prescription therapies such as selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors. However, the single most important discussion a woman will have with her physician is if and when HRT should be used and for how long. Since the tumult surrounding the early results from the Women's Health Initiative (WHI) trial, subsequent investigations have led to greater clarity about the actual benefits of HRT. When the WHI was first conceived, it was not yet known that the effects of estrogen therapy (ET) and the estrogen and progesterone theory (EPT) combination would vary so much by age. After comprehensive analysis of the WHI data, it became apparent that both ET and EPT are options that clinicians can recommend for most symptomatic younger postmenopausal but not older postmenopausal women. In this chapter, clinicians will understand that women today can and should have an open conversation with their physician about hormonal status and that many options are available to facilitate an optimal transition as they age.

In order to manage the constant incoming stresses and pressures in a woman's life while also striving to practice healthy lifestyle habits, it has become apparent that women need to master new life skills to achieve health and wellness in the face of these challenges. Witness then the emergence of credentialed professional health and wellness coaches providing the expert competency to help women achieve and sustain personal focus, responsibility, and motivation as they adapt and adjust to the dramas and traumas of daily life without resorting to self-destruction. In this chapter, Beth Frates and Margaret Moore present the case that although most women know the fundamental things they need to do to achieve mental and physical well-being, they're struggling with how to implement what appear to be simple strategies when they feel psychologically overwhelmed and technically disorganized. Social and behavioral scientists have developed a new approach—the psychology of healthy lifestyle—to guiding an individual through their daily personal and work-related mazes. Clinicians will learn how to empower their female patients with coaching competencies that help women learn how to become more mindful and focused, practice self-acceptance and self-efficacy, and maintain a positive inner dialogue of motivation. All clinicians will benefit from improved communication and coaching skills as they promote sustainable behavioral change leading to healthier lifestyle habits with their patients.

Shari Bassuk and JoAnn Manson provide clinicians with an overview of the epidemiological evidence on the relationship between physical activity and health outcomes in women. In doing so, they tease apart methodological challenges presented by the plethora of observational studies and lack of randomized clinical trials. That being said, there is convincing evidence of the significant impact of regular physical activity on morbidity and mortality. In this chapter, prospective studies are presented that show an inverse relationship between physical activity and all-cause mortality. As well, there is a dose–response relationship between women who exercise and their risk for coronary heart disease. Drawing upon data from the Nurses' Health Study, simply walking for 2.5 h/week was associated with a striking 25% risk reduction in type 2 diabetes. Similar disease risks are seen in a variety of cancers as well. Being more physically active and engaging in resistance training can strengthen bones, helping to reduce fracture occurrence, as well as prevent falls through improvements in flexibility, balance, and strength. Clinicians will appreciate the value of telling their female patients about the power of that 30 min walk every day to improve a woman's overall health status and maintain an active and vibrant life.

A discussion of body composition is a game-changer in the world of weight management. Pam Peeke describes why the prior reliance on body weight with no consideration of the quality of body components has led to consumer confusion and clinician frustration as both strive to achieve optimal physical fitness and health. Many women may share the same age, height, and weight, but their body composition will determine their ultimate physical fitness, shape, size, and disease risk. What begins as a description of the evolution of body composition throughout a woman's life span is followed by a discussion of the relationship between body fat and disease risk, and specifically the metabolic syndrome. Female sex steroid hormones affect body fat distribution and may regulate overall fat mass. Clinicians will learn about the various modalities for body composition measurement including accessible tools for use in routine clinical practice. The clinician will understand the importance of assessing body composition for purposes that include its use: (1) as a motivational tool, (2) in monitoring changes in body composition due to medical or age-related influences, (3) in identifying patients with increased disease risk, and (4) in evaluating the effectiveness of nutrition and exercise programs. In this chapter, the relationship between a woman's lifestyle habits and the status of her fat and lean body mass are presented so that clinicians may see the significant improvement in a woman's physical strength and independence along with a decrease in disease risk and disability. It is hoped that clinicians will monitor both body weight as well as composition as they recommend healthy lifestyle strategies.

22 Menopause

Margery Gass, MD, NCMP

CONTENTS

Introduction 271
Perimenopause 271
Primary Ovarian Insufficiency 272
Paradigms 274
Endocrinology and Physiology 275
Symptoms 276
Diagnosis 277
Interventions 278
Lifestyle Changes 278
Complementary and Alternative Medicine 281
Nonhormonal Medicines 281
Hormone Therapy 281
References 283

INTRODUCTION

Menopause is an important milestone in a woman's life. It heralds the end of her reproductive years. Naturally occurring menopause is characterized by amenorrhea and marked diminution of estrogen/progesterone production resulting from the depletion of viable follicles in the ovary. Clinically, it is officially diagnosed after 1 year of amenorrhea not due to other causes.

Menopause can be spontaneous or the result of an intervention. Spontaneous menopause usually occurs between ages 40 and 55 years, with an average age of 51 years. In a study that enrolled students at the University of Minnesota in the 1930s and followed them through menopause, the age range of the 393 cases of spontaneously occurring menopause was 41–59 years with a mean of 50.7 years.[1] The Massachusetts' Health Study reported the average age of menopause to be 51 years.[2] More recently, the Study of Women's Health Across the Nation (SWAN) reported a mean age of menopause of 51.4 years for a multiracial/multiethnic group of women in the United States.[3] The study also reported that smoking, lower education, and nonemployment were associated with an earlier menopause.[3] Women who smoke reach menopause 1–2 years earlier than their nonsmoking counterparts.[3–6] Japanese race/ethnicity was associated with a later menopause compared to other ethnic groups in the United States.

There is some concordance of age at menopause within families, but both genetics and environmental factors play a role in determining when menopause will occur. Candidate genes have been identified but further research is required to understand the interplay between genes and the environment.[7]

Many women experience a surgical menopause as the result of having both ovaries removed. Hysterectomy is the second most common surgical procedure in women in the United States. Below age 45 years, approximately one-third of women undergo bilateral oophorectomy at the time of hysterectomy. Between ages 45 and 54 years, ~75% of women have a concurrent bilateral oophorectomy (Figure 22.1).[8] Other medical interventions that can lead to iatrogenic menopause include chemotherapy and radiation treatments, both of which can deplete the pool of viable follicles in the ovaries.

Perimenopause

Perimenopause is a defined period around the time of menopause. It includes the year after the final menses plus a variable amount of time leading to the final menstrual period (FMP). The perimenopausal time before menopause is variable because there can be a large difference in the number of months or years women spend with irregular menses and transient menopausal symptoms. The perimenopause construct is important because it is typically the most symptomatic time for women.

Perimenopause is one of several stages of reproductive aging defined by the 2012 Stages of Reproductive Aging Workshop (STRAW).[9] Achieving a consensus on the stages of the reproductive years and menopause as seen in Figure 22.2 provided a basis for standardizing scientific research in addition to serving as a clinical guide.

Women who experience menopause before age 40 years as a result of bilateral oophorectomy, or as a result of irreparable damage to the ovaries from radiation or chemotherapy, are said to have a premature menopause. Until recently, all women who experienced menopause spontaneously prior to age 40 years were considered to have premature menopause or premature ovarian failure. However, these terms are misnomers for a subgroup of these women who are not completely and permanently

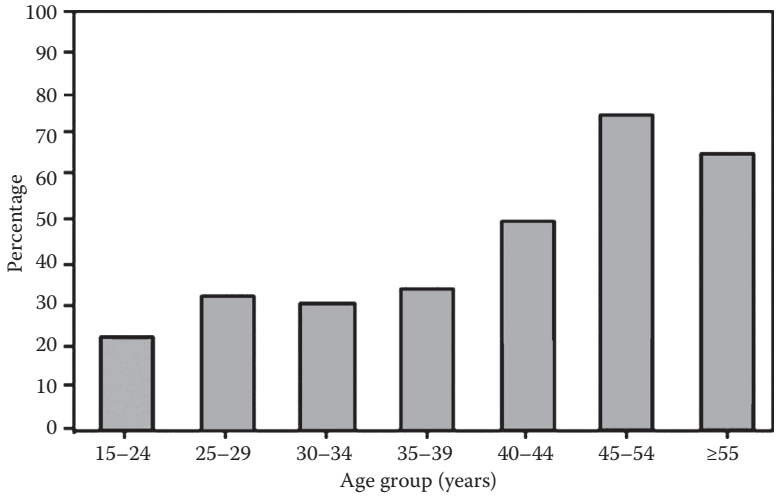


FIGURE 22.1 Percentage of hysterectomies with bilateral oophorectomy, by age group—United States, 1994–1999. (From Keshavarz, H. et al. *Morb. Mortal. Wkly Rep.* 51(SS05), 1–8, 2002.)

Menarche FMP (0)

Stage	−5	−4	−3b	−3a	−2	−1	+1a	+1b	+1c	+2
Terminology	Reproductive				Menopausal transition		Postmenopause			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*Variable*				*Variable*	1–3 years	2 years (1+1)		3–6 years	*Remaining lifespan*
Principal criteria										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/length	*Variable length* Persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
Supportive criteria										
Endocrine FSH AMH Inhibin B			Normal Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable* Low Low		Stabilizes Very low Very low	
Antral Follicle Count 2–10 mm			Low	Low	Low	Low	Very low		Very low	
Descriptive characteristics										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* Symptoms of urogenital atrophy

*Blood draw on cycle days 2–5 ↑=elevated.
**Approximate expected level based on assays using current pituitary standard.[67–69]

FIGURE 22.2 Stages of reproductive aging. (From Harlow, S.D. et al., *Menopause*, 19, 387, 2012. With permission.)

menopausal. The proposed new terminology for women in this category is primary ovarian insufficiency (POI).[10,11]

Primary Ovarian Insufficiency

POI, also descriptively called hypergonadotropic amenorrhea, is a poorly understood condition that affects <1% of women. It is characterized by loss of menses for ≥4 months and a follicle-stimulating hormone (FSH) level in the menopausal range on two separate occasions at least 1 month apart.[10] The condition is distinguished from premature menopause by intermittent ovarian function. The variable estrogen levels can be borderline menopausal and may keep many of these women from having typical menopausal symptoms. From 5% to 10% of women with the diagnosis have conceived and delivered a child.[12–14]

Most women who receive this diagnosis are stunned to learn they have entered a menopause-like state, and they often benefit from social and psychological support. The term "primary ovarian insufficiency" is a more accurate description of the condition, and affected women seem to prefer it to "premature menopause."

Causes of POI have not been completely delineated. Two broad mechanistic categories are follicle dysfunction and follicle depletion. In the former, some follicles still remain in the ovaries, but an aberrant process prevents them from functioning normally. Follicle depletion can result from an inadequate original pool of follicles, accelerated depletion/apoptosis of a normal pool of follicles, or damage to the follicles by a toxin or an autoimmune condition. A cause is identified in ~10% of cases.[12] Table 22.1 gives a list of conditions that have been associated with POI.

TABLE 22.1
Causes of Premature Ovarian Failure/Primary Ovarian Insufficiency[a]

I. X Chromosomal causes
  A. Structural alterations or mutations in or absence of an X chromosome
    1. With the stigmata of Turner syndrome (45,X or mosaic)
    2. Without the stigmata of Turner syndrome
      a. Mutations in premature ovarian failure 1 (Xq26-q28)
      b. Mutations in premature ovarian failure 1 in association with fragile X premutation (Xq27.3)
      c. Mutations in premature ovarian failure 2A (Xq22)
      d. Mutations in premature ovarian failure 2B (Xq21)
      e. Mutations in premature ovarian failure 4 in association with mutations in bone morphogenetic protein 15 (Xp11.2)
  B. Trisomy X with or without mosaicism
II. Mutations associated with a 46,XY karyotype
  A. Mutations in Xp22.11-p21.2 (Swyer syndrome)
  B. Mutations in 5 cen
III. Autosomal causes
  A. Mutations involving enzymes important for reproduction
    1. Galactosemia (galactose-1-phosphate uridyltransferase deficiency) (9p13)
    2. 17α-Hydroxylase deficiency (CPY17A1) (10q24.3)
  B. Mutations involving reproductive hormones, their receptors, and action
    1. Mutations of luteinizing hormone or follicle-stimulating hormone or both rendering them biologically inactive (theoretical)
    2. Mutations of inhibin (theoretical)
    3. Receptor mutations
      a. Follicle-stimulating hormone receptor (2p21-p16)
      b. Luteinizing hormone/human chorionic gonadotropin receptor (2p21)
    4. Mutations in the hormone action pathways
  C. Other mutations
    1. Blepharophimosis, ptosis, and epicanthus inversus, type 1 (BPES) (premature ovarian failure 3) (3q23)
    2. Premature ovarian failure 5 (newborn ovary homeobox) (7q35)
    3. Autoimmune polyendocrine syndrome, type 1 (APS1) (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy, APECED) (autoimmune regulator gene, AIRE) (21q22.3)
    4. Vanishing white matter leukodystrophy with ovarian failure (genes encoding the translation initiation factor E1F2B) (14q24, Chr 12, 1p34.1, 3q27, 2p23.3)
    5. Congenital disorders of glycosylation, type 1a (CDG1a) (genes encoding phosphomannomutase-2, PMM2) (16p13.3-p13.2)
IV. Environmental insults
  A. Chemotherapeutic (especially alkylating) agents
  B. Ionizing radiation
  C. Viral infection (documented for mumps)
  D. Surgical injury or extirpation
V. Immune disturbances
  A. In association with other autoimmune diseases
  B. Isolated
  C. In association with congenital thymic aplasia
VI. Idiopathic causes

Source: Rebar, R.W., *Obstet. Gynecol.*, 113(6), 1355, 2009. With permission.

[a] Chromosomal site of mutations noted in parentheses.

Paradigms

Cultural beliefs play a role in how menopause is perceived and experienced. In some cultures in Africa, women gain respect equal to men when they become menopausal. Childless women may become depressed with menopause.[15] In cultures where the focus is on youth, beauty, and antiaging strategies, older women may perceive less respect and experience lower self-esteem.

Until recently, menopause was not discussed in public and sometimes not even in the home. SWAN interviewed 16,065 women from various ethnic groups in the United States and found generally neutral to positive attitudes toward menopause with some ethnic differences. Among African American, Caucasian, Chinese American, Hispanic, and Japanese American women in the study, the Hispanic women were most positive and the two Asian ethnic groups were the least positive (Figure 22.3).[16]

The medical community can influence how women perceive their menopause. In some professional circles, menopause has been labeled an endocrine deficiency disease and in others it has been described as a natural, normal phase in a woman's life. Researchers have debated whether women were prepared from an evolutionary perspective to live beyond menopause, pointing to the animal kingdom where females of most species die after reproduction. They also cite diseases of aging that become more common after menopause. However, others counter with examples of nonhuman female primates that live beyond their reproductive phase[17,18] and note that chronic diseases of later life are more related to aging than to menopause. Anthropologists report that menopause evolved very early in human history, millennia ago.[19]

Paradigms about menopause are shifting. Risk factors for cardiovascular disease (CVD), for example, may cause earlier menopause instead of the reverse hypothesis that an early menopause leads to CVD.[20,21] With regard to osteoporosis, the short-term accelerated loss of bone density associated with menopause parallels a short-term accelerated gain in bone density at puberty that is greater in girls than in boys.[22,23] The proposed hypothesis for the increased gain in bone mineral content at puberty and greater loss at menopause is the benefit this additional amount of calcium would supply for pregnancy and lactation.[22] In this paradigm, the short-term loss of bone at menopause is physiological, not pathological (Figure 22.4).

On an individual level, menopause conveys different meanings to different women. Just as different cultures have different views toward aging, individual women also have different

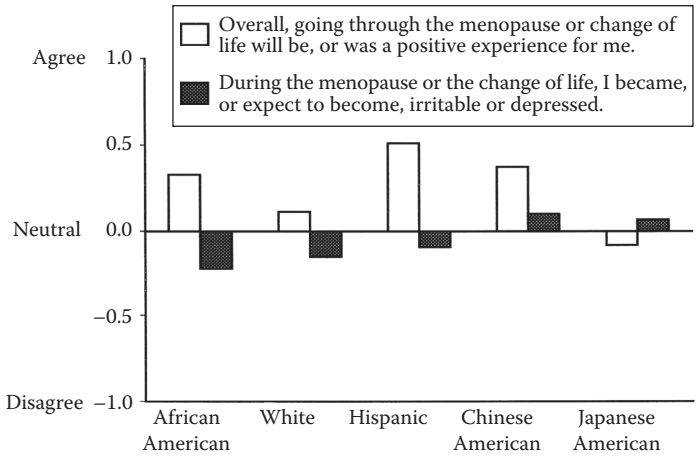


FIGURE 22.3 Degree of agreement and disagreement with affective items by ethnic group (means). (From Sommer, B. et al., *Psychosom. Med*., 61, 868, 1999. With permission.)

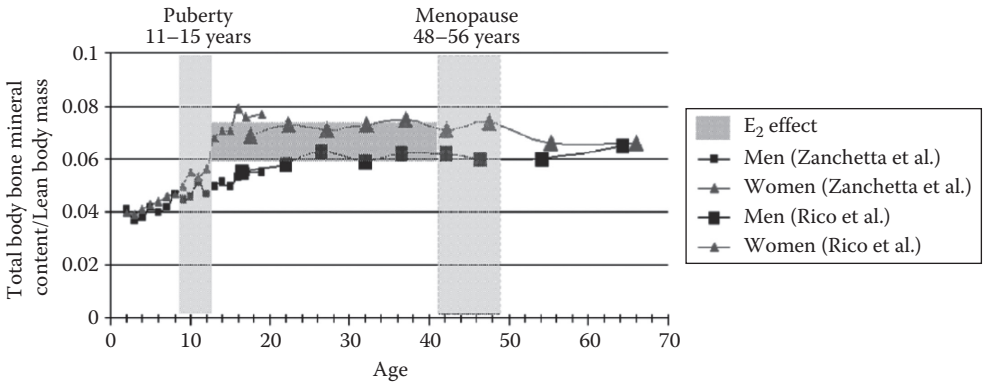


FIGURE 22.4 The ratio of total body bone mineral content to lean body mass plotted against age. (From Järvinen, T.L., Kannus, P., and Sievänen, H.: Estrogen and bone—A reproductive and locomotive perspective. *J. Bone Miner. Res*. 2003. 18. 1921–1931. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission; Data adapted from Zanchetta, J.R. et al., *Bone*, 16(4 Suppl), 393S, 1995; Rico et al., *Metabolism*, 43, 417, 1994.)

views on aging. Menopause is a clear message that the reproductive phase of life has been completed. Loss of reproductive capacity may bring joy to some and sadness to others.

ENDOCRINOLOGY AND PHYSIOLOGY

The decline in the number of ovarian follicles that leads to menopause commences during fetal life. Halfway through the gestation, the female reaches her peak number of follicles, 2–6 million.[24] The decline in the number of follicles begins in utero. By the time of birth, the female infant has ~1 to 2 million and by the time of puberty, the approximate number of follicles is 400,000. Fewer than 500 follicles are used for ovulation with the rest being lost through the process of atresia. This process appears to occur at an ever accelerating rate of decline until menopause (Figure 22.5).[25]

Despite the decline in follicles and the decline in fertility (after a peak in the mid-20s), the ovaries continue to produce normal levels of steroid hormones until 2–3 years before menopause.[26] The irregular cycles that characterize perimenopause clearly signal a phase of markedly compromised fertility.[27] The consistently cycling hormone levels characteristic of the premenopausal years give way to higher-than-normal levels of estradiol resulting from higher FSH levels. These occasional very high levels of estradiol have been reported to occur in what has been called a luteal out-of-phase (LOOP) cycle.[28] In brief, this phenomenon involves the capacity of the elevated FSH levels to recruit a second dominant follicle during the luteal phase of a menstrual cycle, thereby producing the unusually high estradiol levels (Figure 22.6).

A primary cause of the gradual increase in FSH is the decreased production of inhibin B, which is one of two peptides (inhibin A and inhibin B) produced by the granulosa cells of the follicle. Inhibin A is produced by the dominant ovarian follicle in parallel with estradiol, and inhibin B is produced by the small antral follicles. The latter inhibits the production of FSH. The rise in FSH in the early follicular phase of the menstrual cycle that results from the decline in inhibin B is often seen in women over a mean age of 37–38 years.[29–31] The shrinking pool of follicles is related to both decreased fecundity and menopause.[32]

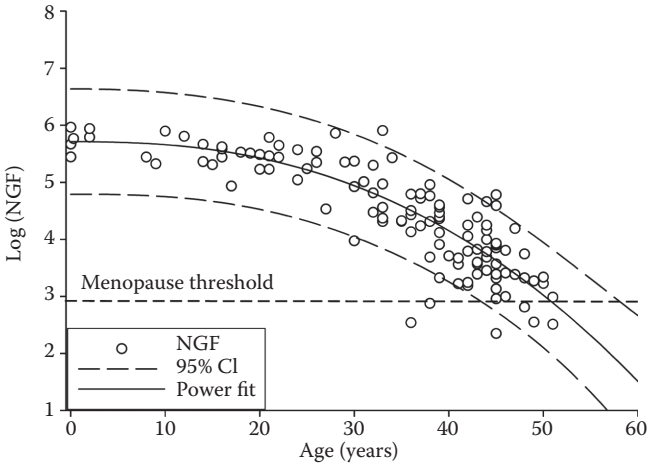


FIGURE 22.5 Power model of ovarian nongrowing follicle (NGF) decay. The log of the ovarian NGF number is plotted versus age (years). (From Hansen, K.R., Knowlton, N.S., Thyer, A.C., Charleston, J.S., Soules, M.R., and Klein, N.A., A new model of reproductive aging: The decline in ovarian non-growing follicle number from birth to menopause. *Hum Reprod* 23, 699, 2008. Reprinted by permission Oxford University Press. Copyright European Society of Human Reproduction and Embryology.)

Anti-Müllerian hormone (AMH), also produced by the granulosa cells, is another biomarker of menopause. This hormone has been found to be predictive of the age at menopause.[33–36] Unlike FSH and inhibin B, which vary across the menstrual cycle, AMH has been reported to be relatively stable in normally cycling women.[37,38] Further, the (log)AMH appears to be linear while the (log)FSH and (log)inhibin B are curvilinear and vary inversely with each other.[35] However, Robertson et al. reported intra-cycle variability in AMH levels in the late reproductive phase when levels were already extremely low.[39]

After menopause, estradiol and progesterone plateau at very low levels, <20 pg/mL and <1 ng/mL, respectively. AMH and inhibin B remain low; FSH peaks in the year after the FMP and may decline slightly thereafter.

Testosterone and dehydroepiandrosterone also decline after a peak in the 20s. There is no abrupt change in androgen levels at the time of menopause. In fact, androgen levels appear to be rather stable across the menopause transition. Two longitudinal studies have reported a rise in testosterone in the seventh and eighth decades.[40,41] In the Rancho Bernardo Study, testosterone levels returned to premenopausal levels in women in their 70s.[41]

The first physical sign of approaching menopause for most women is a change in their menstrual pattern. The most common trend in cycle length across the reproductive years is for the cycles to become shorter. The median length of the cycle in adolescent years is 29 days, and by age of 40 years, it is 26 days. The change occurs in the length of the follicular phase with the luteal phase remaining a relatively constant 14 days. Not all women experience irregular bleeding, but the majority do.

The female reproductive organs are particularly affected by the presence or absence of estrogen. The ovaries enlarge with puberty and after menopause they decrease in size. The uterus, and any leiomyomas therein, also decrease in size after menopause. The cervix typically decreases in size and may become stenotic. In some cases, it effaces to the point of becoming flush with the vault of the vagina.

The labia and the mons pubis tend to lose adipose tissue after menopause, a change that may be related to aging. Vaginal and vulvar mucosa become thinner as a result of low estrogen levels, especially the epithelial layer (Figure 22.7). There is loss of vaginal rugae and elasticity. Color tends to change from red to pale pink. In the absence of vaginal sexual activity, the vagina may constrict.

Breast tissue is also affected by the decrease in estrogen and by aging. There is loss of both the glandular and adipose components of the breast causing them to be less full and firm. Combined with the loss of elastic fibers associated with aging skin, breasts and many skin structures begin to sag. Skin turgor decreases.

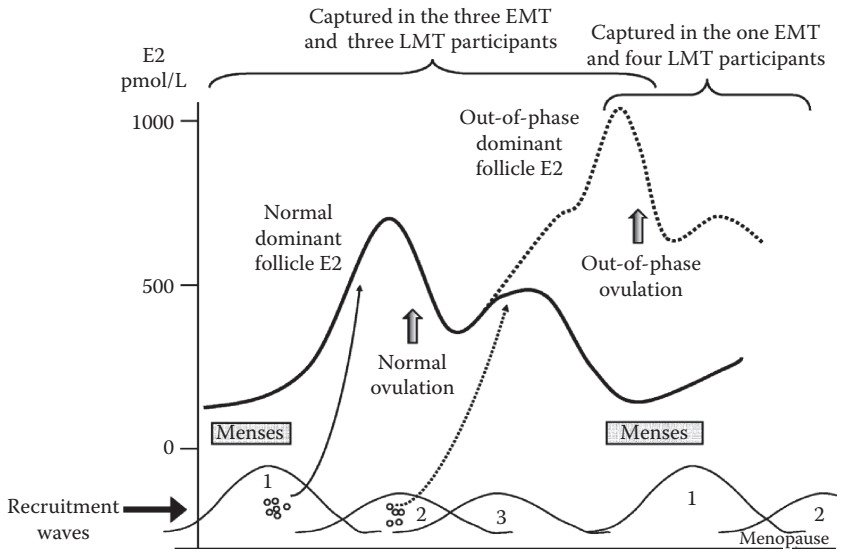


FIGURE 22.6 A luteal out-of-phase (LOOP) event. (From Hale, G.E. et al., *Menopause*, 16, 50, 2009. With permission.)

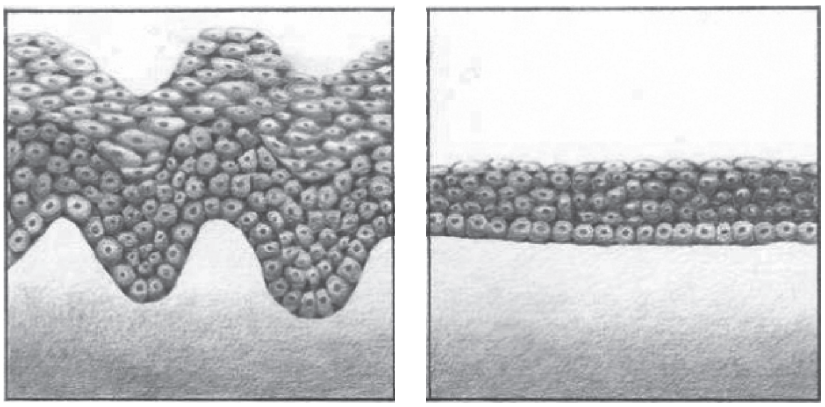


FIGURE 22.7 Illustration of microscopic view of vaginal lining before and after menopause. (a) Vaginal lining with estrogen. (b) Vaginal lining in low-estrogen state. (From North American Menopause Society. Changes in the vagina and vulva, *Sexual Health & Menopause*. http://www.menopause.org. With permission.)

Changes in hair distribution and amount are highly variable. Multiple factors control body hair including health and nutrition status, age, genetics/ethnicity, and hormones. Some women experience generalized hair loss and thinning that can involve a loss of all arm and leg hair along with thinning of scalp and pubic hair. Some women experience changes similar to male pattern hair loss such as receding hairline at the temples and thinning on the crown. Endocrine evaluation of hormone levels rarely finds a cause of hair changes. Products such as minoxidil and finasteride may help, but a catch-up hair loss is often observed when the treatment is discontinued.

SYMPTOMS

The classic symptoms of menopause in the United States are vasomotor symptoms (VMS) and symptomatic vaginal atrophy. The latter usually translates clinically to vaginal dryness, atrophic vaginitis, and dyspareunia. Hot flashes (or flushes) and night sweats are synonymous with VMS. Other symptoms that have variably been included in the list are moodiness; anxiety; irritability; sleep disruption; musculoskeletal discomfort, particularly joint pains; and cognitive concerns such as memory loss, word recall, and forgetfulness. The list of symptoms varies among cultures and in some cultures, VMS are not on the list. In Japan, for example, musculoskeletal symptoms such as shoulder stiffness predominate.[42] Even within the United States, different cultural subgroups rank common symptoms differently. A survey from SWAN indicated that more African American women reported VMS than Caucasian women, while Chinese American and Japanese American women had a much lower incidence of VMS than Caucasian women. It has been suggested that there is no universal menopausal syndrome.[43]

VMS are classified as mild, moderate, or severe with specific definitions provided by the Food and Drug Administration (FDA) for research purposes (Table 22.2).[44] Approximately 75% of women experience VMS and of these women, ~25% report severe symptoms. A drop in the estrogen level of an estrogen-primed individual is an important trigger. Lifelong low estrogen levels, as in Turner syndrome,

TABLE 22.2
Classification of Hot Flashes according to Food and Drug Administration Guidance for Hormone Therapy Research Studies

Severity	Description
Mild	Sensation of heat without perspiration
Moderate	Sensation of heat with perspiration, able to continue activity
Severe	Sensation of heat with sweating, causing the woman to stop activity

Source: U.S. Department of Health and Human Services. Guidance for industry: Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms—Recommendations for clinical evaluation. 2003.

are not associated with VMS. Both natural and iatrogenic (castration, aromatase inhibitors, GnRH agonists) reductions in gonadal hormone levels can result in VMS in both women and men.[45] Treatment with estrogen, progesterone, or androgen therapy can eliminate most of the VMS.[46,47]

There is great variability in how long a woman experiences VMS. In SWAN, women with an onset of VMS earlier in the perimenopause transition tended to experience them for a longer time.[48] Those with the earliest onset of VMS reported them for a median of 11.75 years. Those with onset in the middle of the perimenopause transition reported VMS a median of 7.5 years, and those with late onset of VMS during the transition had a median duration of 3.84 years.[48]

The current understanding of the mechanism of menopausal VMS is based on the concept of a narrowing of the core body thermoneutral zone, which is the core body temperature range within which women are comfortable.[49] Below the lower limit of the thermoneutral comfort zone, the body shivers, and above the upper limit, the body sweats. In the woman with VMS, this zone is very narrow. An increase of 0.1°F in core body temperature can trigger a hot flash in the research laboratory. What produces this change in sensitivity of the thermoregulatory zone of the hypothalamus is not known, nor is it known why some women do not experience this thermoregulatory change. Estrogen is reported to raise the sweating threshold in those women with VMS.[50] An α_2-adrenergic mechanism appears to be involved in triggering VMS.[51]

While menopause is known to cause specific symptoms, it can also eliminate other bothersome symptoms from the premenopausal years such as breast discomfort related to fibrocystic breast condition and cyclic premenstrual engorgement. Women who experienced pelvic pain related to dysmenorrhea, endometriosis, fibroids, ovarian cysts, and Mittelschmerz often have complete resolution of their pain. Menorrhagia disappears and any associated anemia improves. The woman who suffered with menstrual migraines enjoys a complete cure, and contraception is no longer an issue.

With regard to the vagina, there are both positive and negative effects from menopause. Some women appreciate the decrease in vaginal discharge that occurs with menopause. Others find the resulting vaginal dryness a source of dyspareunia. In one perimenopause study, ~20% of women reported vaginal dryness in the preceding 2 weeks.[52] Among postmenopausal women ages 50–59 years in the Women's Health Initiative (WHI) not taking estrogen, ~11% reported moderate to severe vaginal dryness.[53] These figures will vary with the population studied. Vaginal atrophy in and of itself does not usually cause symptoms, especially in the absence of vaginal sexual activity.[54] However, when a postmenopausal woman with vaginal atrophy begins sexual activity or undergoes a speculum examination after a long period of no vaginal activity, she is likely to experience dryness and tightness.

In SWAN, vaginal dryness correlated with vaginal/pelvic pain and with lower arousal, physical pleasure, and emotional satisfaction. However, VMS and the menopause transition were generally not related to arousal, physical pleasure, frequency of sexual activity, or satisfaction with a partner. Sexual function was found to be highly related to health, age, and social and psychological factors.[52]

VMS and symptoms related to vaginal atrophy are the most widely recognized symptoms of menopause in the United States. Other symptoms such as depression, anxiety, cognitive issues, and musculoskeletal aches and pains are reported with variable frequency from study to study. There has been some controversy over the years about the relationship of depression to menopause. A report from the Penn Ovarian Aging Study suggested a slightly higher occurrence of depressive symptoms and depressive disorder around the time of menopause,[55] while a report from SWAN found that women were 2–4 times more likely to experience a depression around the time of menopause compared to premenopause.[56] There is a growing consensus that women have increased vulnerability for depression during the menopause transition.

Memory complaints are common during the menopause transition but perception may be worse than reality. Results from midlife cohort studies suggest that memory is generally unaffected by natural menopause and that there is no link between serum levels of estradiol and objective memory test scores.[57–59] One report from the SWAN study indicated that any small decline in memory or cognition appeared to resolve after the menopause transition.[60]

DIAGNOSIS

An official diagnosis of naturally occurring menopause requires 1 year of no menses and the absence of other causes of amenorrhea. Thus, establishing the FMP as the date of menopause is a retrospective diagnosis. By then, a woman usually knows she is menopausal. Diagnosing perimenopause is based on clinical signs and symptoms. A woman who is over age of 40 years, skipping menstrual cycles, and reporting bothersome VMS is most likely in perimenopause. If there is the possibility of pregnancy, a urine pregnancy test should be performed to be sure that pregnancy is not the cause of amenorrhea. The unintended pregnancy rate among pregnant women in this age group is 38%.[61]

If a woman's presentation is not clearly perimenopausal (e.g., skipping menses without any menopausal symptoms), other

diagnoses should be considered. Pregnancy, thyroid disorder, hypothalamic amenorrhea, and hyperprolactinemia can be eliminated from the differential diagnosis by simple blood tests.

An FSH level is the test most often used to confirm menopause. However, one FSH level in the menopausal range does not assure that a woman will have no more menstrual cycles. It is not uncommon for a woman to have several months of amenorrhea, VMS, and an elevated FSH (>40 mIU/mL qualifies as menopausal in many laboratories), only to resume menstrual cycles again. This meandering course of perimenopause is what necessitates the definition of 1 year of no menses.

Another hormone that may contribute information about the timing of menopause is AMH. Recent publications suggest that AMH levels may predict the approximate age of a woman's menopause years ahead of time.[34] This test could be useful for women whose mother had an early menopause. These women may want to know if they need to complete childbearing sooner rather than later. A history of extensive ovarian surgery is another clinical scenario where this test might be useful. One report suggested that AMH levels could give indication of how much ovarian function remains after ovarian surgery.[62]

The phases of menopause as defined by STRAW in 2012 (Figure 22.2)[9] can provide guidance for determining where a woman is in the menopausal transition, but cannot be used prior to the onset of irregular cycles to predict menopause. AMH, on the other hand, might be useful throughout the reproductive years to estimate approximate age at which menopause will occur.

INTERVENTIONS

Menopause is an ideal time for a woman to reassess her goals and lifestyle, especially with regard to health and well-being. Lifestyle plays a significant role. Each woman chooses whether she will eat healthy food or unhealthy food, exercise or be sedentary, and on what pursuits she will spend her time.

Lifestyle Changes

Healthy food and physical activity are key components of weight control. Women of normal weight have fewer VMS than obese women.[63] Women who smoke have more VMS as well.[64] These two risk factors for VMS could be modified by lifestyle interventions. Exercise has many benefits besides weight control. Paradoxically, women who exercise have more energy. Exercise is reported to increase the sense of well-being.[65] In addition, aerobic exercise produces benefits for cardiovascular health, and weight-bearing exercise preserves and builds muscle mass which in turn helps preserve bone mineral content. Better muscles and bones may help prevent frailty, falls, and fractures.[66] The risks of smoking are well known. Both weight reduction and cessation of smoking could lead to fewer VMS, but data are sparse.[67] Data for a direct effect of aerobic exercise on VMS are less clear.[68]

With a wide variety of food in the diet, supplements may not be needed, but to be sure the basic nutrients are obtained, a multivitamin, along with calcium and vitamin D supplementation, is often recommended. The 2010 Institute of Medicine report recommends calcium intake (through food and/or supplements) of 1200 mg/day and vitamin D intake of 600 IU/day for women ages 51–70 years.[69] Both vitamin D and calcium are vital to bone health. Normal levels of vitamin D (20–60 ng/dL) are required for absorption of calcium from the gastrointestinal tract. Inadequate levels of vitamin D can lead to secondary hyperparathyroidism and osteomalacia. The IOM report recommends a minimum serum level of 20 ng/dL for bone health.[69] A myriad of other benefits have been attributed to vitamin D, but most lack confirmation from randomized controlled trials.

Sexual function requires more attention and nurturing with age. Libido generally diminishes for both partners. A first consideration is whether the couple wants to maintain their sexual relationship. Second, vaginal dryness associated with low levels of estrogen can lead to dyspareunia or pain with any vaginal sexual activity. If not addressed, this discomfort becomes a disincentive for vaginal sexual activity. Elimination of soap on the vulva (clean water is sufficient for hygiene) and elimination of fabric softeners and anticling products on underwear may reduce dryness and irritation. Adequate foreplay is important. Use of a vaginal moisturizer once or twice a week can be beneficial. If these measures are not sufficient, lubricants will often solve the problem. In more severe cases, it may be necessary to use vaginal estrogen until sexual activity becomes comfortable again. Vaginal estrogen is available in several forms: cream, tablet, or ring (Tables 22.3 through 22.7). The most effective

TABLE 22.3
Oral Estrogen Products for Postmenopausal Use in the United States and Canada

Composition	Product Name	Available Dosages/Day (mg)
Conjugated estrogens	Premarin	0.3, 0.45,[a] 0.625, 0.9,[a] 1.25
Synthetic conjugated estrogens, A	Cenestin[a]	0.3. 0.45, 0.625, 0.9, 1.25
	Congest[b]	0.3, 0.625, 0.9, 1.25, 2.5
	C.E.S[b]	0.3, 0.625, 0.9, 1.25
	PMS-Conjugated[b]	0.3, 0.625, 0.9, 1.25
Synthetic conjugated estrogens, B	Enjuvia[a]	0.3, 0.45, 0.625, 0.9, 1.25
Esterified estrogens	Menest[a]	0.3, 0.625, 1.25, 2.5
	Neo-Estrone[b]	0.3, 0.625
17β-Estradiol	Estrace	0.5, 1.0, 2.0
	Various generics	0.5, 1.0, 2.0
Estradiol acetate	Femtrace[a]	0.45, 0.9, 1.8
Estropipate	Ortho-Est[a]	0.625 (0.75 estropipate, calculated as sodium estrone sulfate 0.625), 1.25 (1.5), 2.5 (3.0), 5.0 (6.0)
	Ogen[b]	0.625 (0.75), 1.25 (1.5), 2.5 (3.0)
	Various generics	0.625 (0.75), 1.5 (3.0), 5.0 (6.0)

Source: North American Menopause Society. Hormone products for postmenopausal use in the United States and Canada, http://www.menopause.org/docs/professional/htcharts.pdf?sfvrsn=6. With permission.

Products not marked are available in both the United States and Canada.

[a] Available in the United States but not Canada.

[b] Available in Canada but not the United States.

TABLE 22.4
Transdermal/Topical Estrogen Products for Postmenopausal Use in the United States and Canada

Composition	Product Name	Delivery Rate (mg/Day)	Dosage/Day
17β-Estradiol matrix patch	Alora[a]	0.025, 0.05, 0.075, 0.1	Twice weekly
	Climara	0.025, 0.0375,[a] 0.05, 0.075, 0.1	Once weekly
	Esclim[a]	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
	Estradot[b]	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
	Fempatch	0.025	Once weekly
	Menostar[a]	0.014	Once weekly
	Oesclim[b]	0.05, 0.1	Twice weekly
	Vivelle[a]	0.025, 0.0375, 0.05, 0.075, 0.1[a]	Twice weekly
	Vivelle-Dot[a]	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
	Generics	0.1, 0.05	Once or twice weekly
17β-Estradiol	Estraderm	0.025,[b] 0.05,[a] 0.1	Twice weekly reservoir patch (patch cannot be cut)
17β-Estradiol transdermal gel	EstroGel[a]	0.06%, 0.035	Daily application; 1 metered pump delivers 1.25 g of gel containing 0.75 mg 17β-estradiol
	Estrogel[b]	0.06%	
	Elestrin[a]	0.06%, 0.0375	Daily application; 1 metered pump delivers 0.87 g of gel containing 0.52 mg 17β-estradiol
	Divigel[a]	0.1%[a], 0.003, 0.009, 0.027	Daily application; 3 strengths of packets provide 0.25, 0.5, or 1.0 g of gel
17β-Estradiol topical emulsion	Estrasorb[a]	0.05 (2 packets)	Daily application of 2 packets; 1 packet = 1.74 g of emulsion
17β-Estradiol transdermal spray	Evamist[a]	0.021 mg/90 μL spray (metered-dose pump) 1.5 mg estradiol/90 μL spray	Initial: 1 spray/day of 1.7% solution, increasing to 2–3 sprays/day if needed

Source: North American Menopause Society. Hormone products for postmenopausal use in the United States and Canada, http://www.menopause.org/docs/professional/htcharts.pdf?sfvrsn=6. With permission.

Products not marked are available in the United States and Canada.

[a] Available in the United States but not Canada.

[b] Available in Canada but not the United States.

TABLE 22.5
Vaginal Estrogen Products for Postmenopausal Use in the United States and Canada

Composition	Product Name	Dosage/Day
Vaginal creams		
17β-Estradiol	Estrace Vaginal Cream[a]	Initial: 2–4 g/day for 1–2 week Maintenance: 1 g/day (0.1 mg active ingredient/g)
Conjugated estrogens	Premarin Vaginal Cream	0.5–2 g/day (0.625 mg active ingredient/g)
Esterified estrogens	Neo-Estrone Vaginal Cream[b]	2–4 g/day (1 mg active ingredient/g)
Vaginal rings		
17β-Estradiol	Estring	Device containing 2 mg releases 7.5 μg/day for 90 days (local vaginal with minimal systemic amount)
Estradiol acetate	Femring[a]	Device containing 12.4 or 24.8 mg estradiol acetate releases 0.05 or 0.10 mg/day estradiol for 90 days (systemic levels)
Vaginal tablet		
Estradiol hemihydrate	Vagifem	Initial: 1 tablet/day for 2 week Maintenance: 1 tablet twice/week (tablet containing 25.8 μg or 10 μg of estradiol hemihydrates, equivalent to 25 or 10 μg of estradiol)
	Vagifem LD	10 μg estradiol hemihydrates
Injectable estrogens		
Estradiol valerate	Delestrogen[a]	10–20 mg IM q 4 weeks
Estradiol cypionate	Depo-estradiol[a]	1–5 mg IM q 3–4 weeks
Estrogens-conjugated (dose for excessive bleeding)	Premarin[c]	25 mg IV/IM

Source: North American Menopause Society. Hormone products for postmenopausal use in the United States and Canada, http://www.menopause.org/docs/professional/htcharts.pdf?sfvrsn=6. With permission.

Products not marked are available in both the United States and Canada.

[a] Available in the United States but not Canada.

[b] Available in Canada but not the United States.

[c] Not approved by the FDA for menopausal hormone therapy.

TABLE 22.6
Combination Estrogen/Progestogen Products for Postmenopausal Use in the United States and Canada

Composition	Product Name	Dosage/day (mg)
Oral continuous-cyclic regimen		
Conjugated estrogens (E) + medroxyprogesterone acetate (P) (E alone for days 1–14, followed by E + P on days 15–28)	Premphase[a]	0.625 mg E + 5.0 mg P (2 tablets: E and E + P)
Oral continuous-combined regimen		
Conjugated estrogens (E) + medroxyprogesterone acetate (P)	Prempro[a]	0.625 mg E + 2.5 or 5.0 mg P (1 tablet); 0.3 or 0.45 mg E + 1.5 mg P (1 tablet)
	Premplus[b]	0.625 mg E + 2.5 or 5.0 mg P (2 tablets: E and P)
	Premplus Cycle[b] Oral	0.625 mg E daily with 10 mg P taken for the last 14 days each month
Ethinyl estradiol (E) + norethindrone acetate (P)	femhrt[a]	2.5 µg E + 0.5 mg P (1 tablet); 5 µg E + 1 mg P (1 tablet)
	femHRT[b]	2.5 µg E + 0.5 µg P (1 tablet); 5 µg E + 1 mg P (1 tablet)
17β-Estradiol (E) + norethindrone acetate (P)	Activella,[a] Activelle[b]	0.5 mg E + 0.1 mg P (1 tablet);
	Activelle LD[b]	1 mg E + 0.5 mg P (1 tablet)
17β-Estradiol (E) + drospirenone (P)	Angeliq	1 mg E + 0.5 mg P (1 tablet)[a]; 1 mg E + 1 mg P (1 tablet)[b]
Oral intermittent-combined regimen		
17β-Estradiol (E) + norgestimate (P) (E alone for 3 days, followed by E + P for 3 days, repeated continuously)	Prefest[a]	1 mg E + 0.09 mg P (2 tablets: E and E + P)
Transdermal continuous-combined regimen		
17β-Estradiol (E) + norethindrone acetate (P)	CombiPatch[a]	0.05 mg E + 0.14 mg P (9 cm^2 patch, twice/week)
	Estalis[b]	0.05 mg E + 0.25 mg P (16 cm^2 patch, twice/week)
17β-Estradiol (E) + levonorgestrel (P)	Climara Pro	0.045 mg E + 0.015 mg P (22 cm^2 patch, once/week)

Source: North American Menopause Society. Hormone products for postmenopausal use in the United States and Canada, http://www.menopause.org/docs/professional/htcharts.pdf?sfvrsn=6. With permission.

Note: Products not marked are available in both the United States and Canada.

[a] Available in the United States but not Canada.

[b] Available in Canada but not the United States.

TABLE 22.7
Progestogens Available in the United States and Canada

Composition	Product Name	Dosage/Day
Oral tablet: progestin		
Medroxyprogesterone acetate	Provera, various generics	2.5, 5, 10 mg
Norethindrone	Micronor,[a] Nor-QD,[a,b] various generics	0.35 mg
Norethindrone acetate	Aygestin,[a,b] various generics	5 mg
Megestrol acetate	Megace,[a] various generics	20[b], 40, 40 mg suspension
Oral capsule: progesterone		
Micronized progesterone (in peanut oil)	Prometrium	100, 200[b] mg
Intrauterine system: progestin		
Levonorgestrel	Mirena[a]	20 µg/day approximately release rate (52 mg IUS has 5 year use)
Vaginal gel: progesterone		
Progesterone	Crinone 4%,[a,b] 8%	45 or 90 mg applicator

Source: North American Menopause Society. Hormone products for postmenopausal use in the United States and Canada, http://www.menopause.org/docs/professional/htcharts.pdf?sfvrsn=6. With permission.

[a] Not approved by the FDA for menopausal hormone therapy.

[b] Available in the United States but not Canada.

way to maintain vaginal sexual function with menopause is to continue to have regular sexual activity throughout the menopause transition and thereafter. This is an important lifestyle consideration and option that should be discussed early in the menopause transition.

Other lifestyle changes may also be beneficial in managing symptoms of menopause. VMS are aggravated by heat. Dressing in layers allows one to adjust clothing to the environment. Open-neck clothing is particularly suited to women with VMS because the upper chest, neck, and face are most often affected by a hot flash. Women with VMS should avoid turtle neck shirts and sitting in direct sunlight. Even bright lights or spot lights in the ceiling can trigger hot flashes or red ears.

Becoming too warm while sleeping is a common cause of night sweats. Comforters are major offenders because they trap body heat too well. There are many practical measures for easing night sweats. Switching to a lighter, more loosely woven blanket allows body heat to dissipate. Bed linens and pillows designed to have a cooling effect are available commercially. Some women chose to sleep in exercise clothing designed to wick away perspiration. A gentle overhead fan or bedside fan can be helpful. Often women feel chilled or have cold feet by the time they are ready to get into bed. Rather than piling on blankets that will later create an oven effect, it may be better to don a comfortable pair of socks that can easily be removed later as needed.

Emotional responses to situations are also triggers for hot flashes. It is not easy to avert emotional reactions, but learning a few behavioral techniques can be effective in addition to moving to a cooler environment. A desk fan and commercially available cool neck packs and/or cloths are other options.

Paced respiration has been demonstrated to decrease hot flashes.[70] This breathing technique involves inhaling slowly and exhaling slowly in a controlled fashion. Engaging in this practice on a daily basis was found to decrease VMS by ~50%. In this same study, exercise was not found to be beneficial for VMS.

Complementary and Alternative Medicine

Many studies on complementary and alternative medicine (CAM) products for the treatment of VMS have yielded mixed results. Black cohosh, red clover, and other CAM products have been found to lack strong evidence of benefit.[71] One randomized controlled trial enrolled 351 women for 1 year and randomized them to black cohosh, black cohosh combined with multi-botanicals, black cohosh and dietary soy counseling, conjugated estrogens 0.625 mg, or placebo. Black cohosh in any of the combinations was no better than placebo at any time point.[72] There has been some concern about possible liver damage with use of black cohosh. A review of 69 cases found "little, if any," evidence of causality.[73] Studies on the effect of acupuncture for VMS have also produced mixed results.[74,75] The National Center for Complementary and Alternative Medicine (NCCAM) has a website for clinicians with information on the safety and efficacy of CAM products.[76]

Soy has been the focus of much research because of constituents in the plant that resemble the chemical structure of estradiol. These phytoestrogens or plant estrogens include genistein and daidzein, two isoflavones that are considered to be very weak estrogens. Some prefer to use the term mixed estrogen agonists/antagonists. Studies using soy foods and soy extracts abound. Recently, the focus has been on S-equol.[77] This metabolite of daidzein and daidzin is produced in the intestines of some, but not all, people. The S(–)-equol enantiomer has selective affinity for estrogen receptor-β. It is being investigated as a potentially therapeutic agent for menopausal symptoms. In a comprehensive review of the scientific research, soy-based isoflavones were found to be modestly effective in treating symptoms of menopause, and the supplements with higher levels of genistein or S(–)-equol were thought to provide more benefits.[78]

Nonhormonal Medicines

Nonhormonal prescription therapies for VMS have focused on selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs). Serotonin and norepinephrine are involved in thermoregulation via central and peripheral mechanisms. Studies of the SSRIs citalopram and escitalopram significantly reduced the frequency and severity of VMS.[79,80] The SNRI desvenlafaxine has been extensively investigated and has been found to reduce VMS by 64%, significantly better than placebo.[81] These drugs improved mood as well as VMS.

Another neuroactive drug, gabapentin, has also been found to have a beneficial effect on VMS.[82–84] Gabapentin was approved by the FDA as an adjunct therapy for partial seizures and as a treatment for neuropathic pain. It has been used off-label for many other conditions including VMS. Most studies on the effect of gabapentin on hot flashes have used 900 mg/day and reported an ~20% greater reduction in hot flashes than placebo. Reddy et al. used 2400 mg of gabapentin and also an estrogen comparator. Both estrogen and gabapentin had an ~25% greater reduction in hot flashes than placebo, but there were more side effects with gabapentin, namely dizziness, headaches, and disorientation.[83] This anticonvulsant should be titrated starting at 300 mg (100 mg if the patient is older or sensitive to medication) taken at night in order to minimize the common side effect of dizziness. Similarly, the drug should be tapered slowly to avoid withdrawal symptoms after prolonged use or after use of high doses.[85]

Hormone Therapy

Hormone therapy (HT) is the most effective treatment for menopausal symptoms. The two general categories of HT are estrogen therapy (ET) and combined estrogen/progestogen therapy (EPT).

A summary of HT terminology is listed in Table 22.8. The choice between ET and EPT is based on the presence or absence of the uterus. Women with a uterus should be advised to take a regimen that contains a progestogen in order to protect the endometrium from the development of adenocarcinoma. Prolonged use of unopposed ET can increase the risk of endometrial

TABLE 22.8
Hormone Therapy Terminology

HT	Hormone therapy (encompassing both ET and EPT)
ET	Estrogen therapy
EPT	Combined estrogen/progestogen therapy
Progestogen	Encompassing both progesterone and progestin
Systemic therapy	HT administration that results in absorption in the blood high enough to provide clinically significant effects
Local therapy	Vaginal ET administration that does not result in clinically significant systemic absorption

Source: North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 Position statement of The North American Menopause Society. Menopause 17, 242–255, 2010. With permission.

adenocarcinoma 2- to 10-fold depending on estrogen dose and duration.[86,87] The addition of a progestogen offsets this risk.

Most brands of HT are approved by the FDA for treatment of moderate to severe VMS and symptomatic vaginal atrophy. Some ET products are also approved for prevention of osteoporosis and some are approved for dyspareunia. See Tables 22.3 through 22.7 for an extensive list of hormone products available in the United States and Canada. Menopausal symptoms usually resolve completely with use of HT. Women should be informed that symptoms recur in ~40% of women upon discontinuation of HT.[88]

Benefits and risks are similar across estrogen products, especially with regard to alleviating menopausal symptoms. The risk of venous thrombosis, however, may vary by route of administration. Observational data from Europe suggest that parenteral administration of estrogen may have a lower risk of venous thrombosis, but there have been no direct comparisons of oral and parenteral therapies.[89,90] Personal history of venous thrombosis is generally considered a contraindication to HT.

The WHI Hormone Therapy Trial, a randomized controlled trial that enrolled ~27,000 healthy women ages 50–79 years, was a prevention trial; i.e., healthy women were randomized to an HT intervention to determine if HT would keep them healthier than those women who were randomized to placebo. Both EPT and ET were stopped earlier than planned when signs of harm were seen in the absence of an overriding benefit. The mean duration of intervention in the two groups was 5.2 and 6.8 years, respectively, of an expected 8.5 years. Mean duration of adherence (defined as taking ≥80% of study drug) to EPT and ET was much shorter because at the time of terminating the interventions, 42% of EPT users had already discontinued the drug and 54% of ET users had already discontinued.[91,92]

The EPT intervention was stopped because the incidence of invasive breast cancer in the hormone users reached a predetermined safety limit. In the case of ET, a rising rate of stroke with no obvious benefit for cardiac health prompted the discontinuation of ET. The women continued to be followed, however, and it was noted that most of the benefit (fracture reduction) and risk (thrombosis, stroke, cardiac events) disappeared quickly after treatment was stopped. Two hormone effects persisted in analyses that continued for 3 years after intervention termination. In the EPT arm of the study, more deaths were attributed to breast cancer in those women randomized to EPT compared to those women randomized to placebo (HR, 1.96; 95% CI, 1.00–4.04; $P = 0.049$). New diagnoses of breast cancer were no longer elevated in the former EPT group in the 3 years post-intervention.[93] In the ET arm, the lower breast cancer incidence seen in the ET group during the intervention phase persisted through the follow-up period.[94]

When the WHI was designed, it was not anticipated that the effects of EPT and ET would vary by age.[95] The post hoc analyses by age group yielded results that suggested that most of the risks of HT occur more frequently in older postmenopausal women compared to younger postmenopausal women. For example, using a global index of chronic diseases, the analysis by age revealed a statistically significant increased risk in the global index for women ages 70–79 years assigned to ET (HR 1.15; 95% CI, 1.01–1.32) and a possible statistically significant reduction in the global index risk in women ages 50–59 years (HR 0.85, 95% CI, 0.70–1.03; $P = .009$) for interaction.[94] The exception to this generalization is that breast cancer risk appears to be less in postmenopausal women who have had a few years without use of HT prior to initiating it. In the EPT arm, it was the women who had been using EPT prior to WHI who had the increased risk when they continued EPT in the WHI.[91] In the ET arm, women who had not been taking ET prior to WHI actually had a decrease in breast cancer incidence after starting ET in the WHI.[96,97] These findings suggest that risk of breast cancer, unlike the other adverse outcomes, may be greater in the younger postmenopausal women who have continuous exposure to HT, but further analyses are required to confirm this concept.[98]

Overall, women taking EPT had more adverse events than the women assigned to estrogen alone. In the entire EPT cohort, there were increased risks of cardiovascular events, stroke, and breast cancer along with decreased risks of colorectal cancer and hip fracture.[91] Considering only the 50–59 year olds, there were only four more strokes and five more cases each of breast cancer and coronary heart disease among 10,000 women per year.[99–101] These are small risks. Both the ET and the EPT groups had a decreased risk of hip fracture overall.[91,92] Besides venous thrombosis, the only other statistically significant risk in the entire ET cohort was stroke: 12 additional cases per 10,000 women per year and only one additional stroke in the 50–59 year old group.[92] Fewer deaths occurred in both the EPT and ET arms in the younger group, 11 and 12 fewer deaths, respectively (Table 22.9).[102–110]

After years of analyzing the WHI data from different perspectives, it has become apparent that both ET and EPT are viable options for most symptomatic younger postmenopausal but not older postmenopausal women. ET is acceptably safe for symptomatic women who have had a hysterectomy and no history of venous thrombosis or breast cancer. EPT carries slightly more risk because of the breast cancer cases with EPT that were not seen with relatively short-term use of ET. The elevated risk of breast cancer seen with EPT in the WHI was consistent with findings from observational studies, but the decreased risk of breast cancer among the women assigned to ET in WHI differed

TABLE 22.9
Absolute Risks of Hormone Therapy Ages 50–59 per 10,000 Women per Year, Women's Health Initiative

Event	Estrogen Progestogen Therapy (n = 5522)	Estrogen Therapy (n = 3310)
Venous thromboembolism	+11	+2
Coronary heart disease rate	+5	−10
Stroke	+4	0
Breast cancer	+5	−8
Hip fracture	−2	+3
Death	−11	−10

Sources: Anderson, G.L. et al. for the Women's Health Initiative Steering Committee, *JAMA*, 291, 1701, 2004; Chlebowski, R.T. et al., *JAMA*, 289, 3243, 2003; Manson, J.E. et al. for the Women's Health Initiative Investigators, *N. Engl. J. Med*., 349, 523, 2003; Cushman, M. et al. for the Women's Health Initiative Investigators, *JAMA*, 292, 1573, 2004; Curb, J.D. et al., *Arch. Intern. Med*., 166, 772, 2006; Hsia, J. et al. for the Women's Health Initiative Investigators, *Arch. Intern. Med*., 166, 357, 2006; Wassertheil-Smoller, S. et al. for the WHI Investigators, *JAMA*, 289, 2673, 2003; Hendrix, S.L. et al. for the WHI Investigators, *Circulation*, 113, 2425, 2006; Stefanick, M.L. et al. for the WHI Investigators, *JAMA*, 295, 1647, 2006; Cauley, J.A. et al. for the Women's Health Initiative Investigators, *JAMA*, 290, 1729, 2003; Jackson, R.D. for the Women's Health Initiative Investigators, *N. Engl. J. Med*., 354, 669, 2006; Manson, J.E. and Bassuk, S.S., *Hot Flashes, Hormones & Your Health: Breakthrough Findings to Help You Sail Through Menopause*, McGraw-Hill, New York, 2007.

markedly from the findings of many large observational studies where ET use also conveyed an increased risk of breast cancer, albeit a smaller risk than with EPT.[96,100,111–115]

Hypotheses have been proposed to explain the conflicting findings related to the effect of ET on breast cancer incidence rates. One hypothesis suggests that there is a mammogram screening bias in favor of women using ET that results in more regular use of mammograms which in turn leads to more ET users being diagnosed with breast cancer. The second hypothesis has been called the "gap hypothesis" because it states that the only women who experienced a reduction in breast cancer while using ET were those who had a "gap" in their estrogen exposure after menopause; i.e., these women experienced several years after menopause without taking ET prior to being randomized to it in the study. Certain analyses of the WHI data appear to support this hypothesis.[96,97]

With the abrupt decline in HT use following the published reports of the risks associated with EPT in 2002,[91] many women found themselves symptomatic again and seeking relief. HT in the form of compounded "bioidentical" hormones began to fill the void because these products were being promoted as natural and safe in spite of the absence of scientific evidence supporting such claims. Many clinicians prescribing compounded hormones were also recommending salivary hormone testing to tailor the dose of HT. Medical entities such as The North American Menopause Society, The Endocrine Society, the American Congress of Obstetrics and Gynecology, Nurse Practitioners in Women's Health, and the FDA have published information online regarding the lack of evidence for this approach.

Controversy regarding HT is nothing new. HT has fallen in and out of favor for decades. The more recent emphasis on evidence-based medicine and the emphasis on the superiority of randomized, controlled trials have raised the standards for decision making. Detailed practical guidance for interpreting the many scientific findings related to the use of HT has been published by The North American Menopause Society and The Endocrine Society.[116,117]

Dramatic advances have been made in the understanding of menopause and HT over the last 10 years. More advances are needed to completely understand the complex effects of hormones in different women at different ages. In the meanwhile, women have many choices for alleviating their symptoms and for staying healthy at midlife.

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23 Breast Health
Lifestyle Modification

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CONTENTS

Introduction 287
Epidemiology 288
Breast Development 288
Hormone Replacement in Menopause 289
Genetics 289
Screening 289
Lifestyle Modification 290
Lifestyle Evaluation and Modification 291
Prevention 291
Lifestyle Changes That Can Decrease Risk and Prevent Breast Cancer 292
#1. Do Not Smoke 292
#2. Maintain a Healthy BMI < 25% 292
#3. Avoid Exogenous Estrogen 292
#4. Alcohol Moderation 292
#5. Modify the Foods We Eat 292
#6. Exercise 292
#7. Stress Reduction 293
#8. Reproductive Education 293
#9. Breast-Feeding 293
#10. Vitamins and Antioxidants 293
Vitamin D 293
CoQ10 293
Vitamin A 293
Folate and Vitamin B 294
Vitamins C and E 294
Zinc 294
Selenium 294
Caffeine 294
#11. Pharmacologic Risk Reduction 294
#12. Environmental Choices 295
Future 295
Resources 295
References 295

INTRODUCTION

Breast cancer is the most prevalent cancer in women worldwide and holds a very visible place in society with the pink ribbon awareness campaigns. Technological advances in the diagnosis and treatment of breast cancer have led to a decline in death from breast cancer[1,2]; however, the disease prevalence is increasing. After the Women's Health Initiative (WHI) study was released in 2003, we experienced an initial decrease in the incidence of breast cancer. This was likely due to a rapid discontinuation of hormone replacement therapy.[3] We are now seeing a leveling off and actual increase in the incidence of breast cancer in certain subgroups of women.[4] An even greater concern is in the projected risk: the overall incidence of breast cancer is projected to double by the year 2040 and occur more frequently in younger women.[5,6] This projected risk requires a shift of our focus from simply better treatments and early detection to overall prevention of a disease that currently affects one in eight women. Educating and empowering women to modify their lifestyle can decrease their overall risk of developing breast cancer. This needs to

become a priority in our fast paced society. Positive changes made early in a woman's life can impact her individual risk as well as her children's future risk.[2]

Li et al. studied the modifiable risk factors in women who had been treated for and estrogen receptor–positive breast cancer. They found that women who exhibited poor lifestyle choices (smoked, were obese, and drank more than seven alcoholic beverages per week) had a 7.2-fold elevated risk of contralateral breast cancer than matched counterparts who never smoked, were not obese, and drank less than seven cocktails per week.[7] These data lead us to believe that lifestyle choices and changes can significantly impact not only the risk of a woman who has had breast cancer but also the risk in the average woman.

EPIDEMIOLOGY

Breast cancer is the leading cause of cancer in women worldwide and the most common cause of cancer death in U.S. women between the ages of 20 and 59 years. It accounted for 23% (1.38 million) of the cancers diagnosed in women and accounted for 14% (485,400) of all cancer deaths in 2008.[8] An increased incidence is observed in countries as they become "Westernized." The risk of developing breast cancer is very dependent upon where a woman lives in the world. Nearly half of the total individuals diagnosed and ~60% of the breast cancer deaths occur in economically developed countries, and North America, Western and Northern Europe, New Zealand, and Australia are the high-risk regions. The lowest risk regions are Sub-Saharan Africa and Asia.[8]

Several factors have played a significant role in the increased incidence of breast cancer in Westernized cultures. They include early menarche, delayed childbearing, late menopause, oral contraception, hormone replacement therapy, alcohol consumption, and obesity.[9]

Combined estrogen and progesterone therapy was shown to increase the risk of breast cancer as reported by the WHI in 2003. Since 2004, incidence rates of breast cancer decreased sharply in the United States, United Kingdom, France, and Australia. This decrease in incidence was due to a rapid discontinuation of combined postmenopausal hormone therapy when the study results were released.[10] Recent follow-up data from the same WHI study show that the declining incidence has reached a plateau and may even be increasing in certain populations.[2]

BREAST DEVELOPMENT

The breast is an amazing organ as it has the capability to extract nutrients from the body's circulation and produce a fluid so rich that it can completely and totally sustain an infant from the day of birth well into the second year of life. Understanding breast development and function, we can gain insight into how the breasts are affected by known risk factors and potential breast cancer risk factors.

Breast development can be viewed as several distinguishable phases. Each individual stage is sensitive to environmental factors. Unlike other organs that develop fully in utero, the breast has only completed the first stage of development at the completion of gestation. Breast maturity continues over the course of 10–15 years once they begin to develop.

The breasts develop throughout adolescence and do not reach full maturation and size until a woman reaches her early 20s. The DNA replication process must occur to create new breast cells and therefore they are susceptible to genetic mutations. Radiation exposure in adolescence, for example, is a significant risk factor for developing breast cancer later in life. Even though the breast may appear fully developed externally, it is not until a full-term pregnancy that this maturation process is completed. Immature breast cells are more sensitive to hormonal factors than mature breast cells; therefore, a delay in a woman's first pregnancy can impact her future breast cancer risk.[10]

The breast is fully matured when the first full-term pregnancy comes to fruition and the breasts begin to produce milk. The final maturation of the breasts occurs during the breast-feeding process.[11] Any delay in a woman's first full-term pregnancy can increase her breast cancer risk later in life. Women living in an industrialized nation often delay childbearing to their fourth and sometimes fifth decade of life. This delay allows breast cells to continue to be influenced by the cyclic estrogen and exogenous estrogen (oral contraceptives). Long-term exposure to internal or external estrogen sources can act as a "fuel" on a potential fire.[10]

Breast-feeding has long been evaluated in the role that it plays in breast cancer risk reduction. The true benefits have been likely underestimated and underreported. Women, who were breast-fed when they were infants, were found to have a decreased incidence of premenopausal breast cancer in a meta-analysis.[12] Women who themselves breast-feed their infants, cumulatively over their lifetime for 12–24 months, had a 66% reduction in breast cancer. There is a direct relationship established between the duration of breast-feeding and decreased risk.[13] Young women, who were at high risk due to family history, were found to have a decreased incidence of breast cancer when they breast-fed their children.[14] Recent studies from Brigham and Women's hospital support these findings of breast cancer risk reduction from breast-feeding.[15]

The final phase in the cycle of breast changes occurs in menopause. The dense fibrous tissue of the breasts involutes and is replaced by fat. This enhances the ability of mammography to detect subtle changes in the breasts and represents the final transition that the breasts make in their life cycle. After menopause, breasts are no longer under the cyclic influence of the ovaries; however, they are influenced by estrogen from other internal and external sources.

Many women fail to recognize that the largest source of estrogen after menopause is related to her body fat, particularly fat that is found surrounding her waist. Higher levels of body fat may be the detrimental factor, since estrogen precursors are converted into active estrogens in adipose tissue. This process occurs through the enzyme aromatase, which is

produced in the adrenal gland. Several factors are known to increase aromatase activity. They include age, obesity, insulin, gonadotropins, and alcohol. A woman's basal metabolic index (BMI) has long been associated with an increased risk of cardiovascular disease, diabetes, and estrogen-driven breast cancers.[16] Recent data reveal that higher BMI/obesity has also been linked with the development of a more aggressive subtype of breast cancer that is known as a triple negative or ER–, PR–, Her 2 neu– cancer.[17]

HORMONE REPLACEMENT IN MENOPAUSE

Hormone replacement therapy has been used for years to treat the "symptoms" of menopause, such as hot flashes, mood swings, vaginal dryness, and loss of libido. In a groundbreaking study released in 2003, the WHI's findings brought to light the fact that breast cancer incidence was increased when estrogen and progesterone were taken in combination. Almost immediately after the studies initial findings were released, there was a marked decline in the use of hormone replacement therapy. As a result, there was a decline in the incidence of breast cancer. It was proposed that the breast cancers were found earlier, were more treatable, and were better prognosis tumors, still many women discontinued the use or the combined hormones at that time as they were concerned that the risks were greater than the benefits.[10] In 2010, the follow-up to the study showed that the cancers were more aggressive, higher nodal status with a decrease in survival.[18] A concurrent study of unopposed estrogen revealed that there was actually a slight decrease in the incidence of breast cancer in postmenopausal women who did not have a uterus and were on estrogen only without the progesterone. The combination of estrogen and progesterone appears to be the culprit.[19]

Menopause is a normally occurring process in a woman's life cycle. There are symptoms of menopause that can greatly affect a women's quality of life, but we need to carefully consider the consequences to her overall health and well-being before beginning exogenous estrogen.

GENETICS

Many women are under the mistaken impression that they are not at significant risk if they have no family members with breast cancer. On the contrary, 75%–80% of all breast cancers occur in women who have no prior family history whatsoever. This far too often underemphasized fact is precisely why we need to carefully evaluate how our lifestyle choices impact breast cancer risk. The greatest risk factor for developing breast cancer is being born female. One man for every 100 women is diagnosed with breast cancer. Women, who have either a maternal or paternal family history of breast and/or ovarian cancer, are at a high risk for developing breast cancer and need to clearly understand their lifetime risk. Familial breast cancer can be of environmental or genetic origin. Only 4%–6% of all breast cancers occur as a result of a currently recognized breast cancer mutation.

Risk factors for carrying a known breast and ovarian cancer gene are

- Breast cancer diagnosed before age of 50 years
- Ovarian cancer at any age
- Two primary breast cancers in an individual
- Both breast and ovarian cancer in an individual
- Male breast cancer at any age
- Two or more breast cancers in a family, one under age of 50 years
- Women of Ashkenazi Jewish descent with breast or ovarian cancer at any age
- A previously identified BRCA mutation in the family[20]

Carriers of the BRCA I or II gene mutation have a 56%–87% chance of developing breast cancer and a 27%–44% risk of developing ovarian cancer by the age of 70 years.

Most breast cancer risk assessment models underestimate a woman's risk; therefore, it is important for a woman to discuss her personal individual risk with a health care professional.

There are steps that can be taken to reduce the risk of developing breast cancer.[21] Antiestrogen therapy with tamoxifen or raloxifene has been demonstrated in the STAR trial to reduce the risk of estrogen receptor–positive breast cancers by 48%.[22,23] Surgical removal of the breasts known as prophylactic mastectomies in this high-risk population can reduce the risk of developing breast cancer to ~2%.

Women, who carry the BRCA mutations, need to understand that the cancers they are likely to develop have a higher chance of being a triple negative cancer (BRCA I 67% and BRCA II 35%, general population 11%).[24] Triple negative breast cancers are typically fast growing, aggressive, and are not prevented by blocking the estrogen receptors as these cancers do not have estrogen receptors.

SCREENING

Mammograms do not prevent breast cancer but they prevent death from breast cancer. Population screening studies have shown that with early detection we can experience a 60% reduction in death from breast cancer.[25] While we work to create healthy lifestyle changes globally, we need to remain diligent about screening women for breast cancer to diagnose this disease as early as possible in order to effect mortality.

Digital mammography is the main tool for early detection. On February 11, 2011, the FDA approved 3-D tomosynthesis as an adjunct screening modality in dense breasted women. Tomosynthesis can more readily detect cancers in mammographically dense breasted women and also decrease the rate of recall (false positives) for benign findings on screening mammography.[26]

Magnetic resonance imaging (MRI) of the breasts is also used to screen high-risk populations including BRCA-positive individuals and women with a cumulative lifetime risk of >20% as calculated by the GAIL risk model.[27]

Additional radiological studies are under FDA investigation for use in screening. Ultrasound systems for automated breast ultrasound (ABUS) scanning are in development and show great promise, but not yet considered a standard in screening.

Gamma imaging is also being used in dense breasted patients and patients with a breast cancer diagnosis. Due to the radiation exposure, it is not available as a routine screening tool.

Thermography has received significant interest as an alternative to mammography, but has not been proven in clinical trials to have the sensitivity, specificity of mammography.

The American College of Radiology, American Society of Breast Surgeons, American Cancer Society, and The American College of Surgeons recommend screening mammography annually for women over the age of 40 years unless there is a significant family history of premenopausal breast cancer in which case screening schedules should be individualized and may include breast MRI.[28,29]

LIFESTYLE MODIFICATION

Lifestyle modification can greatly impact a woman's risk of developing breast cancer. A population-based case–control study from Mexico found that a healthy lifestyle, defined as moderate- and/or vigorous-intensity physical activity; low consumption of fat, processed foods, refined cereals, and complex sugars; and the avoidance of tobacco smoking and alcohol consumption, was associated with a reduction in the risk of a woman developing breast cancer. The results showed a protective effect in both pre- and postmenopausal women.[30]

Regardless of a woman's age, there are certain risk factors that cannot be altered such as family history and age of her menarche. If a woman becomes aware of the impact of her life choices while she is young, she has the ability to alter her life's course. She may choose to have her children at a younger age, avoid exogenous estrogen, maintain a healthy BMI with diet and exercise, as well as choose to breast-feed her children.

Our daughters and granddaughters should be empowered to make positive choices early on in their lives so that they can potentially decrease their breast cancer risk profile.

Early puberty and lack of physical activity in adolescence can lead to early menarche and increased risk of developing breast cancer. Studies have found that underweight girls have a delay in menarche, thus decreasing the years of cyclical estrogen stimulation to the breasts. Conversely, being overweight and having an increased BMI leads to a premature menarche and early breast development. This causes estrogen stimulation to those breasts in these young girls whose breasts are still maturing. Young women who are physically active and maintain a healthy BMI have a delay in their menarche.[31,32] This is an opportunity to modify behavior in young girls. Parents need to understand that action, or lack of their action, and influence on their children's lifestyle choices can have significant long-term consequences.

In industrialized nations, for many reasons, women are delaying childbirth to their fourth and fifth decade, creating a delay in the final phase of breast development that occurs after completion of a woman's first full-term pregnancy. Delaying pregnancy or never giving birth increases a woman's risk of developing breast cancer. A woman who delays childbirth until she is 30 years has approximately the same risk of developing breast cancer as a woman who is nulliparous. The more children that you have at a younger age, the less likely you are to develop breast cancer.[33]

A major protective effect of pregnancy, as it relates to breast cancer risk, is breast-feeding. Using the breasts for their intended purpose, feeding our offspring, has also been shown to decrease a woman's risk of breast cancer. The risk reduction gained by breast-feeding is proportional to amount of time that she breast-feeds cumulatively in her life.[13]

We know that having a first-degree relative with breast cancer increases a woman's risk of developing the disease herself. Women who have a first-degree relative who had breast cancer and who breast-fed their own children were found to have a 59% reduction in breast cancer development. This finding strongly suggests a significant protective effect of breast-feeding. In addition, breast-feeding can help to cancel out the effect of delaying childbirth and needs to be embraced by women as an opportunity to decrease their risk profile.

When women are deeply imbedded in their career path, childbearing is often delayed. Understanding that when they do decide to conceive, they should strongly consider building a plan to breast-feed. This act will not only benefit their newborn child, but also benefit their breast health.[33] Every choice we make in life has consequences, and the decision to breast-feed has a positive effect on breast cancer risk reduction.

According to the American Cancer Society and the National Cancer Institute, "The preponderance of observational studies have associated combined hormone therapy use with an increase in breast cancers that have favorable characteristics, lower stage and longer survival compared with breast cancers diagnosed in nonusers of hormone therapy."[34] Despite the initial fall in the incidence of breast cancer that was experienced, we are now back to a plateau and possibly the incidence is on the rise. This supports the thought that the cancer risk was always there and that the estrogen acts to stimulant or promote cancer cell growth.

In the fall of 2010, the second phase of the WHI's follow-up study revealed that the cancers that are occurring on the combined estrogen/progesterone hormone replacement therapy are diagnosed higher stage, have a worse prognosis, and suggests that they have a higher mortality.[9,18]

After the initial decline in breast cancer incidence as a result of the discontinuation of combined estrogen and progestin, we are now seeing a plateau and even an increased incidence of breast cancers in certain subgroups. There is an increase in estrogen receptor–positive cancers and a decrease in estrogen receptor–negative cancers in non-Hispanic white women of age 40–49 years. There was also an annual 5.2% increase in ER+ cancers in black women of age 40–49 years.[35]

The use of exogenous estrogen and progesterone has been clearly shown to increase a woman's risk of developing breast cancer. Oral contraceptives have been associated with as high as 44% increased risk of developing premenopausal breast cancer when they are taken prior to the completion of a woman's first pregnancy.[35] It appears as though these women would likely have developed breast cancer and that the estrogen and progesterone acted as "fuel" for the fire.

These studies beg the question: why are we treating a normal evolutionary process of menopause as a disease that requires pharmacological intervention? The symptoms of menopause can be treated individually with far less risk to women.

LIFESTYLE EVALUATION AND MODIFICATION

The good news is that population studies show that we are living longer. The bad news is that we are unprepared for this longevity. We care for our bodies as if life is short and then still have decades remaining to live in our bodies.

With 75%–80% of breast cancers occurring in women who have no family history, we have to make a change in how we view our personal risk. Changes need to be made in our everyday lives to decrease our individual and global risk.[36] Personal accountability is needed to initiate this shift in thinking. We can no longer wait for the wake-up call of cancer to shift our thinking. We need to be proactive in our lives and empower our sisters, daughters, granddaughter's friends, and colleagues to make these changes NOW.

The best defense is a good offense. We need to begin to empower women and young girls to make tough choices and create healthy changes in their lives. These choices and changes can greatly impact their overall breast cancer risk. A woman cannot change her family history, but she can choose to make conscious choices in her lifetime and do everything in her power to lessen her risk.

PREVENTION

There are pharmacological means of decreasing breast cancer risk. First and foremost is avoiding exogenous estrogen in any form. Oral contraceptives, hormone replacement therapy, and any form of estrogen should be prescribed based upon severity of symptoms being treated and at the lowest dose to achieve relief.

For women at high risk, >20% lifetime or >1.7% 5 years (GAIL risk), tamoxifen and Evista have been proven to decrease the risk of developing breast cancer by 48%. raloxifene (Evista) cannot be used in premenopausal women as it can cause birth defects but is an excellent choice in high-risk postmenopausal women with osteopenia as it can also increase bone density. Tamoxifen is approved for prevention in premenopausal women at high risk. Women who take tamoxifen need to be informed that there is an associated risk of developing uterine cancer of ~2.5%.[37]

Surgical options for risk reduction in high-risk women including women who carry the BRCA I and II mutation include prophylactic oopharectomy and prophylactic mastectomies. A 90% reduction in breast cancer can be achieved; for a BRCA mutation carrier that translates into a *reduction in* risk from 87% to ~2%. Two thousand and five hundred BRCA mutation carriers were followed after prophylactic mastectomy or intensive screening. In the follow-up study reviewing breast cancer development after prophylactic surgery in BRCA I and II carriers, no one had developed breast cancer in the 3 years postmastectomy where 7% of the women who had chosen intensive screening had developed breast cancer. This once again reinforces that intensive surveillance is not equivalent to prevention.[38]

Of significant importance is knowledge of the aggressive subtypes of breast cancer BRCA I and II carriers are likely to develop. In 67% of BRCA I carriers and 35% of BRCA II carriers, the cancers that develop are triple negative or ER–, PR–, Her 2 neu–. Estrogen reduction from oopharectomy does not help to prevent these breast cancers, as the cancers are not responsive to estrogen stimulation.[24]

Cigarette smoking has been clearly associated with the development of lung cancer and heart disease. Smoking has also been shown to increase the breast cancer incidence in postmenopausal women in current and past smokers.[39] A higher incidence of breast cancer has been associated with past and current smokers (16% higher in current smokers, 10% higher in former smokers, and passive smoke exposure is suggestive of a link). An increased risk was also noted in women who began smoking before their breasts had completely developed through their first full-term pregnancy. The breast tissue is particularly vulnerable prior to its complete maturation at childbirth.[40]

Women with a 20 pack-years history after menopause had a slight decrease in risk (HR 0.93, 95% CI, 0.85–1.02). Researchers explained that this may have reflected an antiestrogenic effect from smoking. This supports a decreased incidence in estrogen receptor–positive breast cancers in long-time smokers, but the other health risks of smoking far outweigh any possible benefit.[41]

Alcohol use has become widespread in our society. It is viewed as a normal part of our social lives and few women realize the implications of over indulgence. Rarely do I encounter a patient that understands that the National Cancer Institute considers alcohol in any form a breast cancer carcinogen.[40] The amount of alcohol consumed is directly proportional to the increased risk of developing breast cancer. The alcohol, regardless of what type, not only increases empty caloric intake, but also interferes with the degradation of estrogen. Therefore, alcohol consumption increases a woman's circulating estrogen. We know that estrogen does not cause breast cancer but can act as fuel on a fire that is already burning. Three cocktails per week increases a woman's risk by 6% and more than three cocktails per day increases a postmenopausal woman's risk by 40%.[42] Moderation is the key to success and education of our young women is mandatory.

Obesity in the United States is epidemic. It is a well-established breast cancer risk factor. There has been a threefold increase in obesity in our fast-paced society in

the last 30 years. Body composition plays a significant role in several factors regarding breast cancer occurrence and recurrence. It has been well documented that women who have a BMI > 30% have a significant risk of breast cancer recurrence once they have been diagnosed. This is related to two specific factors. Increased body fat leads to increased estrogen production through the conversion of steroids to estradiol via the enzyme aromatase. This process occurs in fat cells and increased body fat leads to increased estrogen production. The second mechanism is related to insulin resistance. Insulin resistance is a condition where the body does not respond to insulin appropriately. According to a 2009 study in the International Journal of Cancer, high levels of insulin in the bloodstream are related to the development of postmenopausal breast cancer.[43] The Albert Einstein College of Medicine of Yeshiva University as part of the WHI has substantiated these results. Researchers found that the women with the highest levels of insulin, which suggests insulin resistance, have twice the risk of developing breast cancer than women with the lowest insulin production.[44]

A woman's goal should be to achieve and maintain a healthy weight and body composition throughout their lifetime.[45]

When it comes to treating women with estrogen-sensitive breast cancer, percentage body fat is also of concern.

Recent research suggests that obese women may have higher estrogen levels. A study of estrogen suppression by aromatase inhibitors according to basal metabolic levels (BMI) is needed to determine if dosing needs to be adjusted based upon BMI.[46] A BMI < 25% from childhood throughout their lives should be their goal.

Obesity is also associated with chronic inflammation in our body's tissues and inhibition of cellular repair.[47] Obesity in youth can lead to early menarche and the beginning of lifelong poor eating habits.

Studies conducted to evaluate diet are often difficult to interpret and control, as recall and honesty of the participants is mandatory. Dr. Carlo La Vecchia presented data for the International Agency for Research on Cancer in March 2010. This study revealed data that one-third of all breast cancers can likely be prevented with lifestyle modification.[48,49] The European data on the effect of lifestyle are very powerful. Sustainability of diet and exercise habits is required for the long-term lifestyle changes.

We live in a society where instant gratification and quick fixes are the norm. Modifying one's lifestyle requires each individual to look not only at the foods that we eat but also where and how the foods we eat are grown.

LIFESTYLE CHANGES THAT CAN DECREASE RISK AND PREVENT BREAST CANCER

How can we begin to create a healthier lifestyle? There is no reason to spend time lamenting over the risk factors that are out of our control. First and foremost, we need to change the risk factors that we can control.

#1. Do Not Smoke

Smoking is the leading cause of lung cancer and is associated with the increased incidence of many other cancers including breast cancer. It is also associated with heart disease and stroke. Choosing to smoke is choosing to invite cancer into your life.

#2. Maintain a Healthy BMI < 25%

Women who are overweight produce and store more estrogen. After menopause, the fat deposited between a woman's breasts and her hips is estrogen waiting to happen. Increased exposure to estrogen and risk of breast cancer are directly related. Since estrogen receptor–positive breast cancer is the most common subtype of breast cancer diagnosed after menopause, controlling obesity needs to be a priority. Obese women tend to have a larger breasts' potentially making it more difficult to detect palpable breast tumors in obese women, as compared to lean women.

#3. Avoid Exogenous Estrogen

Given all of the data on estrogen and its relationship to the development of breast cancer, women and girls need to carefully weigh the potential risks with the benefits before beginning any form of hormone therapy. If hormones are needed, go for the lowest dose for the shortest time period.

#4. Alcohol Moderation

Women who have a family history of breast cancer should consider avoiding alcohol altogether or drink it sparingly. Women in general should limit their alcohol intake to less than one drink per day.

#5. Modify the Foods We Eat

By looking at the foods we eat, we can make simple sustainable changes for a healthier tomorrow. We know that certain fruits and vegetables are more susceptible to pesticides, and therefore organically grown varieties are considered superior.

"THE DIRTY DOZEN." The fruits and vegetables that should be considered as safer when they are organic are cherries, grapes, blueberries, strawberries, apples, nectarines, peaches, peppers, celery, spinach kale, and potatoes.

Fruits and vegetables with thick skin are acceptable to buy nonorganic, as pesticides are less likely to penetrate the skin.[50] Eating a diet high in fruits and vegetables makes up the majority of the nutrients in your diet. Eating small meals can also enhance your ability to maintain a healthy weight and fuel your body appropriately. Fiber is also associated with a decreased risk of breast cancer. This is a direct result of the fiber escorting estrogen substrates out of the body via the colon.

#6. Exercise

Exercise and physical activity have been documented to decrease a woman's risk of developing breast cancer. Three to

five hours of physical exercise weekly decreases a woman's risk of breast cancer by 18%. The more lean muscle mass you have the more fat you burn and the less fat remains to be a substrate for estrogen production.[51] Exercise should be varied and include cardiovascular and strength training. Making a sustainable plan and having physical activity be a part of a plan for success is essential.[52] Before beginning any exercise program, a woman should consult with her physician to determine if there are specific limitations and then get to it.

Regular exercise also improves mood, increases self-esteem, and creates a positive body image. Doing regular exercise improves muscle tone, strength, and endurance. Exercise has the protective effect of decreasing heart disease and diabetes risk. It can help lower body weight, which in turn, reduces risk of breast cancer due to obesity.

#7. Stress Reduction

Stress is a major factor in the production of cortisol and inflammatory factors. Managing stress in our overscheduled and technological word can be a challenge. If you fail to plan, then plan to fail. Creating opportunities for you to organize and manage stress before it takes its toll is essential.[53]

#8. Reproductive Education

Young women need to be educated about the choices they can make in their lives that can significantly impact their risk. As a society, over the past 50 years, women have moved into the workforce and delayed childbearing. This change has had a negative impact upon our breast cancer risk. Choosing to have their children younger completes their breast development, which can significantly decrease their risk.

#9. Breast-Feeding

Breast-feeding is directly related to risk reduction. The reduction of the risk is proportional to amount of time breast-feeding occurs (>12 months of breast-feeding is associated with a 60% decreased risk).

#10. Vitamins and Antioxidants

There are several vitamins and antioxidants that can have a significant impact on breast cancer development and risk. The best source of vitamins comes directly from the food that we eat with rare exception. Before beginning a regimen of vitamins and supplements, a woman should discuss the plans with her physician.

Vitamin D

Vitamin D modulates cell growth, neuromuscular and immune function, and reduction of inflammation.[54–56]

Vitamin D deficiencies have been linked to an increased risk for breast cancer. A healthy level of 25-OH vitamin D should be maintained above 40 ng/mL. Women who do not have significant sun exposure (15 min/day) are oftentimes deficient. In addition, sunscreens that protect us from UV sunburn can impair our body's ability to produce vitamin D, leading to low levels. Women should understand the significance of being deficient. Vitamin D3 supplements can be taken to attain a normal level. Antioxidants may play a role in risk reduction by blocking the formation of free radicals and protecting cells from free radical damage.[57] The FDA recommends 1000 IU/day of vitamin D3 or sun exposure of 10 min/day.[58]

CoQ10

Coenzyme Q10 (CoQ10) is considered an important cellular antioxidant, as it is a component of the mitochondrial electron transport chain. A recent multiethnic cohort study found that higher CoQ10 levels in postmenopausal women may be associated with increased breast cancer risk.[59,60] Conversely, low circulating levels of CoQ10 have been associated with an increased incidence of a number of cancers as well as poor prognosis for a number of cancer types. In the Shanghai Women's Health Study, a prospective evaluation of CoQ10 levels was assessed. Circulating levels of CoQ10 were generally low in this population. The observed association with breast cancer risk may be limited to those women with exceptionally low values.[61] Lower levels of CoQ10 in the SWHS population suggest that the two studies may not be contradictory, actually suggesting a nonlinear (U-shaped) association of CoQ10 with risk. Clearly more research on CoQ10 is needed. CoQ10 has not been carefully tested in combination with chemotherapy to see if it is safe and effective. Because CoQ10 is sold as a dietary supplement, the FDA does not regulate it.[62]

Vitamin A

Retinol and β-Carotene

Vitamin A plays an important role in immune surveillance, cell differentiation, and cell division as well as many other functions. The genetic expression of inflammatory mediators in women with breast cancer was evaluated in a case–control study looking at levels of α-tocopherol, retinol, and β-carotene. A study published in the *European Journal of Cancer Prevention* (2011) showed that antioxidant nutrients have a possible biological effect in preventing breast cancer. It also supports the belief that immune response is activated in the course of breast cancer.[63] A large population-based case–control study of women residing in the states of Massachusetts, New Hampshire, and Wisconsin was performed. Five thousand seven hundred women with breast cancer and 6300 controls were interviewed regarding their intake of carotenoid-rich fruits and vegetables for the five previous years. Among premenopausal women who reported ever smoking, these results were stronger than among never smokers, although tests for interaction were not statistically significant. Results from this study are comparable to previous prospective studies. Findings suggested that a high consumption of carotenoids may reduce the risk of premenopausal breast cancer, but not postmenopausal breast cancer. The benefit was greatest in women who smoke.[64]

Daily vitamin A requirements should be obtained from a diet rich in vitamin A. The best food sources are liver, beef, carrots, spinach, kale cantaloupes, apricots, papaya, and mango to name a few of the richest sources.

Folate and Vitamin B

Folate and vitamin B play important roles in the production and maintenance of new cells. They are also needed to make DNA and RNA. In the midst of a cardiac study of folic acid, vitamin B6, and vitamin B12 treatment, a side study revealed that there was no significant effect on overall risk of total invasive cancer or breast cancer among women during the folic acid fortification era.[65] In contrast, the Shanghi Women's Study suggests that vitamins E and B supplements may confer protection against breast cancer among women who have low dietary intake of those vitamins.[66]

High folate intake in a prospective study of 62,000 French women was associated with decreased postmenopausal breast cancer risk.[67] In a study of 19,000 Japanese women of age 40–64 years, folate was found to have a protective effect on women who drink alcohol. In the women who had low folate intake and drank alcohol, there was an increased incidence of breast cancer observed.[68] This suggests a protective effect of folate.

Dietary sources of vitamin B are liver, beef, and many breakfast cereals. Excellent sources of folate include romaine lettuce, spinach, asparagus, turnip greens, mustard greens, calf's liver, parsley, collard greens, broccoli, cauliflower, beets, and lentils.

Vitamins C and E

Vitamins C and E are powerful antioxidants that also play a role in immune surveillance. There have been numerous case–control studies as well as prospective trials looking at the potential protective effect of vitamin C and breast cancer risk with no significant effect.[69] The Nurses' Health Study found no correlation between vitamins E and C with breast cancer prevention, but did find a protective correlation with vitamin A. Vitamin E may confer protection against breast cancer as indicated by the Shanghi Women's Study.[66]

More recently, the University of Rochester looked at the role of α-tocopherol (vitamin E)-associated protein. It is coexpressed with estrogen receptor in the luminal cells of normal/benign breast tissue. They found α-tocopherol-associated protein acting as an antiproliferative factor in estrogen receptor–positive luminal cells in normal/benign breast tissue, which serves as indirect evidence to support a role for vitamin E in breast cancer prevention.[70] More research is needed in the vitamins E and C breast cancer prevention arena.

Nuts, sunflower seeds, and many vegetable oils are the best dietary sources of vitamin E. Citrus fruits are the best source of vitamin C.

Zinc

Zinc is essential for all highly proliferating cells in the human body, especially the immune system. It is advertised on many websites as a breast cancer prevention supplement, but the data to support this are limited. Low levels of zinc impair immune function of many cells. This gives credence to the theoretical anticancer benefit.[71]

Zinc is found in meat, seafood, liver, eggs, milk, and whole-grain products.

Selenium

Selenium helps to produce selenoproteins, which are important antioxidant enzymes that prevent cell damage from free radicals.[72,73] The Nurses' Health Study, a prospective analysis, previously had found no association with selenium levels and breast cancer risk. In this study, the selenium concentrations were assessed through nail clippings.[74] In contrast, McConnell et al. identified a statistically significant inverse relationship between dietary selenium concentrations in the blood and the incidence of human breast cancer. Low selenium levels in the blood were identified in women with breast cancer.[75]

Tissue analysis of selenium and CEA levels correlated with serum levels revealed that the tissue concentrations in tumors had statistically higher concentrations compared to controls.

There was no correlation between serum/tissue selenium concentration and stage of the disease. The decrease in serum selenium combined with the increase level in the neoplastic breast tissue may reflect part of the defense mechanisms against the carcinogenetic process in the development of breast cancer.[76]

In a study of selenium and glutathione peroxidase activity, Moradi et al. found no difference in the levels of selenium in healthy controls compared to breast cancer patients, but did show an increased glutathione peroxidase activity that may have a protective effect against oxidative damage.[77] The relationship between serum selenium levels and breast cancer risk is still not completely delineated.

The best source of selenium is through the diet. Sources include brazil nuts, tuna, cod, turkey, and beef.

Caffeine

Coffee is a major source of antioxidants in the American diet. Previous studies have indicated that high coffee consumption might modestly reduce breast cancer risk; however, a meta-analysis of more than 500 reports about coffee's relationship to several types of cancer showed no association with breast cancer.[78] In a recent study, coffee consumption was found to be associated with a strong reduction in breast cancer risk for the ER–tumor subtype by up to 50% odds reduction. This effect was independent of hormone replacement therapy, smoking, highest education level attained, and average daily alcohol consumption.[79] The good news is that coffee consumption is not associated with any increased risk of breast cancer. The data are looking favorable for risk reduction in certain breast cancer subtypes.

#11. Pharmacologic Risk Reduction

There are two medications known as selective estrogen receptor modulators or SERMs. SERMs act like estrogen in some tissues but behave as antiestrogen in others. Tamoxifen

(Nolvadex) and raloxifene (Evista) are approved for breast cancer prevention for high-risk women (GAIL risk >1.7% 5 years and >20% lifetime risk). Tamoxifen and raloxifene are not recommended as prevention for women at low risk for breast cancer or its recurrence. Women with a history of current risk factors for stroke or heart disease should discuss with their doctors whether raloxifene is an appropriate choice. Raloxifene can cause birth defects and is approved only for postmenopausal women. Women at high risk for breast cancer should discuss the risks and benefits of antiestrogen therapy with their personal physician.

#12. Environmental Choices

In your daily life, make conscious choices to improve how you purchase, store, and cook your food. Limit the use of canned foods and plastic containers as chemicals can leach out of them. Use plastics with the recycling codes #1, #2, #4, and #5.[80–82] Prepare your foods to maintain the nutrients you need to remain healthy. Steaming, poaching, stir-frying, roasting, broiling, grilling, and sautéing will give you your best opportunity to retain the nutrients. Microwaving is acceptable but do not microwave in plastic.[81] Avoid using nonstick pans at high heat as they can release harmful chemicals.[83] The choice is yours on a daily basis to create positive changes in your life.

FUTURE

The only constant thing in life is change.

Despite significant advances in screening and treatment, breast cancer incidence is on the rise. Family history cannot be changed, but there remain many lifestyle modifications that can greatly impact individual breast cancer risk and ultimately the global breast cancer risk. If we as a society are going to impact the overall incidence of breast cancer, we need to get to work now. We need to create positive changes in our lives and increase personal accountability. Young women and girls need to be encouraged to make sustainable healthy choices and changes in their lives that will reduce their risk of developing breast cancer.

RESOURCES

1. Think Pink, Live Green: A Step-By-Step Guide to Reducing Your Risk of Breast Cancer, www.breastcancer.org/about_us/press_room/press_kit/think_pink.jsp
2. Breast Cancer.org, www.breastcancer.org
3. American Society of Breast Surgeons, www.breastsurgeons.org
4. American Cancer Society, www.cancer.org
5. National Cancer Institute, www.cancer.gov
6. National Institutes of Health, www.health.nih.gov
7. Myriad Genetics, www.myriad.com

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24 Osteoporosis

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CONTENTS

Introduction 300
Epidemiology 300
Genetics of Osteoporosis 300
Pathophysiology of Osteoporosis 301
Risk Factors for Osteoporosis 301
- Physiological Risk Factors 301
- Heritable Risk Factors 301
- Pathological Risk Factors 301
- Medications as Risk Factors 301
- Lifestyle Risk Factors 302

Screening Recommendations for Osteoporosis 302
Evaluation and Diagnosis of Osteoporosis 303
- Identifying Causes of Secondary Osteoporosis 303

Osteoporosis in Premenopausal Women 304
Prevention and Treatment of Osteoporosis 304
- Lifestyle 304
- Nonpharmacological Treatment 305
  - Calcium Supplementation 305
  - Vitamin D or Vitamin D Analogs 305
  - Vitamin K 305
  - Prevention of Fractures by Use of Hip Protectors 305
- Pharmacological Treatment 305
  - Bisphosphonates 306
  - Controversies in Treatment with Bisphosphonates 307
  - Estrogen Agonists and Antagonists 308
  - Teriparatide 308
  - Estrogens 308
  - Calcitonin 308
  - Combination Therapies 308
  - Tibolone 309
  - Denosumab 309
  - New Horizons for Treatment 309

Monitoring the Therapy of Osteoporosis 310
Individualizing the Treatment of Osteoporosis: Case Discussions 310
- Case 1 310
- Case 2 310
- Case 3 310
- Case 4 310
- Case 5 310

Pearls 311
References 311

INTRODUCTION

Osteoporosis, from the Greek words *osteon* for bone and *poros* for pore, is a skeletal system disorder characterized by decreased bone strength leading to increased susceptibility to fracture [1]. The peak bone mass that is achieved by the third decade of woman's life is a major determinant of future bone health and osteoporosis risk. The process of bone loss also begins at that time and accelerates at menopause. By age of 80 years, many women have lost, on average, ~30% of their peak bone mass [2]. Bone strength (and hence, fracture risk) depends on many qualities of bone, of which bone mineral density (BMD) is the most commonly measured [1]. The World Health Organization (WHO) and the International Society of Clinical Densitometry have defined osteoporosis in a postmenopausal woman or a man over age of 50 years as a BMD that lies 2.5 standard deviations or more below the average value of less than or equal to *T*-score of −2.5 at the total hip, femoral neck, or lumbar spine (Table 24.1). If anatomic factors such as obesity or arthritis make measurements invalid, the distal one-third radius bone density may be measured [3]. Microarchitectural changes result in less bone mass, which causes decreased bone density, thus predisposing the skeleton to fractures that may occur with minor force or trauma [1]. Fractures that are secondary to osteoporosis are called fragility (low-trauma) fractures, because they result from trivial trauma commonly involving vertebrae, the hip, and the distal radius but in general they can affect any bone of the skeletal system. The diagnosis of osteoporosis can be made clinically by the presence of a fragility (low-trauma) fracture regardless of the *T*-score.

Osteopenia is a state of low bone density, which is a precursor of actual bone disease, that is, osteoporosis. Osteopenia is defined by WHO as a *T*-score between −1.1 and −2.4 standard deviations below the mean [4]. It has been identified as an independent risk factor for future fracture, yet it remains underdiagnosed and undertreated in postmenopausal women. If early intervention with preventive measures is incorporated among the osteopenic population, it may significantly minimize future morbidity, mortality, and health care costs.

TABLE 24.1
World Health Organization and National Osteoporosis Foundation Criteria for Classification of Osteoporosis and Osteopenia

Category	*T*-Score
Normal	−1.0 or more
Osteopenia	−1.1 to −2.4
Osteoporosis	−2.5 or less or fragility fracture
Severe osteoporosis	−2.5 or less and fragility fracture

EPIDEMIOLOGY

Osteoporosis has been recognized as an established and well-defined disease that affects more than 75 million people in the United States, Europe, and Japan [5]. Osteoporosis causes more than 8.9 million fractures annually worldwide, of which more than 4.5 million occur in United States and Europe. According to the National Osteoporosis Foundation, it has been diagnosed in 10 million Americans, and another 34 million are at risk. In 2005, osteoporosis was responsible for an estimated 2 million fractures and $19 billion in cost. By 2025, experts predict that osteoporosis will be responsible for ~3 million fractures and $25.3 billion in cost each year. Estimates suggest that about half of all women older than 50 years will break a bone because of osteoporosis [4]. Many more women have osteoporotic fractures (1.4 million) [6] than new strokes (373,000) [7], heart attacks (345,000) [7], or invasive breast cancer (213,000) [8] combined, according to recent statistics (2004–2006).

Osteoporosis not only is a major cause of fractures but also ranks high among diseases that cause disability with serious complications. These complications may be life-threatening in elderly people. In the United States and Europe, osteoporotic fractures account for 2.8 million disability-adjusted life years annually, somewhat more than accounted for by hypertension and rheumatoid arthritis [5], but less than diabetes mellitus or chronic obstructive pulmonary diseases.

GENETICS OF OSTEOPOROSIS

Bone mass is a complex trait that is affected by multiple hereditary, physiological, and environmental factors. Osteoporosis is often a multifactorial disease and has a strong genetic component. Twin studies have shown that genetic factors play a role in determining BMD, skeletal geometry, and bone turnover markers. Peak bone mass and rate of bone loss have separately been shown to be under genetic control [9,10]. In the search for genes responsible for bone strength, linkage studies in humans and animals have developed to map chromosomal regions that may be involved in the bone mass and skeletal geometry.

Linkage studies involve genotyping large number of polymorphic markers throughout the genome and relating them to the inheritance of a phenotype among members of a family. This technique has localized genes for various Mendelian inheritances and has identified components of complex (i.e., non-Mendelian) traits [11]. Genome-wide linkage studies in humans have identified foci on several chromosomes associated with BMD. To date, the genes that regulate bone mass are only partially characterized [10]. In order to determine their known or hypothetical effect on bone metabolism, candidate gene evaluation is performed. Approximately 20 candidate genes have been shown to be associated with BMD; most important are the vitamin D receptor (VDR), type I collagen alpha (COL1A1 and COL1A2), estrogen receptor alpha (ER-α), and transforming growth factor beta (TGF-β) [10].

The demonstration of association with these genes does not prove a cause-and-effect relationship; instead, multiple genes affect bone mass and each individual gene has a relatively small effect.

PATHOPHYSIOLOGY OF OSTEOPOROSIS

The skeleton is composed of two types of bones: cortical bone constituting the long bones and providing structure and stability, and trabecular bone found in the spine, both involved in calcium homeostasis. Our bones are in a dynamic state of remodeling throughout life, in which the old bone is destroyed by osteoclasts and new bone is formed osteoblasts. Osteoclasts are multinucleated giant cells that develop from hematopoietic stem cell precursors. Activated osteoclasts bind along the ruffled borders of internal bone surfaces and secrete acid proteolytic enzymes and free radicals, which dissolve the underlying bone, leaving resorption pits [12]. As osteoclasts migrate along bone surfaces, they also release cytokines that activate nearby osteoblasts, which develop from mesenchymal cell precursors. Multiple osteoblasts are recruited in the recently excavated resorption pits and fill these cavities by secreting osteoid, a bone-specific collagen. If the calcium and phosphate concentration in the circulation and extracellular fluid are adequate, calcium phosphate (hydroxyapatite) crystals precipitate into the new osteoid, causing it to harden and mature. Osteoblasts then develop into mature osteocytes and reside in the crypts within bone tissue. These cells act as mechanoreceptors that sense developing areas of skeletal stress and then orchestrate local bone remodeling by sending signals to the other bone cells to activate or suppress new bone remodeling units in the appropriate areas.

Peak bone mass is the major determinant of future osteoporosis risk, and optimal achievement is usually multifactorial [12]. Uncoupling of bone turnover, leading to either increase or decrease formation, may result in either net bone gain, as occurs in Paget's disease of bone, or net bone loss, as occurs in postmenopausal women, primary hyperparathyroidism, glucocorticoid use, estrogen deficiency, and rheumatoid arthritis [13,14]. Bone resorption occurs by two main biochemical pathways: the cathepsin K and the metalloproteinase-dependent pathways, leading to increased osteoclastic activity.

Recently, the receptor activator of nuclear factor-κb (nuclear factor kappa-light-chain-enhancer of activated B cells) (RANK), its ligand RANKL, and a decoy receptor, osteoprotegerin (OPG), have emerged as major local regulators of bone remodeling [15]. RANKL, synthesized by osteoblasts and stromal cells and present in the bone microenvironment, binds to RANK, expressed in osteoclast progenitor cells in the bone marrow, and promotes osteoclastogenesis. OPG is also synthesized by osteoblasts and stromal cells and serves as a decoy receptor for RANKL, preventing the binding of RANKL to RANK. Regulation of osteoclast activity depends, at least in part, on the balance between RANKL and OPG. The relative amount of these two molecules is governed, in turn, by systemic hormones (e.g., estrogen), local factors (such as interleukin-6 and tumor necrosis factor), and perhaps other factors as well [15,16].

RISK FACTORS FOR OSTEOPOROSIS

Potential risk factors should be classified into two broad categories: risk factors for *osteoporosis* as defined by BMD (both primary and secondary causes) and risk factors for *osteoporotic fracture*. For BMD-defined osteoporosis, common risk factors in women are advanced age, genetics, lifestyle factors, and menopause status.

Among risk factors for osteoporotic fractures, the most common ones are prior fragility (low trauma) fracture, parental history of hip fracture, current tobacco smoking, and long-term glucocorticoid use.

Women with multiple risk factors are at greater risk of fracture if they also have lower BMD. The use of BMD *T*-scores to assess fracture risk can be markedly improved by combining it with other significant risk factors [17], as used in the FRAX model.

Physiological Risk Factors

Age has been identified as a nonmodifiable risk factor for osteoporosis and hip fracture. After age of 50 years, risk of osteoporotic fracture doubles every 7–8 years. In women, the median age of vertebral fractures is calculated to be in the 70s; and the median age for hip fractures is 82 years [18].

Heritable Risk Factors

Heredity has the most basic influence on a woman's peak bone mass, that is, the maximum BMD gained during the skeletal development and maturation phase is determined by their genetic makeup. Studies have suggested that up to 80% of the variability in peak BMD might be attributable to genetic factors [19,20]. Daughters of women who have osteoporotic fractures have lower BMD than would be expected for their age [21,22]. First-degree relatives of women with osteoporosis also tend to have lower BMD than those with no family history of osteoporosis [23]. In a recent meta-analysis, hip fracture risks were 50%–127% higher if a hip fracture had occurred in a parent [24]. The importance of occurrence of hip fracture in parents is highlighted further by taking it into consideration in the FRAX score.

Pathological Risk Factors

Certain pathological causes have a severe impact on attainment of peak bone mass. Anorexia nervosa, hyperthyroidism, hyperparathyroidism, cystic fibrosis, malabsorption syndromes (e.g., celiac disease), and inflammatory arthritis are associated with lower bone mass compared to age-matched controls (Table 24.2).

Medications as Risk Factors

Many life-saving medications pose a threat to bone health. The most notorious of them all are glucocorticoids. A dose-dependent effect was noted with a dose of prednisolone of ≥7.5 mg/day (relative risk of vertebral fracture 5.2), whereas

TABLE 24.2
Causes of Secondary Osteoporosis

Endocrine disorders
Hyperparathyroidism
Hyperthyroidism
Hypercortisolism
Hyperprolactinemia
Acromegaly
Parathyroid hormone–releasing hormone-secreting tumor

Eating disorders
Type 1 diabetes mellitus
Exercise-induced amenorrhea
Premature ovarian insufficiency

Gastrointestinal disorders
Chronic liver disease
Short bowel syndrome
Celiac disease
Pancreatic insufficiency
Inflammatory bowel disease
Parenteral nutrition

Renal disorders
Chronic renal failure
Hypercalciuria

Hematologic disorders
Leukemia/lymphoma
Mastocytosis
Amyloidosis
Multiple myeloma
Hemochromatosis
Benign gammopathies
Thalassemia
Pernicious anemia
Sickle cell anemia

Genetic disorders
Marfan syndrome
Homocysteinuria
Hypophosphotasia
Type I collagen mutation
Osteogenesis imperfecta
Ehler–Danlos syndrome
Neurofibromatosis
Congenital porphyria

Medications
Glucocorticoids
Aromatase inhibitors
Heparin
Cytotoxic agents
Chronic depo-MPA
Anticonvulsants
GnRH agonists
Thyroxin
Selective serotonin reuptake inhibitors
Lithium

with 5.0–7.5 mg/day, the risk was lower (relative risk 2.6). Ever-use of glucocorticoids has been associated with significantly increased risk of any fracture at all ages compared with the risk faced by people with no glucocorticoid exposure [25]. Among other medications, aromatase inhibitors, excess thyroid hormones, unfractionated (high-molecular-weight) heparin, cyclosporine, gonadotropin-releasing hormone agonists, chronic depo-medroxyprogesterone acetate (depo-MPA), methotrexate, phenobarbital, phenothiazines, phenytoin, and tamoxifen rank high in lowering BMD and increasing the risk of fractures.

Lifestyle Risk Factors

Several randomized controlled trials have demonstrated that brisk walking increases the bone density of both the spine and the hip in postmenopausal women. Physical activities, specifically weight-bearing exercises, increase the bone density of the spine. Moreover, several epidemiologic studies have demonstrated that smoking decreases bone density and increases the risk of fractures in both men and women. Drinking alcohol heavily also poses a risk to bone health. An increased tendency to fall, due to many factors (such as impaired vision and poor body balance), may be reduced effectively by doing Tai'Chi exercises, muscle and balance training, and reducing psychopharmacological therapies. Making healthy choices in diet that can provide optimum calcium and vitamin D in the most natural way or facilitate its absorption, if taken in the form of supplements, is pivotal.

SCREENING RECOMMENDATIONS FOR OSTEOPOROSIS

There is no convincing direct evidence that screening for osteoporosis reduces fractures. However, there is good indirect evidence that screening is effective in identifying postmenopausal women with low BMD and that treating osteoporosis can reduce the risk of fractures of the wrist and spine in this population.

The January *2011 USPSTF Guidelines* state that any woman younger than age of 65 years whose fracture risk is equal to or greater than that of a 65-year-old white woman should be screened with dual-energy x-ray absorptiometry (DXA). The USPSTF also reinforced its existing guidelines calling for all women 65 years of age and older to receive regular screening [26].

The North American Menopause Society (NAMS) recommends that BMD be measured in the following populations [27]:

- All women age of 65 years and over, regardless of clinical risk factors
- Postmenopausal women with medical causes of bone loss (e.g., steroid use, hyperparathyroidism), regardless of age

- Postmenopausal women age of 50 years and over with additional risk factors
- Postmenopausal women with a fragility (low trauma) fracture (e.g., fracture from a fall from standing height)

BMD testing should be considered for postmenopausal women age of 50 years and older who have one or more of the following risk factors:

- Previous fracture (other than skull, facial bone, ankle, finger, and toe) after menopause
- Thinness (body weight ≤127 lb [57.7 kg] or BMI ≤21 kg/m^2)
- History of hip fracture in a parent
- Current smoking
- Rheumatoid arthritis
- Excessive alcohol intake

There are no recommendations for a specific age at which screening should no longer be offered because the risk of fracture continues to increase with age and the evidence indicates that benefits can be realized within 6–24 months after starting treatment.

EVALUATION AND DIAGNOSIS OF OSTEOPOROSIS

Like any medical evaluation of a pathological cause, *history taking* is the cornerstone in risk-stratifying the patients for the screening of osteoporosis. Medical, surgical, family, menopause, social, and medication histories all facilitate the early screening, timely diagnosis, and prevention/treatment of osteopenia/osteoporosis among high-risk populations. Determining the number and the severity of existing vertebral fractures can help predict the risk of future fracture as well.

The *physical examination* should include an annual measurement of height and weight, along with an assessment for acute or chronic back pain, kyphosis, and clinical risk factors. Height should be measured annually with an accurate method, such as a wall-mounted ruler or a stadiometer. Loss of 1.5 in. (3.8 cm) or more calls for evaluation by a lateral thoracolumbar radiograph or vertebral fracture assessment (VFA) by DXA to identify vertebral fractures [27]. Grading of vertebral fractures and percentage of height reduction (grade 1, mild, 20%–25%; grade 2, moderate, 25%–40%; grade 3, severe, over 40%) by a Genant semiquantitative methodology or equivalent are most important in the evaluation of height loss in the patient with severe osteoporosis [27]. Weight should be measured annually and BMI calculated to identify patients with a low BMI and to be aware of weight changes, as it may interfere with the interpretation of BMD changes overtime [27].

Various methods of imaging exist for the assessment of low BMD. The gold standard for densitometry today is DXA.

TABLE 24.3
Indications for Bone Mineral Density Screening

Age 65 years and older in female patients
Prior fragility fracture, defined as occurrence after 40 years of age
History of hip fracture among first-degree relatives
Low body mass index, i.e., <21 kg/m^2, or low body weight, i.e., <127 lb
Corticosteroid use of 7.5 mg daily for ≥3 months ever in lifetime
Personal history of smoking
Alcohol intake more than three drinks per day
Estrogen-deficient or postmenopausal state in female patients
Monitoring of treatment with agents to prevent or treat osteoporosis

Quantitative computed tomography (QCT) identifies individuals with low bone density as well. Quantitative ultrasonography (QUS), radiodensitometry, peripheral DXA (pDXA), peripheral QCT (pQCT), and single-energy x-ray absorptiometry (SXA) are less commonly used to determine risk of fracture in the United States [28]. Bone architecture can be assessed to determine trabecular connectivity and trabecular volume using magnetic resonance and micro-CT [29]. When BMD testing is indicated (Table 24.3), central DXA is the preferred technique. The total hip, femoral neck, and posterior anterior lumbar spine should be measured, using the lowest of the three BMD scores.

The prediction of hip fracture and other osteoporotic fractures has been based on assessment algorithms [30] that include clinical risk factors alone, or the combination of clinical risk factors plus BMD at the femoral neck (available at www.shef.ac.uk/FRAX). The FRAX algorithms are suitable for men and postmenopausal women.

The FRAX models have been developed by WHO from studying population-based cohorts from Europe, North America, Asia, and Australia. The FRAX algorithms give the output as a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture). By utilizing the FRAX model, treatment is indicated if the 10-year risk of hip fracture is greater than 3% or the 10-year risk of any osteoporotic fracture is greater than 20%.

The routine use of biochemical markers of bone turnover (Table 24.4) is not generally recommended in clinical practice and not used for diagnosis of osteoporosis.

Identifying Causes of Secondary Osteoporosis

It is important to identify and treat the potential underlying disorders that may be the basic etiology of osteopenia or osteoporosis. To date, there are no guidelines for the initiation of a workup for secondary causes. However, it is intuitive to screen women who have very low age-matched score *Z*-scores. The ISCD recommends screening for secondary causes in those with a low *Z*-score (–2 or less), men with osteoporosis, unexplained fracture (i.e., low trauma fracture with a normal BMD), poor response to treatment, or a high index of clinical suspicion based on the history and physical examination [31].

TABLE 24.4
Commonly Used Bone Turnover Markers

Bone Marker	Formation	Resorption	Measured
Bone-specific alkaline phosphatase (SPAP)	Yes	—	Serum
Amino-terminal propeptide of type I collagen (PINP)	Yes	—	Serum
Osteocalcin	Yes	—	Serum
Amino-terminal cross-linked telopeptide of type I collagen (NTX1)	—	Yes	Serum or urine
Carboxy-terminal cross-linked telopeptide of type I collagen (CTX1)	—	Yes	Serum or urine
Carboxy-terminal propeptide of type I collagen (PICP)	Yes	—	Serum
Pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP)	—	Yes	Serum
Tartrate-resistant acid phosphatase (TRAP-5β)	—	Yes	Serum
Deoxypyridinoline cross-linked carboxy-terminal of collagen (DPD)	—	Yes	Serum

There are various endocrine/metabolic, gastrointestinal, renal, hematologic, genetic, and hormonal disorders that can lead to osteoporosis (Table 24.2). Malignancy, organ transplantation, and various medications such as glucocorticoids, anticonvulsants, aromatase inhibitors (e.g., Arimidex, Femara, Aromasin), chronic depo-MPA (Depo-Provera) use for contraception for more than 2 years, GnRH agonists like Lupron, high doses of thyroxine, and cytotoxic drugs are also recognized to cause secondary osteoporosis.

Patients with *Z*-scores of −2 or less or with the clinical suspicion of secondary bone disease should have a minimum workup including a complete blood count, blood urea nitrogen, serum creatinine, serum calcium, phosphorous, thyroid-stimulating hormone, 25-OH vitamin D, intact parathyroid hormone (PTH; if the calcium level is normal), and 24 h urine calcium/creatinine (Table 24.5; [32]).

TABLE 24.5
Laboratory Workup to Evaluate the Causes of Secondary Osteoporosis

In all cases	Complete blood count (CBC)
	Comprehensive metabolic profile (CMP)
	Serum calcium
	Serum phosphorous
	Serum parathyroid hormone (PTH)
	Thyroid-stimulating hormone (TSH)
	25-OH vitamin D
In some cases	24 h urine calcium/creatinine
	Spot urine NTX/Cr
	SPEP/UPEP if anemic
	ESR/CRP if anemic
	Testosterone
	Urine cortisol
	Transglutaminase IgA and total IgA if anemic and vitamin D deficiency

OSTEOPOROSIS IN PREMENOPAUSAL WOMEN

Peak bone density is achieved between the ages of 20 and 39 years. During the reproductive years of a woman's life, various hormonal, physical, and biochemical factors influence the attainment and preservation of bone mass. Dietary habits, physical activity, hormonal breast cancer treatment, gonadotropin-releasing hormone agonists, pregnancy, and lactation are few important factors that may contribute to BMD gain or loss during young age [28].

Low bone density in a premenopausal woman on a single study should be interpreted with extreme caution, as it is only a single snapshot of bone health and does not demonstrate that patient has attained peak bone density. It should always be correlated to the present physical, clinical, social, and environmental condition, and the secondary causes (Table 24.2) should be explored before starting treatment.

It has been reported that GnRH agonist and norethindrone acetate alone or combined with low-dose conjugated equine estrogens administered to symptomatic endometriosis patients for 12 months provides extended pain relief and BMD preservation after completion of therapy [33].

PREVENTION AND TREATMENT OF OSTEOPOROSIS

Lifestyle

Prevention of a disease process always begins with lifestyle modifications, as they form the foundation of healthy living. Regardless of their bone density or clinical risk factors for osteoporosis, everyone should be encouraged to eat a balanced diet, optimize their intake of calcium and vitamin D, participate in weight-bearing exercises for at least 30 min daily, avoid cigarette smoke and excessive caffeine and alcohol consumption, and institute fall-prevention measures. The success of these approaches is heavily dependent on patient education and motivation to institute them [27].

Nonpharmacological Treatment

Calcium Supplementation

Adequate calcium intake is a simple and inexpensive strategy to prevent osteoporotic fractures. In a consensus statement, the United States National Institutes of Health claimed that the intake of high levels of calcium—for example, from milk and cheese—reduces the risk of osteoporosis. Furthermore, various clinical trials have demonstrated that combination of calcium and vitamin D intake is more effective than vitamin D alone.

A recent cohort study of 36,282 women showed that women older than 60 years who receive calcium plus vitamin D supplements have a significantly reduced risk of hip fractures (about 30% less risk) if they adhere to treatment.

Lifelong adequate calcium intake is pivotal for the acquisition of peak bone mass and subsequent maintenance of bone health. Our skeleton stores 99% of the body's calcium; when the exogenous supply is inadequate, resorption of calcium from bone tissue begins in order to maintain serum calcium within normal range. The National Osteoporosis Foundation [34] supports the National Academy of Sciences recommendation (1997) that women older than age of 50 years consume at least 1200 mg/day of elemental calcium. Intakes in excess of 1200–1500 mg/day have limited potential for benefit and may increase the risk of developing kidney stones or cardiovascular disease [34].

A small, nonstatistically significant increase in myocardial infarction (hazard ratio 1.31, 95% CI 1.02–1.67, $P = 0.35$) in patients taking elemental calcium supplements >500 mg/day was reported in a meta-analysis [35]. However, there was no increase in mortality seen among the calcium supplementation group. This study excluded patients taking a multivitamin containing calcium and patients taking a combination calcium and vitamin D supplement. Observational studies comparing calcium obtained from dietary sources versus supplements in postmenopausal females showed that the former group had a 30%–40% lower risk of cardiovascular mortality if they consumed more than 1400 mg of calcium in their diet [36].

Vitamin D or Vitamin D Analogs

Vitamin D is the sunshine vitamin synthesized in the skin in response to ultraviolet B radiation. It exists in two biochemical forms: vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). The source of vitamin D3 is from skin exposure to sunlight, animal sources (salmon, sardines, cod liver oil, egg yolks), or supplements. Vitamin D2 is found in some plants and produced commercially by irradiation of yeast for food fortification and vitamin supplements. Both forms of vitamin D are converted to 25-OH vitamin D in the liver, and its serum levels are measured to determine the clinical adequacy [37]. It is essential for the absorption of calcium from the gut, mineralization of the skeleton, muscle strength, balance, and prevention of falls [37–39]. The National Academy of Sciences recommends 400 IU of vitamin D in normal adults 51–70 years old and 600 IU/day for those above 70 years of age. Many experts now believe that these recommendations are too low [15,16]. For adults 50 years old or older, the National Osteoporosis Foundation recommends 800–1000 IU of vitamin D per day, but many experts recommend more—1000–2000 IU/day (see http://www.aace.com/alert/alert11302010.php); 4000 IU/day is the "safe upper limit"—and some patients require considerably more supplementation to achieve desirable levels [40]. Homebound individuals with limited mobility, patients who have intestinal malabsorption, or those who are receiving long-term anticonvulsant or glucocorticoid therapy are particularly at risk for vitamin D deficiency. The currently accepted minimal level for 25-OH vitamin D adequacy is 30–32 ng/mL, on the basis of a growing body of evidence indicating that secondary hyperparathyroidism is increasingly common as 25(OH) D levels decline below 30 ng/mL [41] and that fractional calcium absorption improves with vitamin D supplementation in patients with levels below 30 ng/mL. A reasonable upper limit, based on levels in sun-exposed healthy young adults, is 60 ng/mL [42].

Vitamin K

Dark green vegetables are rich in vitamin K, which is also produced by the body. Some epidemiologic studies have found that low intake of vitamin K is associated with low bone density and increased prevalence of fractures. This association is difficult to verify, since deficiency of vitamin K also is a marker of poor dietary intake.

Prevention of Fractures by Use of Hip Protectors

A hip protector usually consists of specially designed underwear with a built-in plastic shield for the hip protection. Several trials of hip protectors found both positive and no effects. A recent systematic review of 15 trials pooled data from 11 of these and showed evidence of a marginally significant reduction in the incidence of hip fracture. The authors of the review point to the great heterogeneity of the patients studied in the different trials, which were included in this meta-analysis. In reviewing data from three individually randomized trials, involving 5135 community-dwelling participants provided with hip protectors, no reduction in the incidence of hip fractures was demonstrated [43].

Pharmacological Treatment

The AACE categorizes the pharmacological treatment of osteoporosis in two groups:

First priority: Agents approved by the U.S. Food and Drug Administration (FDA) for the prevention or treatment (or both) of osteoporosis (Table 24.6).

Second priority: Agents not approved by the FDA but for which level 1 or level 2 evidence for efficacy and safety is available. These agents may be appropriate for patients who are unable to take approved agents.

Adherence and persistence are poor for osteoporosis therapies [44], as they are for other silent diseases such as hypertension and hyperlipidemia. Compliance with therapy

TABLE 24.6
FDA-Approved Drugs for Preventing and Treating Osteoporosis

Generic Name and Relative Cost	Brand Name	Dosing Method	Dosing Interval	Postmenopausal Osteoporosis		Glucocorticoid-Induced Osteoporosis	
				Prevention	Treatment	Prevention	Treatment
Alendronate $	Fosamax, Fosamax Plus D, generic	Pill liquid (in weekly dose only)	Daily, weekly	Yes 5 mg daily 35 mg weekly	Yes 10 mg daily 70 mg weekly	No	Yes
Calcitonin $$	Miacalcin, Fortical	Nasal spray, SQ or IM injection	200 μm (1 spray to nostril daily) or injection 100 U every other day	No	Yes	No	No
Denosumaub $$$$	Prolia	SQ injection	60 mg every 6 months	No	Yes	No	No
Estrogen $	Many	Various	Various	Yes	No	No	No
Ibandronate $$	Boniva	Pill	Daily, monthly	Yes 2.5 mg daily 150 mg monthly	Yes 2.5 mg daily 150 mg monthly	No	No
Ibandronate $$	Boniva	Intravenous injection	Every 3 months	No	Yes 3 mg every 3 months	No	No
Raloxifene $$	Evista	Pill	60 mg daily	Yes	Yes	No	No
Risedronate $$	Actonel, Atelvia	Pill	Daily, weekly, monthly	Yes 5 mg daily 35 mg weekly 150 mg monthly	Yes 5 mg daily 35 mg weekly 35 mg weekly delayed release 150 mg monthly	Yes	Yes
Teriparatide $$$$$	Forteo	SQ injection	25 μg (250 μg/mL) daily for up to 2 years	No	Yes	No	No
Zoledronate $$$$	Reclast	Intravenous injection	IV	Yes 5 mg every other year	Yes 5 mg every year	Yes	Yes

As the number of $ signs increases it means the medication is more costly.
$, least expensive.
$$$$, most expensive.

should be reinforced by educating the patients, addressing their concerns, and scheduling periodic follow-up visits to ensure appropriate intake of medication and check for any possible side effects [16]. Correction of disorders of mineral metabolism such as calcium and/or vitamin D deficiency is mandatory before initiating therapy.

Bisphosphonates

This class of drugs works by inhibiting the activity of osteoclasts and shortening osteoclast lifespan, thereby reducing bone resorption. The most common adverse effect of oral bisphosphonate therapy is esophageal and gastric irritation, particularly affecting individuals who dose inappropriately. Serum creatinine should be used to estimate the glomerular filtration rate; treatment may be initiated only if the rate is 30 mL/min or greater (35 mL/min with IV zoledronic acid [Reclast]) [16,45].

Clinical trials have demonstrated that bisphosphonates significantly increase BMD at the spine and hip in a dose-dependent manner in both younger and older postmenopausal women. In women with osteoporosis, bisphosphonates have been shown to reduce the risk of vertebral fractures by 40%–70% and reduced the incidence of nonvertebral fractures, including hip fracture, by about 20%–35%.[88,191] Most of the bisphosphonates approved for osteoporosis therapy in both the United States (alendronate, ibandronate, and risedronate) and Canada (alendronate, etidronate, and risedronate) are available in oral formulations for daily and intermittent dosing regimens. Zoledronic acid (Reclast) is available only as an IV injection 5 mg yearly (Table 24.6).

Alendronate

Alendronate (marketed as Fosamax) is FDA approved as an oral tablet in the United States for postmenopausal osteoporosis prevention (5 mg/day or 35 mg/week) and treatment

(10 mg/day or 70 mg/week). It is also available in a single weekly oral tablet of 70 mg with 5600 IU of vitamin D (Fosamax Plus D; Fosavance). It is also approved for treatment of osteoporosis in men and for glucocorticoid-induced osteoporosis. In the Fracture Intervention Trial (FIT), daily alendronate therapy for 2.9 years significantly reduced the risk of vertebral fracture by 47% and of hip fracture by 51% in women with low BMD and previous vertebral fracture [46].

Risedronate

Risedronate, marketed as Actonel, is FDA approved in the United States for the prevention and treatment of postmenopausal osteoporosis. It is available in oral tablet doses of 5 mg/day, 35 mg/week, and 150 mg/month. Atelvia is a new formulation that is taken on a full stomach after breakfast and is dosed as 35 mg/week.

Risedronate is also approved for osteoporosis in men and glucocorticoid-induced osteoporosis. Its efficacy has been studied in clinical trials for up to 7 years, but clinical experience of its use extends to 9 years. It is recommended to offer a 1-year drug holiday after 3 years of use. After 1 year of drug holiday, it should be resumed [16].

Ibandronate

Ibandronate has been FDA approved for the prevention and treatment of osteoporosis in postmenopausal women. It reduces the vertebral fractures but not proven to reduce the risk of nonvertebral or hip fractures. It is available as an oral dose of 2.5 mg daily, 150 mg monthly, and 3 mg monthly given intravenously. Its efficacy has been studied in the clinical trials for 3 years duration [16].

Zoledronic Acid

Zoledronic acid (Reclast) is given intravenously as 5-mg infusion over a minimum of 15 min every year for treatment and every other year for prevention of osteoporosis. It has been approved for prevention and treatment of glucocorticoid-induced osteoporosis, osteoporosis in postmenopausal women, in men, and in patients after surgical repair of hip fracture [47]. Patients should have their serum calcium and creatinine levels checked and be appropriately hydrated before each infusion. It has been shown to reduce hip, vertebral and nonvertebral fractures. Its efficacy has been studied for 3–6 years in clinical trials [16].

Controversies in Treatment with Bisphosphonates

Duration of Treatment with Bisphosphonates

The Fracture Intervention Trial long-term extension (FLEX) was the largest study done in this regard. In this trial, 1099 patients from the FIT trial [46] who had received alendronate for 3 years were randomized to receive alendronate 10 mg/day, alendronate 5 mg/day, or placebo for another 5 years. In comparison to those treated for 8 years, those treated for 3 years showed significant declines in BMD at total hip (−2.4%, 95% CI −2.9% to −1.8%, $P < 0.001$) and spine (−3.7%, 95% CI −4.5 to −3.0, $P < 0.001$). There was a reduction in clinically recognized vertebral fractures for those receiving 8 years of alendronate (RR 0.45, 95% CI 0.24–0.85) but no significant reduction in fracture at other sites. Interestingly, bone turnover markers (which signal bone resorption) increased in those taken off treatment, 56% for C-telopeptide and 60% for serum *N*-propeptide of type I collagen but sill remained lower than pretreatment levels [48].

However, patients on alendronate for 3–5 years also maintained BMD and showed reduction in turnover markers. No increased rate of fracture was seen over 5 or 10 years. From the best current evidence, patients at low risk who are well supplemented with calcium and vitamin D can be monitored off bisphosphonates after completing 3–5 years of bisphosphonate treatment. Patients at high risk can go on a 1–2-year drug holiday after completion of 10 years of treatment. The therapy should be reinitiated if a substantial decrease in BMD, increase in bone turnover markers, or fracture occur [16].

Bisphosphonates and Risk of Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been defined as a delay in healing of an oral lesion after surgery or tooth extraction for more than 6–8 weeks. This may be a rare side effect (risk is 0.7–1.5/100,000) associated with the use of high doses of bisphosphonates. This possible association was first recognized in multiple myeloma patients undergoing treatment with IV pamidronate and zolendronate for hypercalcemia due to malignancy. These patients had poor dental hygiene at baseline and active cancer; these high-risk conditions are not consistent with the typical presentation of the postmenopausal osteoporotic patient. The American Dental Association does not discourage use of bisphosphonates, and routine dental checks are recommended for all patients. Research shows that estrogen deficiency may trigger periodontal disease and that risedronate use for at least 3 months had less clinical attachment loss and better soft tissue periodontal health [49].

The following are recommended to prevent ONJ when patients are on bisphosphonates [27,49]:

1. Regular dental assessment
2. Removal of abscessed and nonrestorable teeth and teeth with severe periodontal disease involvement before beginning the therapy
3. Avoidance of invasive dental procedures unless absolutely necessary
4. Ensure good fit of dentures
5. Aggressive nonsurgical management of dental infections

Bisphosphonates and Subtrochanteric Fractures of Femur

There are limited data to suggest atypical femoral fractures, secondary to microcracks in the bone (due to suspected suppressed bone turnover), occur from prolonged bisphosphonate use. An analysis of the three randomized controlled trials (the FIT, FLEX, and HORIZON trials) showed that the incidence of subtrochanteric or diaphyseal femur fractures associated with 10 years of bisphosphonate treatment in osteoporotic

patients is very low and not statistically significant [50]. It is postulated that specific population of patients (i.e., those with glucocorticoid-induced osteoporosis) may be at increased risk for these atypical fractures, but this remains to be validated. A recent large case–control study in older postmenopausal women (age > 68 years) on bisphosphonates found that 0.35% sustained a subtrochanteric fracture. Bisphosphonate treatment for more than 5 years may carry a low risk of atypical fracture (OR 2.74, 95% CI 1.25–6.02) [51]. However, the minimal risk is outweighed by the benefits achieved from the treatment of osteoporosis and subsequent reduction in risk of hip fractures.

Estrogen Agonists and Antagonists

These nonsteroidal agents of various chemical structures act as estrogen agonists and/or antagonists [27]. Raloxifene (marketed as Evista oral tablets) is FDA approved for the prevention and treatment of postmenopausal osteoporosis at a dose of 60 mg/day and is also approved to reduce breast cancer risk among high-risk postmenopausal women. It is contraindicated in childbearing women and those at risk of venous thromboembolic disease. It has been proven to decrease risk of vertebral fractures. Its clinical efficacy has been studied for up to 4 years.

Teriparatide

Teriparatide (recombinant human PTH 1–34), marketed as Forteo, is FDA approved for the treatment of osteoporosis in postmenopausal women who are at high risk for fracture or who have failed or are intolerant of other forms of therapy. It is also approved in men with idiopathic and hypogonadal osteoporosis, at high risk of fractures, and who have failed or are intolerant of other therapies. It is given as a 20-µg subcutaneous injection once daily via a disposable multiple dose pen device designed to provide 28 doses. It is an anabolic agent that directly stimulates osteoblastic bone formation, resulting in substantial increases in trabecular bone density and connectivity in women with postmenopausal osteoporosis. In postmenopausal women with prior vertebral fracture [52], 19 months of teriparatide treatment (20 µg/day) significantly increased bone density in the spine by 8.6% and in the femoral neck by 3.5% compared with placebo. The incidence of new vertebral fractures was reduced by 65% and new nonvertebral fragility fractures by 53%, although the study was not designed to examine the effect on hip fractures [27].

Drug-related adverse effects include muscle cramps, infrequent hypercalcemia, nausea, and dizziness. High-dose teriparatide treatment has caused bone tumors (osteosarcoma) in a rat model at doses ranging from 3 to 60 times the 20 µg/day dose in humans, although the significance of this finding in humans is uncertain [53]. Teriparatide should not be administered to postmenopausal women with hypercalcemia, bone metastases, disorders that predispose them to bone tumors such as Paget's disease, or those who received prior skeletal irradiation. It is approved for no longer than 24 months in the United States and for no longer than 18 months in Canada. After its discontinuation, there is abrupt decrease in BMD but prevention of fracture risk may persist for 1–2 years. Use of alendronate after teriparatide is discontinued may prevent this bone loss and maintain or improve BMD [54,55].

Estrogens

Systemic estrogen products (estrogen plus progestogen [EPT] for women with a uterus or estrogen therapy [ET] for women without a uterus) are government approved in the United States and Canada for prevention, but not treatment, of postmenopausal osteoporosis [27]. The beneficial effects of systemic oral or transdermal ET/EPT at standard doses on BMD preservation are well established. A 2002 meta-analysis [56] of 57 randomized controlled trials comparing ET/EPT against placebo in postmenopausal women found consistent BMD increases with ET/EPT at all sites. In trials of 2 years duration, the mean difference in BMD after ET/EPT was 6.8% at the lumbar spine and 4.1% at the femoral neck. The two largest and best controlled trials support these findings. In the Postmenopausal Estrogen/Progestin Interventions trial ($N = 875$), standard daily doses of 0.625 mg conjugated estrogens (CE), with or without a progestogen (either medroxyprogesterone acetate [MPA] or micronized progesterone), for 3 years significantly increased spinal BMD by 3.5%–5.0%, with a 1.7% increase in hip BMD [57]. The Womens' Health Initiative [58], a 5-year randomized controlled trial in postmenopausal women ages 50–79 years ($N = 16{,}608$), reported that standard doses of daily EPT (0.625 mg CE plus 2.5 mg MPA) significantly increased spine and total hip BMD by 4.5% and 3.7%, respectively, relative to placebo [27]. As soon as the ET/EPT treatment is discontinued, the antifracture benefit is gone and there is 5% decrease in BMD in the first year after that.

Calcitonin

Salmon calcitonin is government approved for postmenopausal osteoporosis treatment but not for prevention. It is available in the United States as a 200 IU nasal spray (marketed as Miacalcin Nasal Spray, Fortical Nasal Spray) and a 100 IU subcutaneous or intramuscular injection (marketed as Miacalcin Injection). Calcitonin is an inhibitor of bone resorption. In clinical use, the reduction in bone turnover with calcitonin is much less than with other antiresorptive agents. A small, dose-finding study of intranasal calcitonin in postmenopausal women with osteoporosis showed significant increases in spinal BMD of 3% relative to baseline [59]. Calcitonin has been shown to reduce bone pain from osteoporotic vertebral compression fractures more quickly than placebo immediately after a fracture. Intranasal calcitonin can cause allergic rhinitis or epistaxis. Parental administration can cause nausea, local inflammatory reaction, or vasomotor symptoms like flushing or sweating. Its safety and efficacy data are available through 5 years.

Combination Therapies

Combining potent antiresorptive agents results in small additional increments in bone density. In postmenopausal women (mean age 61–62 years) with low bone mass, BMD

improvements in the spine and hip with combined alendronate and ET were significantly greater (8.3%) than results for either agent alone (6.0%) [60]. Combined risedronate and ET/EPT also has shown favorable, although modest, BMD effects compared with either agent alone [61]. Whether increases in BMD result in better fracture protection is not known, the long-term safety of combination therapies has not been evaluated. One concern is that combining two antiresorptive therapies might oversuppress bone turnover, adversely affect bone quality, and thereby increase the likelihood of fracture. Combining antiresorptive agents is not generally recommended. Combining an anabolic agent such as teriparatide with an antiresorptive agent has been considered but is usually done sequentially [27].

Tibolone

Tibolone is approved in many countries for the prevention of osteoporosis, but not in the United States or Canada. In the Long-term Intervention on Fractures with Tibolone (LIFT) study [62], tibolone reduced the risk of vertebral and nonvertebral fracture, breast cancer, and possibly colon cancer, but increased the risk of stroke in older postmenopausal women with osteoporosis.

Denosumab

Denosumab, marketed as Prolia, is a fully human monoclonal antibody against receptor activator of nuclear factor-JB ligand (RANKL), a member of the tumor necrosis factor superfamily expressed on the surface of osteoblasts. RANKL binding to its receptor RANK on the surface of osteoclast precursors promotes the proliferation and differentiation of osteoclasts. By blocking the interaction between RANKL and RANK, denosumab inhibits bone resorption by osteoclasts. Denosumab is dosed as a subcutaneous 60-mg injection every 6 months for postmenopausal women at high risk for fractures. It decreases the risk of spine, hip, and other nonvertebral fractures by improving the BMD. Its efficacy has been studied for 6 years [63]. It does not require dose adjustments needed for patients with renal disease. Side effects reported are skin infections, eczema, and dermatitis.

New Horizons for Treatment

Several new drugs show promise for the treatment and/or prevention of osteoporosis. Some are now available outside North America, and others are in clinical development. These include strontium ranelate, PTH 1–84 (PreOs), additional Ea/EAg (bazedoxifene, lasofoxifene), oral calcitonin, and odanacatib, an inhibitor of cathepsin K [27].

Strontium Ranelate

Oral strontium ranelate (marketed as Protelos) is approved for the prevention and treatment of osteoporosis in many countries outside North America. Dosing involves dissolving 2 g of strontium ranelate in water and drinking it before bedtime.

A large randomized controlled trial in postmenopausal women in Europe and Australia with the primary end point of vertebral fractures demonstrated that 3 years of therapy significantly increased bone density at the spine (14%) and femoral neck (8%) [64]. Compared with placebo, the risk of spine fractures in strontium-treated women was significantly reduced by 49% after 1 year and 41% after 3 years compared with placebo.

Modest changes in markers of bone turnover have been observed with strontium therapy, but the exact mechanism by which strontium ranelate exerts its effect is unknown. Drug-related adverse effects included venous thromboembolism and significant increases in nausea and diarrhea that resolved after 3 months [27].

Parathyroid Hormone 1–84

The full-length PTH, PTH 1–84, marketed in Europe and other countries as PreOs, is not yet approved in the United States. In a randomized controlled trial in 2532 women with postmenopausal osteoporosis, PTH 1–84 administered as a daily subcutaneous injection in a 100-kg dose increased BMD in the lumbar spine by 6.9% and in the total hip region by 2.1% compared with placebo [65]. Vertebral fracture risk was reduced by 58%. No effect was observed on nonspine fractures. Hypercalcemia and hypercalciuria occurred more commonly with PTH 1–84 compared with placebo [27].

Bazedoxifene

This Ea/EAg has prevented bone loss and decreased bone turnover without stimulating the endometrium in healthy postmenopausal women with normal or low BMD [66]. In a 3-year randomized controlled trial involving 6847 postmenopausal women with osteoporosis (average age 66 years), bazedoxifene 20 or 40 mg/day reduced the incidence of vertebral fracture by 42% and 37%, respectively, in the active control group [67]. Side effects included an increased incidence of vasomotor symptoms, venous thromboembolism, and leg cramps compared with placebo.

Lasofoxifene

Lasofoxifene is another selective estrogen receptor modulator that increased lumbar spine BMD and reduced bone markers modestly more than did raloxifene in young postmenopausal women without osteoporosis [68].

Nitroglycerine Ointment

In Toronto, Ontario, Canada, a single-center, double-blind, placebo-controlled randomized trial was conducted for 24 months. Postmenopausal women with lumbar spine *T*-score between 0 and −2.0 who used nitroglycerine ointment 15 mg/day showed a significant increase in BMD at the lumbar spine, total hip, and femoral neck; an increase in bone-specific alkaline phosphatase of 34.8%; and a decrease in urine *N*-telopeptide of 54.0%. It was concluded that among postmenopausal women, nitroglycerine ointment modestly increased BMD and decreased bone resorption [69].

MONITORING THE THERAPY OF OSTEOPOROSIS

In the present era, we have highly effective treatments for osteoporosis; however, studies have shown that more than 50% of patients who are prescribed osteoporosis therapy do not fill their prescriptions and of those who do, many discontinue treatment within the first year. Regular follow-up coupled with testing of biochemical markers of bone turnover may be useful interventions to improve adherence. Follow-up BMD should be performed at regular intervals every 2 years until stable on treatment to make sure that there is no further bone loss and to understand the concept of least significant change when monitoring therapy with BMD testing. This is a measure calibrated regularly for each individual DXA machine, change greater than which is clinically significant. Knowing the least significant change is important when interpreting the serial bone density scans. Annual rates of bone loss in untreated postmenopausal women vary between 0.6% and 1.7% but may be as high as 4%.

Biomarkers of bone formation (bone alkaline phosphatase, osteocalcin, procollagen type I propeptides) and resorption (hydroxyproline, urinary pyridinoline and deoxypyridinoline, N-telopeptide of collagen type I NTX and CTX in urine and serum) reflect the overall osteoblastic and osteoclastic activity in the skeleton and in some situations may serve as surrogates for histological examination of bone (Table 24.5). Their use in clinical practice, however, is limited by high in vivo and assay variability (resorption markers), poor predictive ability in individual patients, and lack of evidence-based thresholds for clinical decision making [27]. Nevertheless, biochemical markers of bone turnover may be useful in certain situations, including for assessment of fracture risk in elderly patients when the finding of elevated levels would influence the decision to begin pharmacotherapy, as an early indicator of therapeutic response to anabolic or antiresorptive therapy or in the laboratory evaluation of patients losing BMD despite antiresorptive therapy, and for assessment of medication compliance [27].

INDIVIDUALIZING THE TREATMENT OF OSTEOPOROSIS: CASE DISCUSSIONS

Case 1

A 51-year-old healthy Caucasian woman without other significant comorbidities. She had hysterectomy for fibroids/menorrhagia at age of 45 years and currently experiencing disruptive hot flashes and night sweats for the last 1.5 years. Her family history is significant of maternal hip fracture. BMD shows a *T*-score of −2.2 in the femoral neck. No secondary causes of low bone density are identified on a thorough history, physical examination, and appropriate laboratory workup.

She will get maximum benefit from ET along with calcium and vitamin D supplementation. She should be reevaluated annually to assess the dose adjustment or screen for any side effects.

Case 2

A 55-year-old African American woman whose last menstrual period was at age of 50 years denies vasomotor symptoms. Her mother had multiple vertebral fractures with dowager's hump. The patient's mammogram indicates high breast density, and she has a history of two breast biopsies in a 3-year period. BMD shows *T*-score at spine = −2.2, hip = −1.4. Ea/EAg therapy, for example, raloxifene will provide reduction in spine fracture and prevention of estrogen receptor–positive breast cancer.

Case 3

A 56-year-old Caucasian woman status postmenopause for 5 years with controlled hypertension on hydrochlorothiazide presents post wrist fracture after she slipped on the ice. BMD shows a *T*-score of −1.2 at the spine and −1.3 at the hip. Clinically, she has osteoporosis; however, she needs a secondary workup to identify any underlying disease contributing to it. She will require treatment in addition to calcium and vitamin D.

Case 4

A 72-year-old Caucasian woman with past medical history of hypertension, hyperlipidemia, and gastroesophageal reflux disease, stable on medications. No prior history of cancer or fractures. She presents with acute low back pain with midline tenderness; x-ray reveals a vertebral fracture at T7. Lumbar spine *T*-score = −3.4, *T*-score at femoral neck = −2.8. Secondary evaluation reveals only borderline low 25-OH vitamin D of 30 ng/mL.

She has severe osteoporosis and should be treated with anabolic agent, Teriparatide for 2 years, after her low vitamin D is treated. Two years after the completion of treatment, she should be reevaluated and possibly treated with bisphosphonates or preferably with denosumab.

Case 5

A 56-year-old postmenopausal Caucasian woman presented with persistent pain along the anterior aspect of her left lower leg. X-ray failed to identify fracture; a bone scan showed intense uptake over anterior part of tibia consistent with a stress fracture. Her BMD is consistent with total hip −2.5. Laboratory workup is significant for anemia, low vitamin D, and normal thyroid function. The patient denies any diarrhea or eating disorder and her BMI is stable at 24. She was further screened for hyperparathyroidism and celiac disease and turned out to have gluten-sensitive enteropathy.

She should be treated with gluten-free diet, calcium, iron, and vitamin D supplementation. Once her vitamin D level is within normal limits, she could be treated with IV or oral bisphosphonates.

PEARLS

1. Identify osteoporosis as a major public health problem
2. Initiate timely screening and treatment of osteopenia and osteoporosis to prevent morbidity and mortality associated with hip fractures
3. Interpretation of the DXA reports and screening the at-risk population for causes of secondary osteoporosis
4. Individualization of the various options of pharmacotherapy available
5. Institute awareness regarding the risks associated with osteoporosis and address the misconceptions, due to rare side effects reported with treatment
6. Incorporate the use of new FDA-approved medications for osteoporosis by educating ourselves and our patients

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25 Physical Activity and Health in Women

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CONTENTS

Introduction....313
Methodological Considerations....314
All-Cause Mortality....315
Cardiovascular Disease....316
Type 2 Diabetes....318
Cancer....319
Colon Cancer....320
Breast Cancer....320
Endometrial Cancer....321
Ovarian Cancer....321
Lung Cancer....321
Other Cancers....321
Osteoporotic Fracture, Bone Mineral Density, and Falls....321
Fracture....321
Bone Mineral Density....322
Falls....322
Neuropsychological Outcomes....322
Cognitive Decline....322
Depression and Anxiety....323
Weight Control....323
Pregnancy Outcomes....323
Risks of Physical Activity....324
Musculoskeletal Injuries....324
Acute Cardiac Events....325
Menstrual Dysfunction....325
Conclusion....325
References....326

INTRODUCTION

To improve health and lower risk for certain chronic diseases, the U.S. Surgeon General, the American Heart Association, and the American College of Sports Medicine have long recommended that adults perform a minimum of 30 min of moderate-intensity aerobic physical activity on most days of the week or, alternatively, vigorous-intensity physical activity for at least 20 min on 3 days of the week.[1–3] In 2008, the U.S. Department of Health and Human Services issued a similar guideline—at least 150 min/week of moderate-intensity physical activity or 75 min/week of vigorous-intensity physical activity for "substantial health benefits" (basic guideline) and 300 min/week of moderate or 150 min/week of vigorous-intensity physical activity for "additional and more extensive health benefits" (advanced guideline).[4] However, only 28% of U.S. women and 31% of men exercise enough to meet the basic guideline, and 41% of women and 39% of men engage in no leisure-time physical activity at all.[5]

Aerobic exercise has been the focus of most epidemiologic investigations of physical activity to date, but there is growing evidence that resistance exercise also confers health benefits, including the preservation of bone density and musculoskeletal function,[6] which is particularly important for women, as they are more susceptible to osteoporotic fracture than are men. Yet only 17.5% of U.S. women engage in strength training at least twice per week,[7] as recommended by current guidelines.[4,6,8]

Aerobic exercise intensity is typically measured in kilocalories burned per minute of activity or in metabolic equivalents (METs), defined as the ratio of the metabolic rate during exercise to the metabolic rate at rest. Moderate-intensity activities, such as brisk walking (i.e., at a pace of ≥3 miles/h), are those that burn 3.5–7 kcal/min or, equivalently, those that expend 3–6 METs. Vigorous activities, such as running, are those that burn >7 kcal/min or expend >6 METs. Epidemiologic findings are often presented in

TABLE 25.1
Effects of Physical Activity on Health

All-cause mortality	↓	Cognitive decline	↓
		Depression and anxiety	↓
Cardiovascular disease	↓		
Coronary heart disease	↓	Pregnancy outcomes	
Stroke	↓	Gestational diabetes	↓
		Preeclampsia	↓
Type 2 diabetes	↓	Low birthweight	↑ (vigorous activity)
Cancer	↓	Risks of physical activity	
Colon cancer	↓	Musculoskeletal injury	↔ (at recommended levels)
Colon adenoma	↓	Acute cardiac events	↑ (especially vigorous activity)**
Breast cancer	↓	Menstrual dysfunction	↑ (female athletes)
Endometrial cancer	↓		
Ovarian cancer	↔	CVD or cancer risk factors	
Lung cancer	*	Body weight/weight gain	↓
Other cancers	↔	Blood pressure	↓
	↔	Triglycerides	↓
		HDL cholesterol	↑
Osteoporotic fracture		Insulin sensitivity/glycemic control	↑
Hip fracture	↓	Inflammatory biomarkers	Favorable effect
Vertebral fracture	↔	Immune function biomarkers	Favorable effect
Bone mineral density	↑	Estrogen and progesterone	↓
Falls	↓		

↓, Decreases risk for outcome; ↑, increases risk for outcome; ↔, no effect on risk for outcome, or insufficient evidence to determine effect on risk.

* Inconsistent results in smokers and nonsmokers.

** In terms of the balance of cardiovascular benefits and risks, regular physical activity of moderate or vigorous intensity is associated with an overall decrease in cardiovascular disease events that far outweighs the transient cardiac risks associated with physical exertion.

terms of MET-h (total volume) per week of physical activity, but because physical activity of long duration at low intensity and physical activity of short duration at high intensity can yield the same MET-h score, such analyses cannot disentangle the effects of duration and intensity of activity on health outcomes.

This chapter reviews epidemiologic evidence on the relation between physical activity and health outcomes in women (Table 25.1), with a focus on results that are presented in a manner that translates into easily understood public health recommendations for exercise for disease prevention, such as walking for a certain number of hours per week as opposed to achieving a certain number of MET-hours week. The emphasis is on studies that use self-reported physical activity, a behavior, rather than physical fitness, an attained physiologic state, as the exposure variable for this reason as well.

METHODOLOGICAL CONSIDERATIONS

Most investigations of physical activity in relation to disease endpoints have been observational studies rather than randomized clinical trials. When interpreting the inverse associations between physical activity and risk for disease reported in observational studies, one must consider various possibilities: that unmeasured or unknown factors may influence the selection and participation of study respondents (selection bias), that unmeasured or unknown third factors may account for the association (confounding), that imperfectly measured exposure or disease status could influence the results (misclassification), and—for case–control studies—that knowledge of disease status may affect recall of past exposures (recall bias). Surveillance bias should also be considered; for example, respondents with putative risk factors such as physical inactivity may be more likely to be screened by their physicians for occult diseases such as diabetes or cancer and be diagnosed with the condition earlier than other respondents, leading to an overestimate of the strength of the exercise–disease association. In addition, self-reported physical activity questionnaires—the most common method for assessing physical activity in epidemiologic studies—may more accurately capture actual activity levels in some groups than in others (e.g., women vs. men, or normal-weight vs. obese persons), causing spurious interaction effects. However, for outcomes such as CVD and diabetes, the consistency of the main effects results across studies—including studies that relied on exercise testing rather than physical activity questionnaires to assess exposure or, in the case of diabetes, on glucose tolerance

or fasting glucose tests rather than self-reported diagnoses to assess outcome—supports a causal association, as does the biologic plausibility due to the known salutary effects of increased physical activity on cardiometabolic risk factors, many of which have been demonstrated in small randomized trials. It should also be noted that, in an effort to control confounding, many studies statistically adjust for baseline conditions such as hypertension, dyslipidemia, and glucose tolerance. Because these represent biological intermediates in the causal pathway between physical activity and cardiometabolic disease outcomes, statistical overcontrol may result in an underestimate of the strength of the association.

ALL-CAUSE MORTALITY

Many prospective studies show an inverse association between physical activity and all-cause mortality. A systematic evidence review conducted to develop the 2008 federal physical activity guidelines found a 30% risk reduction in all-cause mortality comparing the most with the least active persons.[9] The dose–response gradient appears curvilinear in that larger risk decreases are seen at the lower end of the physical activity spectrum than at the upper end. Compared with <0.5 h/week, there was an approximate reduction of 20% in risk for all-cause mortality from 1.5 h/week of moderate to vigorous activity, and a further 20% reduction for an additional 5.5 h/week (i.e., a total of 7 h/week) of activity.

A 2011 meta-analysis of 22 large cohort studies with a total of 643,000 women and 335,000 men quantified the relation between moderate-intensity physical activity and all-cause mortality.[10] Compared with inactive individuals, those who performed 2.5 h/week of moderate activity (equivalent to 30 min/day on 5 days/week) experienced a 19% (95% confidence interval 15%–24%) reduction in mortality risk, and those who performed 7 h/week of light and moderate activity reduced their mortality risk by 24% (19%–29%). Five studies included in the meta-analysis specifically examined walking—the most common leisure activity among U.S. adults—and found a smaller effect. Compared with not walking, 2.5 h/week of brisk walking was associated with a relative risk (RR) of 0.89 (0.82–0.96). A 2008 meta-analysis of 10 prospective studies with a total of 106,000 women and 39,000 men found a stronger effect for walking; there was a 20% (9%–29%) reduction in mortality risk associated with an exposure approximately equivalent to walking 3 h/week at a normal pace (3 km/h [1.9 miles/h]), with the relation similar in women and men.[11]

Among 253,000 women and men aged 50–71 years who were followed for an average of 5 years in the National Institutes of Health (NIH)-AARP Diet and Health Study, engaging in physical activity of at least moderate intensity for >3 h/week predicted a 27% decreased risk for mortality compared with no physical activity, while engaging in vigorous exercise for 20 min for ≥3 times/week predicted a 32% reduction in risk.[12] Among those with little vigorous activity, women and men who engaged in recommended levels of moderate physical activity were 35% and 40% less likely to die, respectively, than their inactive counterparts. In this cohort, engaging in physical activity at less than recommended levels was also related to reduced mortality risk (RR = 0.81).

Data from a recent study of >416,000 Taiwanese women and men aged ≥20 years followed for 8 years also support the idea that even minimal levels of physical activity can favorably affect health.[13] Compared with their inactive peers, individuals who reported a low volume of leisure-time physical activity—i.e., those who exercised for an average of 92 min/week (~15 min/day)—had a 14% reduced risk for total mortality and a 3-year longer life expectancy. (RRs were 0.86 and 0.73 for those reporting moderate- and vigorous-intensity exercise, respectively.) Each additional 15 min of daily exercise beyond the minimum amount of 15 min/day (up to 100 min/day, after which additional exercise gave no benefit) further reduced total mortality by a statistically significant 4%. In other words, the dose–response gradient was curvilinear, with the largest health gains from the first 1–2 h/week of exercise. These benefits were observed in both sexes and across all age groups.

Recent studies have also implicated amount of time spent sitting as risk factor for mortality independent of amount of physical activity. Among 70,000 women and 53,000 men aged 50–74 years followed for 14 years in the American Cancer Society's Cancer Prevention Study II (CPS-II) Nutrition Cohort, physical activity level and time spent sitting were independently associated with total mortality in both sexes.[14] For women with total physical activity of <17.5 (bottom decile), 17.5 to <24.5, 24.5 to <31.5, 31.5 to <42, 42 to <52.5, 52.5 to <63, and ≥63 MET-h/week, RR were 1 (referent), 0.98, 0.81, 0.78, 0.76, 0.75, and 0.73 (p, trend <0.0001). Each categorical increase in the exposure is roughly equivalent to 3 h/week (25 min/day) of light-intensity activity, which suggests that an increase of 1 h/day of such activity reduces mortality risk in women by 19%. Daily sitting time was also predictive of total mortality in both sexes, with the relation stronger in women (for ≥6 vs. <3 h/day, RR = 1.37) than in men (RR = 1.18) (p, heterogeneity = 0.003). These associations remained "virtually unchanged" after adjustment for physical activity. The RR for the joint effects of sitting and physical inactivity (≥6 h/day sitting and <24.5 MET-h/week of physical activity) were 1.94 and 1.48 in women and men, respectively, compared with their counterparts who reported both sitting the least (<3 h/day) and being the most physically active (≥52.2 MET-h/week). Similarly, in a cohort of 17,000 Canadians aged 18–90 years followed for an average of 12 years, there was a dose–response relation between daily time spent sitting and total mortality, after adjustment for total physical activity.[15] For women who sat "almost none," "1/4," "1/2," "3/4," and "almost all of the time," RR were 1 (referent), 1.17, 1.37, 1.61, and 1.85, respectively (p, trend <0.0001); for men, there was a weaker though still significant trend.

CARDIOVASCULAR DISEASE

A 2011 meta-analysis of data from nine prospective studies that quantified the dose–response relation between leisure-time physical activity found that persons who met the federal government's basic guideline had a 14% (4%–23%) lower risk for coronary heart disease (CHD) than those who engaged in no activity, whereas those who met the advanced guideline had a 20% (12%–26%) lower risk.[16] There was a significant interaction by sex. Women who met the basic guideline were at 20% (8%–31%) lower risk than those who engaged in no leisure-time activity, whereas women who met the advanced guideline were at 28% (17%–37%) lower risk. For men who met the basic and advanced guidelines, respectively, the RR were 0.91 (0.79–1.04) and 0.82 (0.74–0.91).

A look at findings from specific studies strongly supports the prescription of either vigorous or moderate-intensity physical activity to prevent CVD in sedentary women.[17] Among 73,000 postmenopausal participants aged 50–79 years in the Women's Health Initiative Observational Study, walking briskly for ≥2.5 h/week (e.g., a half-hour 5 times/week) was associated with a 30% reduction in cardiovascular events over a 3-year follow-up.[18] After controlling for total exercise energy expenditure, brisk walking and more vigorous exercise were associated with similar risk reductions in CVD events, and the results did not vary substantially by race, age, or baseline body mass index (BMI; Figure 25.1). Prolonged sitting also predicted an increased risk for CVD, even after accounting for time spent in recreational exercise. Women who spent ≥16 h/day sitting were 68% more likely to develop CVD than those who spent <4 h/day sitting.

Cardiovascular benefits of walking have been observed in other studies of women. For example, in an 8-year follow-up of 72,000 healthy female nurses aged 40–65 years in the Nurses' Health Study, 3 h/week of brisk walking had the same protective effect as 1.5 h/week of vigorous exercise.[19] Women reporting either type of exercise were 30%–40% less likely to develop myocardial infarction than their sedentary peers. Among 39,000 healthy female health professionals aged ≥45 years followed for 7 years in the Women's Health Study, walking ≥1 h/week was associated with a 50% reduction in CHD risk among participants reporting no vigorous physical activity.[20] In the Study of Osteoporotic Fractures, which followed 9704 women aged ≥65 years for 10 years, participants whose weekly walking energy expenditures averaged ≥300 kcal (about ≥1 h/week of walking) were 34% less likely to die from a cardiovascular cause than were those with weekly walking energy expenditures <70 kcal.[21] Independent of physical activity, more time spent sitting has also been significantly associated with cardiovascular mortality in several cohorts.[14,15]

Cardiovascular benefits of moderate-intensity activities have been observed in males, although somewhat less strongly, perhaps because background activity levels in men are generally higher than those in women. For example, in the Health Professionals Follow-up Study, which followed 44,000 men aged 40–75 years for 12 years, brisk walking for ≥30 min/day was associated with an 18% reduction in CHD incidence.[22] Studies in men suggest that vigorous exercise is even more beneficial than moderate-intensity exercise for CVD risk reduction. For example, in the Health Professionals Follow-up Study, each 1-MET increase in exercise intensity was associated with a 4% reduction in CHD risk independent of total exercise energy expenditure.[22]

Resistance exercise may also lower risk for CHD, although existing data are equivocal and more research is needed.[6] Men in the Health Professionals Follow-up Study who trained with weights for ≥30 min/week were 23% less likely to develop CHD during an 8-year follow-up than men who did not train with weights.[22] Comparable studies in women are lacking.

Findings from prospective studies suggest that aerobic physical activity may reduce the risk for stroke, although data are less extensive and consistent than for CHD. A meta-analysis of 18 cohort studies with follow-up periods ranging from 5 to 26 years found that moderately active and highly active persons were 17% and 25% less likely to have a stroke or die from stroke-related causes than were persons with low activity.[23] On the basis of six ischemic and three hemorrhagic stroke studies in the meta-analysis, physical activity appears to protect against both types of stroke. However, variation in the measurement and classification of physical activity in the original studies precluded a precise definition of "high," "moderate," and "low" activity, and sex-specific estimates were not provided. In the Nurses' Health Study, there was a strong inverse gradient of risk with volume of physical activity that was primarily due to the relation with ischemic rather than hemorrhagic stroke, with the most active women experiencing only half the risk for ischemic stroke as the least active women.[24] More recently, a 12-year follow-up of the Women's Health Study cohort found an inverse relation between walking time or pace and risk for stroke.[24a] Compared with women who did not walk, women who walked ≥2 h/week had 30% lower risk for stroke, and women whose usual walking pace was brisk (>4.8 km/h) had a 37% lower risk; associations were found for both ischemic and hemorrhagic stroke, although they were significant only for the latter outcome. However, vigorous-intensity physical activity was unrelated to stroke risk in this cohort.

Research indicates that previously sedentary individuals who become physically active in mid- or late life derive cardiovascular benefits. For example, among initially sedentary participants in the Nurses' Health Study, 6-year changes in activity level were significantly associated in dose–response fashion with CHD incidence during the subsequent 8 years.[19] Compared with women who remained sedentary, women with increasing quintiles of total physical activity energy expenditure were 15%, 21%, 33%, and 29% less likely to have a coronary event. In the Study of Osteoporotic Fractures, which assessed changes in physical activity over 6 years among 7553 women aged 65 years at baseline, women who increased their physical activity were 36% less likely to die from cardiovascular causes during the subsequent 7 years than were women who remained sedentary.[21] However, exercise must

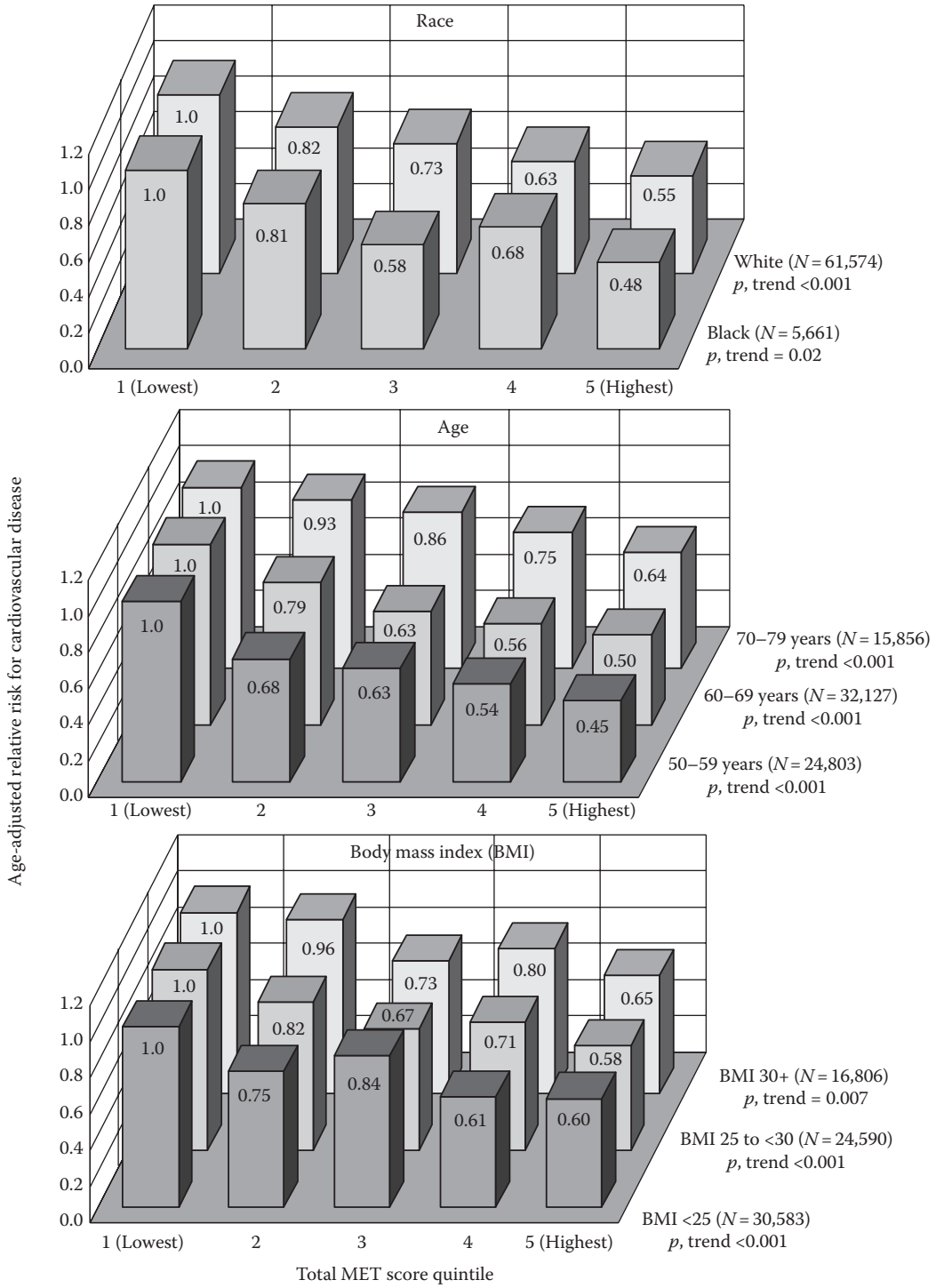


FIGURE 25.1 Age-adjusted relative risks for cardiovascular disease according to quintile of energy expenditure from recreational activities in subgroups defined by race, age, and body mass index, Women's Health Initiative. Quintile medians (ranges), in MET-h/week, are as follows: quintile 1, 0 (0–2.4); quintile 2, 4.2 (2.5–7.2); quintile 3, 10.0 (7.3–13.4); quintile 4, 17.5 (13.5–23.3); quintile 5, 32.8 (≥23.4). Quintile 1 is the reference category. (Adapted from Manson, J.E. et al., *N. Engl. J. Med.*, 347, 716, 2002.)

be current and habitual to confer cardiovascular protection; women who became inactive in later life had a similar risk of cardiovascular mortality as those who had remained inactive over the course of follow-up. From a public health perspective, knowing that "it's not too late" may motivate older individuals to become physically active.

Short bouts of activity (10–15 min) favorably affect the cardiovascular risk profile of otherwise sedentary persons.[25] One prospective study has examined the relation between brief bouts of exercise and clinical CVD. After controlling for total energy expenditure, exercise sessions lasting 15, 30, or 45 min offered equal protection against incident CVD

in a cohort of 7307 middle-aged and elderly male Harvard alumni followed for 5 years.[26] Although there are no studies of this issue in women, it is reasonable to speculate that similar results would be observed. Such findings may help motivate busy individuals to view exercise as a manageable part of their daily routine rather than as a time-consuming activity reserved for rare occasions.

Cardiorespiratory fitness as assessed by maximal treadmill exercise test is inversely correlated with cardiovascular mortality in persons without coronary symptoms at baseline. A 2009 meta-analysis of data from 24 prospective cohorts with a total of >84,000 initially healthy participants and nearly 4500 CVD endpoints (primarily cardiovascular mortality) found a significant 15% decline in cardiovascular risk for each 1 MET increase in exercise capacity.[27] The relation was similar in the 16 studies that included only men (risk reduction, 14%) and in the eight studies that included both sexes or only women (risk reduction, 16%).

Physical activity appears to slow the initiation and progression of CVD through beneficial effects on adiposity, insulin sensitivity, glycemic control, type 2 diabetes incidence (see the following section), blood pressure, lipids, endothelial function, hemostasis, and inflammatory defense systems.[17] In the Women's Health Study, these factors explained 59% of the observed inverse relation between physical activity and incident CVD over 11 years of follow-up.[28] Inflammatory/hemostatic risk factors (C-reactive protein, fibrinogen, and soluble intercellular adhesion molecule 1) made the largest contribution to lower risk (32.5%), followed by blood pressure (27.1%), traditional lipids (19.1%), the novel lipids lipoprotein(a) and apolipoproteins A1 and B100 (15.5%), BMI (10.1%), and hemoglobin A1c/diabetes (8.9%). Findings from observational studies and randomized trials indicate that regular moderate-intensity activity is as effective as more vigorous activity in reducing blood pressure and improving insulin sensitivity.[17] In contrast, strong dose–response associations between exercise intensity and blood lipids—specifically, triglycerides and high-density lipoprotein cholesterol—have been reported.[17] Resistance exercise has also been shown to reduce blood pressure.[29] A randomized trial in patients with type 2 diabetes found that a combination of aerobic and resistance exercise yielded greater improvement in glycemic control than did either type of exercise alone.[30] However, whether resistance exercise alone can favorably affect other cardiovascular risk markers in patients with type 2 diabetes remains unclear.[31]

TYPE 2 DIABETES

Cohort studies consistently show a marked reduction in the incidence of type 2 diabetes among physically active individuals as compared with their sedentary peers. A 2007 meta-analysis of 10 cohort studies involving 301,000 participants found that individuals who regularly engaged in moderate-intensity physical activity were 17% (10%–24%) less likely to develop type 2 diabetes than inactive individuals, after adjustment for BMI.[32] A look at findings from specific studies, some of which were included in the meta-analysis, provides empirical support for the prescription of 30 min/day of moderate-intensity activity in women. Among >70,000 participants in the Nurses' Health Study, walking briskly for at least 2.5 h/week—e.g., 30 min/day for 5 days/week—was associated with a 25% reduction in diabetes over 8 years of follow-up among those reporting no vigorous exercise, after adjustment for BMI and other risk factors for diabetes.[33] This is a conservative estimate that excludes the risk reduction attributable to lower body mass from physical activity. Given equivalent total exercise energy expenditures, brisk walking and more vigorous exercise were associated with similar magnitudes of risk reduction. In a 7-year follow-up of the Women's Health Study cohort, participants who reported walking 2–3 h/week were 34% less likely to develop diabetes than women who reported not walking.[34] In the Iowa Women's Health Study, which tracked >34,000 participants aged 55–69 years for 12 years, women engaging in moderate-intensity exercise 1, 2–4, and >4 times/week were 10%, 14%, and 27% less likely, respectively, to develop diabetes than women engaging in such exercise <1 time/week.[35] Among >86,000 women followed for an average of 5 years in the Women's Health Initiative Observational Study, walking was inversely related to diabetes risk, with RR for increasing quintiles of walking of 1.0 (referent), 0.77, 0.87, 0.74, and 0.82 (p, trend = 0.009). The relation was significant in white women but was less clear-cut in women of other races/ethnicities.[36] All estimates reflect adjustment for the effects of BMI and potential confounders.

Metabolic benefits of moderate-intensity exercise have also been observed in male populations. For example, among 38,000 men followed for 10 years in the Health Professionals Follow-up Study, each 10 MET-h increment in weekly walking energy expenditure was associated with a statistically significant 11% reduction in diabetes risk; an equivalent increase in weekly vigorous activity conferred a 12% reduction in diabetes risk.[37] Some data suggest that the inverse association between physical activity and risk for diabetes may be somewhat stronger for women than for men, perhaps due to generally lower baseline activity levels for former as compared with the latter, but this is not a consistent finding.[17]

Cardiorespiratory fitness as assessed by bicycle ergometer or treadmill test has been shown to correlate inversely with type 2 diabetes risk. Among 6249 women aged 20–79 years followed for 17 years in the Aerobics Center Longitudinal Study, the adjusted RR for incident diabetes across increasing tertiles of fitness were 1.0 (referent), 0.86 (0.59–1.25), and 0.61 (0.38–0.96).[38] In 834 women and 709 men (mean age, 37 years) followed for 15.5 years in the Canadian Physical Activity Longitudinal Study, the risk for incident diabetes was 70% lower for each standard deviation increase in cardiorespiratory fitness; sex-specific analyses were not reported.[39]

Randomized trials in high-risk populations provide strong evidence that regular physical activity can prevent or postpone the onset of type 2 diabetes. To date, four large (>500 participants) randomized studies of exercise and diet in the prevention of type 2 diabetes have been conducted.

In the Da Qing IGT and Diabetes Study, 577 middle-aged Chinese women and men with impaired glucose tolerance (IGT) were randomized to one of three treatment groups—diet only, exercise only, or diet plus exercise—or to a control group.[40] Participants assigned to exercise were encouraged to increase their daily physical activity by ≥1 units, with a unit defined as 30 min of mild-intensity activity (e.g., walking), 20 min of moderate-intensity activity (e.g., brisk walking or cycling), 10 min of strenuous activity (e.g., slow running or climbing stairs), or 5 min of very strenuous activity (e.g., jumping rope or swimming). Over the 6 years of the trial, the three interventions were associated with statistically significant reductions of 31%, 46%, and 42% in diabetes risk, respectively, with similar benefits for both lean and overweight individuals. The protective effect of the lifestyle intervention persisted for a lengthy period; there was a statistically significant 43% reduction in diabetes incidence among persons assigned to any of the treatment groups—and a statistically significant 49% reduction among those assigned to exercise alone—14 years after the trial's end.[41]

In the Finnish Diabetes Prevention Study, 522 middle-aged, overweight women and men with IGT were randomized to an intensive lifestyle intervention designed to promote healthy eating and exercise patterns or to a control group.[42] Members of the intervention group lost significantly more weight than did the control group (3.5 vs. 0.8 kg) and reduced their risk of developing diabetes by 58% over 3 years. There was a strong correlation between the number of lifestyle goals achieved during the first year of the trial—weight loss of >5%, reduction in fat intake to <30% of calories, reduction in saturated fat intake to <10% of calories, increase in fiber intake to ≥15 g/1000 kcal, and performing the equivalent of ≥150 min/week of moderate-intensity exercise—and diabetes incidence. Of note, exercise reduced diabetes risk even when participants did not attain the weight loss goal. Among intervention group members who did not lose >5% of their initial body weight, those who achieved the exercise goal were only one-fifth as likely to develop diabetes as compared with their counterparts who stayed sedentary; the association remained strong after adjustment for baseline BMI. The corresponding exercise-associated risk reduction in the control group was ~40%. Data from a subsample of participants who had a frequently sampled intravenous glucose tolerance test at baseline and at the end of the trial suggest that improved insulin sensitivity, rather than preserved insulin secretion, largely explained the reduction in diabetes risk.[43] Participants who had not developed diabetes by trial's end were observationally followed for a median of 3 additional years; during this time, a significant 36% reduction in diabetes incidence was noted in the intervention as compared with the control group.[44]

The U.S. Diabetes Prevention Program, which randomized 3234 adults aged 25–85 years with IGT and BMI ≥24 kg/m^2 to either a diet and exercise program, the drug metformin, or placebo, also found a 58% reduction in risk for diabetes associated with the lifestyle intervention (vs. placebo).[45] (Metformin was also effective; the drug vs. placebo comparison yielded a 31% risk reduction.) On average, participants assigned to lifestyle modification exercised at moderate intensity for 150 min/week and lost 5%–7% of their body weight during 3 years of follow-up. The lifestyle intervention reduced diabetes risk in both sexes and in all age, racial/ethnic, and BMI groups. A 10-year follow-up, in which all participants were offered lifestyle intervention and metformin was continued in the metformin group, found that, although incidence rates of diabetes were similar in the three groups during follow-up, the cumulative incidence remained lowest in the original lifestyle group.[46]

The Indian Diabetes Prevention Programme, a randomized trial among 531 middle-aged Asian Indian adults with IGT, reported a 28% reduction in diabetes risk associated with a diet and exercise intervention.[47]

A meta-analysis of 17 randomized trials involving 8084 participants followed for an average of 4 years—12 trials evaluated lifestyle interventions, mainly weight loss and exercise; 12 trials evaluated pharmacologic interventions, mainly metformin and acarbose; and several trials evaluated both—reported a pooled RR for developing diabetes of 0.51 (0.40–0.60) with lifestyle intervention and 0.70 (0.62–0.79) with oral diabetes drugs.[48] An ongoing large randomized trial, the Look AHEAD (Action For Health in Diabetes) trial, should provide valuable information about the long-term (≥10 years) effects of sustained weight loss through decreased caloric intake and exercise on the risk for CVD in obese individuals with diabetes; results are expected in 2012.[49]

CANCER

For cancer prevention, the American Cancer Society recommends at least 30 min of moderate to vigorous physical activity on 5 or more days of the week but notes that 45–60 min is preferable.[50] Similarly, the World Cancer Research Fund and the American Institute for Cancer Research recommend moderate physical activity for at least 30 min every day but state that, "as fitness improves, aim for 60 min or more of moderate, or for 30 min or more of vigorous, physical activity every day."[51]

Observational studies show an association between physical activity and a reduced risk for several types of cancer, particularly colon, breast, and endometrial cancer. (Some studies have found an inverse relation between physical and total cancer incidence or mortality,[12,13,52] but most studies have examined site-specific cancers only.) Data from observational studies and small randomized trials suggest that physical activity may protect against cancer by reducing risk for overweight/obesity and favorably affecting circulating levels of sex hormones, insulin, and inflammatory cytokines, as well as immune function and apoptosis.[53–55] Other biological mechanisms that may account in part for a chemoprotective effect of physical activity include decreases in insulin-like growth factors; favorable changes in prostaglandin profile; strengthened DNA repair systems; increased gut motility and reduced intestinal transit time for potential carcinogens (colon cancer); and improved pulmonary function

and shortened exposure time between lung tissue and carcinogens (lung cancer).[54] However, the evidence regarding mechanistic pathways is not definitive. Additional studies are needed to clarify which mechanisms, individually or in combination, account for the physical activity–cancer link.

Colon Cancer

Dozens of observational studies have found an inverse relation between physical activity and risk for colon cancer. A 2009 meta-analysis of 28 cohort and 24 case–control studies found an overall RR of 0.76 (0.72–0.81) comparing the most with the least active individuals.[56] The risk reduction was similar for women (RR = 0.79) and men (RR = 0.76). However, the risk reduction observed in the cohort studies (RR = 0.83) was smaller than that observed in the case–control studies (RR = 0.69), perhaps because of recall bias in the latter type of study. Moreover, the risk reduction in the cohort studies (although not the case–control studies) was smaller in women (RR = 0.89) than in men (RR = 0.81), perhaps because of sex differences in the absolute physical activity levels being compared. Women typically engage in less physical activity than men, and higher amounts may be needed to prevent colon cancer.

The studies included in the meta-analysis did not quantify physical activity uniformly, precluding the ability to determine the amount of physical activity necessary for the observed risk reduction. However, at least 30–60 min/day of moderate- to vigorous-intensity physical activity appears to be required to lower colon cancer risk significantly.[4,50] For example, among 79,000 Nurses' Health Study participants followed for up to 16 years, there was a 23% risk reduction comparing the most with the least active women (RR = 0.77 [0.58–1.01]).[57] The most active women expended >21.5 MET-h/week in leisure-time physical activity, whereas the least active expended <2 MET-h/week. These levels are equivalent to brisk walking for ~5 to 6 h/week in the most active and 0.5 h/week in the least active women. However, among women whose only reported activity was walking, there was a 31% risk reduction in those who walked 1–1.9 h/week (RR = 0.69 [0.47–1.03]) compared with those who did not walk, with little additional benefit for more time spent walking. A faster walking pace was also associated with reduced risk (very brisk vs. easy walking pace: RR = 0.43 [0.17–1.05]). Among women who participated in moderate or vigorous activity other than walking, those exercising >4 h/week had a 44% lower risk for colon cancer than those exercising <1 h/week, with a significant dose–response relation (p, trend = 0.01). On the other hand, in a 6-year follow-up of the CPS-II Nutrition Cohort, walking alone (without other recreational physical activity) was not significantly related to colon cancer risk,[58] although a protective association was observed for those who reported walking plus other recreational activity. For women, the RRs for <4, 4–6, and ≥7 h/week of activity vs. no activity were 0.99 (0.67–1.47), 0.72 (0.43–1.19), and 0.59 (0.36–0.98) (p, trend = 0.07).

Colon adenoma is the precursor lesion to colon cancer that is detected and removed during sigmoidoscopy or colonoscopy. A 2011 meta-analysis of 20 observational studies (cohort and case–control studies were not analyzed separately) of physical activity in relation to colon adenoma risk found an overall RR of 0.84 (0.77–0.92) when comparing the most with the least active persons.[59] The associations were similar for women (RR = 0.87 [0.74–1.02]) and men (RR = 0.81 [0.77–0.92]).

Breast Cancer

A 2011 systematic review of 33 cohort and 40 case–control studies found an average decrease of 25% in risk for breast cancer when comparing the most physically active with the least active women, with a stronger effect in the case–control studies (average risk reduction, 30%) than in the cohort studies (average risk reduction, 20%).[60] The majority of studies with significant results found a dose–response relation between increasing levels of physical activity and decreasing breast cancer risks. The risk reductions observed for recreational and household activities were generally greater than for walking or cycling alone or occupational activity. Some though not all studies suggest a stronger protective effect for physical activity among women who are postmenopausal, of normal weight (BMI < 25 kg/m^2), parous, and who have no family history of breast cancer.

Many studies suggest that at least 4–7 h/week of moderate to vigorous physical activity is necessary to yield a statistically significant reduction in breast cancer risk. For example, among 95,000 postmenopausal women followed for 20 years in the Nurses' Health Study, women who engaged in ≥27 MET-h/week of physical activity (equivalent to ~1 h/day of brisk walking) during follow-up were 15% less likely to develop breast cancer than those who engaged in <3 MET-h/week of physical activity. In analyses specifically of brisk walking, this activity was associated with lower risk (per 20 MET-h/week [5 h/week]: RR = 0.91). Compared with women who were least active at menopause and remained so through follow-up (<9 MET-h/week [walking at an average pace for ~30 min on most days of the week]), women who increased their activity were at reduced risk (<9 MET-h/week at menopause and ≥9 MET-h/week during follow-up: RR = 0.90).

Some studies suggest that a lower level of physical activity may also be beneficial for breast cancer prevention. For example, among 74,000 participants followed for 4.7 years in the Women's Health Initiative, women who engaged in 5.1–10 MET-h/week of physical activity (the equivalent of 1.25–2.5 h/week of brisk walking) at the start of the study had an 18% decreased risk for breast cancer compared with inactive women, while women who exercised >40 MET-h/week (the equivalent of >10 h/week of brisk walking) had only a slightly greater reduction in risk.[61] In this cohort, the beneficial effect of exercise was most pronounced in women in the lowest tertile of BMI (<24.1 kg/m^2) but was also apparent in women in the middle tertile (24.1–28.4). The protective effect did not vary by family history of breast cancer, parity, or menopausal hormone therapy use.

Endometrial Cancer

A 2010 meta-analysis of 11 prospective cohort studies found a significant inverse relation between physical activity and endometrial cancer risk.[62] In the nine studies that assessed recreational physical activity, a comparison of women who reported the most activity with those who reported the least yielded a pooled RR of 0.73 (0.58–0.93); adjustment for BMI—obesity is a strong risk factor for endometrial cancer—produced only a small attenuation (RR = 0.78 [0.63–0.95]). Eight of the nine studies reported significant or nonsignificant inverse associations. Seven of the nine studies included a statistical test for trend; of these, four found a significant dose–response relation. In the five studies that assessed occupational physical activity, a comparison of women reporting the most vs. the least activity yielded a summary RR of 0.79 (0.71–0.88).

Some reviewers have suggested that ~1 h/day of moderate-intensity physical activity appears to confer protection against endometrial cancer.[54] However, results of large prospective studies published recently (2008 or later) have been equivocal regarding the intensity required for risk reduction. Among >109,000 women aged 50–71 years followed for an average of 7 years in the NIH-AARP Diet and Health Study, vigorous physical activity was inversely associated with endometrial cancer risk after adjustment for BMI and other potential confounders (≥5 times/week for ≥20 min vs. never/rarely: RR = 0.77), but light/moderate, daily routine, and occupational physical activity were not predictive of risk.[63] Among >32,000 women followed for an average of 9 years in the Women's Health Study, women reporting any vigorous activity had lower risk than those reporting none (BMI-adjusted RR = 0.74, with no trend of declining risk with increasing energy expended in such activities), but walking was unrelated to risk.[64] In the CPS-II Nutrition Cohort, which followed >42,000 women for up to 10 years, recreational physical activity (primarily low to moderate intensity) was significantly associated with lower risk in analyses unadjusted for BMI (≥31.5 vs. <7 MET-h/week: RR = 0.67 [0.44–1.03]; *p*, trend = 0.007), but the association was attenuated after adjustment for this variable (RR = 0.79 [0.52–1.22]; *p*, trend = 0.18).[65]

Ovarian Cancer

Whether physical activity plays a role in the prevention of ovarian cancer remains uncertain, as results from epidemiologic studies have been inconsistent. A 2007 meta-analysis of seven case–control studies and six cohort studies of recreational physical activity in relation to ovarian cancer risk estimated a 20% reduced risk for the most vs. least active women.[66] For the case–control studies, the summary OR was 0.79 (0.70–0.85); for the cohort studies, the summary RR was 0.81 (0.57–1.17). However, results from several large prospective studies published since completion of the meta-analysis fail to provide support for a protective effect of physical activity against ovarian cancer.[67–70] Indeed, data from one such study, the NIH-AARP Diet and Health Study,[70] suggest that vigorous physical activity may be associated with an increase in ovarian cancer risk, a result also seen in two earlier studies, the Iowa Women's Health Study[71] and the Nurses' Health Study.[72] Such a relation could be explained by detection bias if more vigorously active women tend to exhibit cancer symptoms earlier than their less active counterparts. Additional research is needed to clarify the relation between physical activity and ovarian cancer.

Lung Cancer

A 2011 systematic review of 20 cohort and seven case–control studies of physical activity and lung cancer risk concluded that physical activity is associated with risk reductions of 20%–30% in women and 20%–50% in men, with evidence of a dose–response effect.[73] Because cigarette smoking is the major determinant of lung cancer, controlling for its effect is a critical methodological consideration in studies of this cancer site. Although most studies adjusted for smoking status or history, the potential for residual confounding remains high. Indeed, most studies that provide results stratified by smoking status have found either no effect or a much smaller protective effect of physical activity on lung cancer risk among nonsmokers than among current or former smokers.[74] Additional studies are needed to clarify whether there is an association between physical activity and lung cancer among never smokers.

Other Cancers

Cancers with insufficient data to determine whether physical activity plays a role in risk reduction include pancreatic, esophageal, kidney, bladder, cervical, and hematological cancers.[54] Results from epidemiologic studies have been inconsistent or null for these outcomes.

OSTEOPOROTIC FRACTURE, BONE MINERAL DENSITY, AND FALLS

Osteoporosis is a significant public health problem among older women in developed countries. It is characterized by rapid loss of bone density after menopause, which appears to be directly related to a decrease in estrogen levels and is associated with an increased risk for hip, spine, and wrist fracture. Physical activity may reduce the risk for osteoporotic fracture by increasing bone strength (weight-bearing aerobic and resistance exercise) and preventing falls (resistance, balance, and flexibility exercise).

Fracture

Observational investigations of physical activity in relation to fracture risk have largely focused on hip fracture, for two reasons. One, virtually all individuals with hip fracture seek medical attention, facilitating use of this endpoint in

epidemiologic studies. Second, because the proximal femur (part of the hip bone) undergoes loading during walking and all activities that involve ambulation, it is likely that any effect of physical activity on fracture risk would be most pronounced at this site. Indeed, a 2008 meta-analysis of 13 prospective studies found that moderate to vigorous physical activity was associated with a hip fracture risk reduction of 38% (31%–44%) in women and 45% (31%–56%) in men.[75] For example, among >61,000 postmenopausal women followed for 12 years in the Nurses' Health Study, each increase of 3 MET-h/week of physical activity (equivalent to 1 h/week of walking at an average pace) was associated with a statistically significant 6% reduction in risk for hip fracture.[76] Women performing ≥24 MET-h/week of physical activity had a 55% lower risk for hip fracture compared with women performing <3 MET-h/week. Among women who reported no other exercise, walking for ≥4 h/week was associated with a 41% lower risk for hip fracture compared with walking <1 h/week.

Fewer prospective studies have examined the association between physical activity and risk for vertebral fracture, and the results have been largely nonsignificant.[75] However, among 7239 women followed for 3.7 years in the Study of Osteoporotic Fractures, moderate to vigorous physical activity (>2 h/day) reduced the risk for radiographically assessed vertebral fracture by 33% as compared with no activity.[77] Limited data from prospective studies suggest that physical activity may *increase* the risk for wrist and other upper-limb fractures.[75]

Randomized clinical trials with fracture as a primary prespecified endpoint are lacking. A 2011 meta-analysis of 43 randomized trials (4320 participants) designed to test the effect of various exercise interventions on bone mineral density (BMD) in postmenopausal women reported a nonsignificant reduction in fracture risk (OR = 0.61 [0.23–1.64]), but most trials were not powered to detect this endpoint.[78]

Bone Mineral Density

Many randomized clinical trials have evaluated changes in BMD in response to exercise training in women. The aforementioned 2011 meta-analysis of 43 such trials in postmenopausal women reported that interventions that utilized a combination of exercise types slowed loss of BMD at the spine by a statistically significant 3.2% and that exercise interventions of any type slowed loss of BMD at the hip by a statistically significant 1.0%.[78] However, the magnitude of this effect is of questionable biological significance for reduction of fracture risk.[75] Also, most trials were ≤12 months in duration, so the extent to which age-related decreases in BMD can be attenuated through longer-term exercise training needs additional study.[9]

Falls

Prospective studies of the relation between usual physical activity and risk for falling suggest a U-shaped effect, with the most inactive and the most active persons at highest risk.[75] Several randomized trials have assessed the effect of exercise on fall prevention. In a meta-analysis of 12 such trials conducted in older community-dwelling persons, the pooled RR was 0.71 (0.61–0.82).[9] Of these trials, seven assessed strength and balance training; three assessed tai chi; one assessed endurance training and/or strength training; and one assessed computerized balance training and tai chi independently. An earlier meta-analysis of eight randomized trials showed a marginally significant 10% reduction in risk for falls associated with general exercise and a significant 17% reduction associated with balance training but no significant effect of aerobic, resistance, or flexibility training.[79]

NEUROPSYCHOLOGICAL OUTCOMES

Cognitive Decline

Many though not all prospective cohort studies show that physical activity is associated with better cognitive function in older populations.[9,80] For example, among >18,000 women aged 70–81 in the Nurses' Health Study, higher levels of long-term regular physical activity (average of biennial assessments occurring in 8–15 years prior to cognitive testing) were strongly predictive of better cognitive performance (a global score created by averaging scores on the Telephone Interview for Cognitive Status; a category fluency test; working memory and attention tests; and a verbal memory test).[81] The apparent benefit for women in the highest vs. lowest quintile of physical activity was similar in magnitude to that conferred by being ~3 years younger in age. A higher level of physical activity was also predictive of less cognitive decline over the subsequent 2 years. Notably, the protective effect of physical activity was not restricted to women engaging in vigorous activity; those who performed the equivalent of walking at an easy pace for ≥1.5 h/week had significantly better cognitive function than those who walked <40 min/week, with the magnitude of the difference equivalent to that observed for women ~1.5 years apart in age. Among 5925 women aged ≥65 years followed for 6–8 years in the Study of Osteoporotic Fractures, there was also a significant inverse relation between the number of blocks walked per week and cognitive decline as assessed by the Mini Mental State Examination.[82] Taken in aggregate, prospective cohort studies of physical activity in relation to incident dementia have also found an inverse relation. A 2009 meta-analysis of 16 prospective studies reported that, compared with individuals in the lowest activity category, those in the highest activity category experienced a 28% (14%–40%) reduction in risk for dementia and a 45% (16%–64%) reduction in risk for Alzheimer's disease.[83] Small, short-term randomized trials in nondemented older adults have demonstrated that exercise training, particularly a combination of aerobic, strength, and flexibility regimens, can improve certain cognitive processes, particularly executive function.[84] Moreover, imaging trials have shown beneficial changes in brain activity[85] and volume[86] in aerobically trained older adults. Animal studies

demonstrate that exercise has favorable effects on cognition (water maze performance), neurogenesis, neurotransmitter systems, and expression of brain-derived neurotrophic factor in young and aged rodents,[80] suggesting mechanisms by which physical activity may protect against cognitive decline. Physical activity also likely sustains the vascular health of the brain by lowering blood pressure, improving lipoprotein profiles, promoting endothelial nitric oxide production, ensuring adequate cerebral perfusion, and favorably affecting insulin and glucose parameters.[81]

Depression and Anxiety

In an analysis of data from 28 prospective cohort studies with a mean follow-up of 4 years, the average odds of experiencing elevated depressive symptomatology was 14%–25% lower among physically active compared with inactive individuals, after adjustment for potential confounders.[9] There was a protective benefit for people meeting the basic physical activity guideline (OR = 0.77 [0.72–0.82]) as well as for people who engaged in physical activity at less than recommended levels (OR = 0.84 [0.78–0.90]). Prospective observational data also suggest a protective effect for clinical depression. Prospective observational data on the relation between physical activity and anxiety are limited. However, short-term randomized trials indicate that physical activity can reduce depressive and anxiety symptoms in healthy adults,[9,87] medical patients without psychiatric disorders,[9,88] and depressed or anxious patients.[9,89]

WEIGHT CONTROL

Together with caloric intake, physical activity is a key determinant of energy balance and thus degree of adiposity. The Institute of Medicine first highlighted the issue of weight control in its 2002 recommendation espousing 60—rather than 30—min/day of moderate-intensity physical activity for weight maintenance and maximal health benefits.[90] In 2005, the Dietary Guidelines for Americans issued by the U.S. Department of Health and Human Services and U.S. Department of Agriculture included a physical activity guideline of 60 min/day to prevent weight gain and 60–90 min/day to sustain weight loss.[91] In 2009, the American College of Sports Medicine reviewed the empirical literature on physical activity in relation to weight control and concluded that, in the absence of caloric restriction, 150–250 min/week of moderate-intensity activity appears to be effective for preventing weight gain but not for producing clinically significant weight loss, while >250 min/week of such activity appears to be necessary for clinically significant weight loss as well as for the prevention of weight gain following weight loss.[92]

Recent large cohort studies in women provide perspective. Among 34,000 participants in the Women's Health Study, physical activity was associated with less weight gain among normal-weight women (BMI < 25 kg/m^2) but not among overweight (BMI 25 to <30) or obese women (BMI ≥ 30).[93] Women who were successful in maintaining a normal weight and gaining <2.3 kg over a 13-year follow-up period averaged ~60 min/day of moderate-intensity activity throughout the study. On the other hand, in an 8-year follow-up of >46,000 women aged 25–43 years in the Nurses' Health Study II, physical activity for ≥30 min/day was associated with a significantly lower likelihood of weight gain of >5%, with the strongest effect in those who were overweight. Compared with women who maintained <30 min/day of physical activity over 8 years, women were less likely to gain weight if they sustained ≥30 min/day (OR = 0.68) or increased to this level (OR = 0.64). However, there was a clear dose–response relation, such that even a small increase in physical activity in sedentary women (11–20 min/day) appeared beneficial. There was also no threshold above which physical activity and risk for weight gain were unrelated. Indeed, data from this study suggest that the amount of daily discretionary physical activity needed to eliminate, not just reduce, the risk for weight gain was 1.6 h for normal-weight women, 1.5 h for overweight women, and 45 min for obese women.[94] The Nurses' Health Study II investigators also examined physical activity as a predictor of weight maintenance after intentional weight loss among 4558 cohort members who had intentionally lost >5% of their body weight in the previous 2 years. Women were less likely to regain >30% of the lost weight over a 6-year period if they maintained ≥30 min/day of physical activity (OR = 0.69) or increased to this level (OR = 0.48), compared with those who remained inactive.[95]

Recent genetic epidemiologic research has shown that physical activity may counteract a genetic predisposition toward weight gain. In a 2011 meta-analysis of data from 45 studies with a total of 218,000 adults, the relation between the "fat mass and obesity associated" (FTO) gene—the strongest known susceptibility locus for obesity, albeit with low penetrance—with risk for obesity was attenuated by 27% in physically active compared with inactive persons.[96]

It should be noted that although weight control is an important goal, focusing on it as the main reason for engaging in physical activity gives an incomplete assessment of exercise's impact on disease risk. For example, with few exceptions, prospective observational studies find that inverse relations between physical activity and risk for cardiometabolic diseases persist even after factoring out the effects of BMI, suggesting that the benefits derived from physical activity are not solely attributable to weight regulation. As shown in Figure 25.2, data from the Nurses' Health Study indicate that physical inactivity and obesity independently contribute to the development of CHD and type 2 diabetes in initially healthy women.[97] Findings from other large cohorts are similar.

PREGNANCY OUTCOMES

The American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant women participate in ≥30 min of moderate-intensity physical activity on most days of the week in the absence of medical or obstetrical contraindications.[98] ACOG neither endorses nor recommends against participation in vigorous activities, for which information on pregnancy outcomes is sparse. Similarly, the

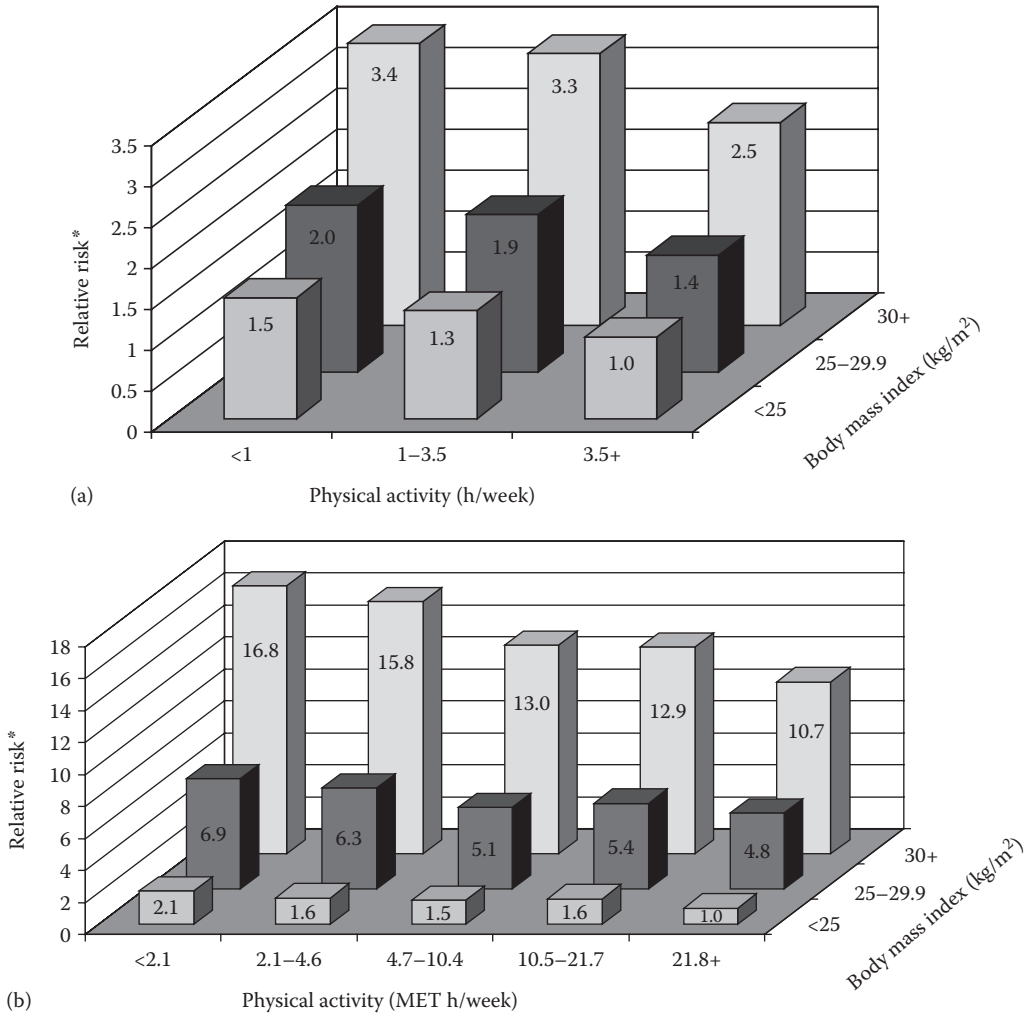


FIGURE 25.2 (a) Relative risk for coronary heart disease according to body mass index and physical activity level, Nurses' Health Study, 1980–2000. *Relative risks are adjusted for age, smoking status, alcohol consumption, menopausal status, postmenopausal hormone use, aspirin use, and parental history of CHD. (Data from Li, T.Y. et al., *Circulation*, 113, 499, 2006.) (b) Relative risk for type 2 diabetes according to body mass index and physical activity level, Nurses' Health Study, 1986–2002. *Relative risks are adjusted for age, smoking status, alcohol consumption, menopausal status, postmenopausal hormone use, and family history of diabetes. (Data from Rana, J.S. et al., *Diabetes Care*, 30, 53, 2007.)

2008 federal physical activity guidelines advise pregnant women that "it is reasonable … to follow the moderate-intensity physical activity recommendations set for adults unless specific medical concerns warrant a reduction in activity."[9] A 2011 meta-analysis of observational studies (five prospective cohort studies, two retrospective case–control studies, and two cross-sectional studies) found that physical activity before pregnancy (OR = 0.45 [0.28–0.75]) or in early pregnancy (OR = 0.76 [0.70–0.83]) was associated with a significantly lower risk for gestational diabetes.[99] The inverse association did not differ by study design, alleviating the concern for recall bias among the retrospective studies. Observational and very limited randomized trial data suggest that physical activity during pregnancy may also reduce risk for preeclampsia.[100–102] Moderate-intensity activity during pregnancy does not appear to increase risk for low birth weight, preterm delivery, or early pregnancy loss, although vigorous activity has been associated with small reductions (~200 to 400 g) in birth weight.[100,101] Sufficiently powered randomized trials of the effect of physical activity on pregnancy outcomes are needed.

RISKS OF PHYSICAL ACTIVITY

Along with its many benefits, physical activity has certain risks, including musculoskeletal injuries, cardiac events, and—particularly in athletes—menstrual dysfunction.

Musculoskeletal Injuries

Musculoskeletal injuries are the most common adverse events associated with physical activity. The risk for injury varies by activity type, with low-impact activities such as walking, gardening, cycling, and swimming associated with the fewest

risks.[9] Available data suggest that engaging in regular physical activity at currently recommended levels is associated with a low risk for musculoskeletal injury, although this risk has not been precisely quantified.[9] Research has also shown that when individuals increase their usual amount of physical activity, the risk for injury is related to the size of the increase.[9] Gradual, modest increases in physical activity allow for bodily adaptation and have been shown to reduce injury risk. Safely achieving a desired level of activity may require up to a year, especially for sedentary, elderly, or obese persons.[9]

With respect to sex differences in susceptibility to injury, available data suggest that, aside from stress fractures and injuries to the anterior cruciate ligament of the knee, which occur more frequently in females, women and men are equally likely to experience activity-related injuries, after adjustment for differences in activity and fitness levels.[9]

Acute Cardiac Events

Physical exertion can trigger acute cardiac events. A 2011 meta-analysis of case-crossover studies—a study design useful for examining a brief period of risk related to a brief exposure and in which cases serve as their own controls—found that episodic physical activity of ≥5–6 METs (moderate to vigorous intensity) was associated with an increased risk for myocardial infarction (10 studies; RR = 3.45 [2.33–5.13]) and sudden cardiac death (3 studies; RR = 4.98 [1.47–16.91]).[103] The associations appear to be similar for women and men, although more data are needed to determine this conclusively.[104] Importantly, the absolute increase in incidence of transient adverse cardiac events was low—i.e., 2–3 per 10,000 person-years for myocardial infarction and 1 per 10,000 person-years for sudden cardiac death. Also, habitual physical activity significantly attenuated the association between episodic physical activity and adverse cardiac events. For every additional time per week an individual habitually engaged in physical activity, the RR for myocardial infarction triggered by episodic physical activity dropped by 45% and that for sudden cardiac death dropped by 30%. The meta-analysis did not assess the transient cardiac risks associated with moderate-intensity physical activity only. However, limited data on this issue are consistent with the expectation that such risks are lower than those associated with vigorous activity. In terms of the balance of cardiovascular benefits and risks, it is critical to recognize that regular physical activity of moderate or vigorous intensity is associated with an overall decrease in CVD events that far outweighs the transient cardiac risks associated with physical exertion.[9]

Menstrual Dysfunction

Most of the research on the relation between physical activity and menstrual dysfunction has focused on competitive athletes rather than the general female population. Indeed, the American College of Sports Medicine coined the term "female athlete triad" nearly 20 years ago to describe a constellation of disordered eating, amenorrhea, and osteoporosis that occurs in these women.[105] Women engaged in sports that emphasize leanness, such as gymnastics, ballet, figure skating, and long-distance running, are particularly susceptible to the condition, suggesting that exercise alone is not the main culprit of reproductive abnormalities and that chronic-restricted caloric intake that does not balance energy expenditure also plays a role.[106]

CONCLUSION

Epidemiologic studies suggest that as little as 30 min/day of moderate-intensity physical activity can improve health and reduce risk for a variety of chronic diseases among sedentary women. A critical challenge for clinicians and policymakers is identifying and implementing approaches to facilitate sustained physical activity at this level.

Although more than two in three U.S. adults do not exercise enough to meet the basic federal guideline of 30 min/day, national survey data indicate that only one in three persons who saw a physician in the prior year reported receiving advice about physical activity at his or her last visit.[107] On the other hand, a survey of primary care physicians in Canada found that 70% reported routinely counseling patients about physical activity.[108] Although the prevalence of clinician counseling is uncertain, failure to counsel may result from a perceived lack of time, training, and appropriate patient materials. However, counseling need not be time intensive or intricate. Data from the multicenter Activity Counseling Trial suggest that clinicians can easily learn to incorporate 3–4 min of physical activity advice into routine office visits[109] and that counseling can increase activity in sedentary patients.[110]

A simple blueprint for physicians who wish to incorporate brief counseling about physical activity into their daily practices is available.[111] Lay publications to help sedentary individuals become more active can be retrieved online at no charge from various agencies.[112–114] Elements for an exercise "prescription" for patients are provided in Table 25.2. Data from randomized trials suggest that lifestyle activity interventions, which encourage the incorporation of short bouts of physical activity into daily routines (e.g., walking during lunch breaks, doing yard work or gardening, and taking the stairs rather than

TABLE 25.2
Possible Elements for a "Prescription" for Increased Physical Activity

- Take the stairs whenever possible
- Purchase a pedometer; aim for 10,000 steps/day
- Display "exercise prescription" in a visible place
- If you drive to work or stores, park in a space far away from the door and walk
- If you take public transportation, get off a stop early and walk
- Walk on your lunch break
- Try exercising with friends or a group
- Consider strength training for 20 min 2–3 times/week

Source: Manson, J.E. et al., *Arch. Intern. Med*., 164, 249, 2004.

the elevator), can be more effective than structured exercise programs in increasing physical activity and improving fitness and cardiometabolic risk profiles.[115] The use of self-monitoring strategies such as pedometers or exercise diaries also encourages regular activity. A meta-analysis of data from 26 studies (including eight randomized trials) in which 85% of the participants were women found that use of pedometers led to a significant 27% increase in physical activity as well as significant reductions in BMI and blood pressure.[116] Additional studies are needed to elucidate the features of individual- and community-based interventions and policies that successfully promote healthful levels of physical activity.[117]

In a sedentary society such as the United States, a widespread effort to help patients achieve even modest increases in regular physical activity should lead to measurable improvements in health. As observed by the eminent British epidemiologist Geoffrey Rose,[118] the reduction in disease burden in a given population is greater when a large segment of the population makes small improvements in health behaviors than when a small segment of the population makes large improvements.

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26 Women's Body Composition and Lifestyle

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CONTENTS

Introduction....331
Genetics....332
Age, Race, and Ethnicity....332
Female Sex Hormones....333
Glucocorticoids....334
Adipokine Influences....334
Body Composition and Disease....334
Measurement of Body Composition....335
Women's Body Composition and Exercise....337
Conclusion....339
References....340

INTRODUCTION

Interest in body composition can be traced back to the Greeks who believed that the human body was composed primarily of the cosmic elements: earth, water, fire, and air. More formal contemporary body composition investigation was launched in the 1850s as the chemical composition of body tissues began to be scrutinized. Throughout the twentieth century, scientists soon discovered novel methods for the measurement of body composition. The spectrum of discoveries included tetrapolar bioelectrical impedance analysis by J. Nyboer, A. Keys' densitometric technique, N. Lifson's use of the $D_2{}^{18}O$ dilution method for the measure of total body water and carbon dioxide production, and S. Heymsfield's application of dual-energy x-ray absorptiometry (DXA) in the measurement of appendicular skeletal muscle.[1] Air-displacement plethysmography (BodPod) soon replaced the older and less practical underwater weighing as both a research tool as well as a commercial offering by health clubs and sports medicine centers. More recently, the use of multislice axial computed tomography (CT) and magnetic resonance imaging (MRI) heralded a new era of both clinical and research applications.

Three historical events occurred bringing the importance of body composition front and center to the lives of women. The first was the emergence of the diet and weight loss industry which traditionally use one metric, overall body weight loss, as the hallmark of success. To achieve their numeric goal, women have often used any means possible, from cycles of self-induced starvation, to dieting and binging, often with little or no exercise component. In doing so, the maintenance and integrity of lean body mass (LBM) was typically neglected and sacrificed.

Second, the latter part of the twentieth century witnessed the growth of the fitness sector. Health clubs and gyms began to offer aerobic and strength training programs customized to women's needs. The emphasis shifted from a goal of weight loss to one of increased fitness, improved physical activity performance, and optimized body composition. The emergence of an athletic physique as a goal to strive for was supported by women's increasing participation in recreational and competitive sporting events. This new fitness focus has especially been integrated into the lives of the approximately 40 million women over the age of 50 years for whom beauty is less motivating than the need for strength and endurance to achieve and sustain physical independence.

The third historic milestone is the publication of data now linking suboptimal body composition to increased morbidity and mortality and decreased quality of life. In a 15-year study of 19,518 Finnish men and women aged 20–92 years, researchers found that obese, unfit participants had a significantly increased number of unhealthy life-years due to premature work disability, hospitalization for coronary heart disease, and need for long-term medication.[2] Comprehensive analyses of the relationship between fat distribution and health provide correlations between waist circumference (WC) and cardiovascular risk and mortality.[3]

This chapter begins with a description of the evolution of body composition through a woman's lifespan including the effect of genetics, age, ethnicity, and hormonal milestones. Next, a brief summary of the different modalities available for the measurement of body composition is presented as well as methodological challenges. This is followed by an epidemiologic review of the relationship between body fat and disease risk, including diabetes, heart disease, and

cancer. Finally, the impact of exercise as a lifestyle habit on body composition is examined with suggestions for ways to advise and guide women as they strive to achieve optimal body composition and well-being.

GENETICS

Clearly a host of factors influence body composition, including age, gender, genetics, and environment. To date, no major gene effect has been demonstrated for muscle or fat-free mass (FFM).[4] However, the investigation of the heritability of body fat content proved to be more forthcoming. The National Heart, Lung and Blood Institute Twin Study[5] suggested that genetic factors could explain between 57% and 86% of variability in BMI over a 10-year period. Other researchers began to document trends in heritability. In two clinical experiments, Bouchard et al. overfed pairs of monozygotic twins (MZT) by 1000 kcal/day for 22 days and then 100 days, noting that the amount of weight gained or fat stored was significantly influenced by the genotype of the subject.[6] In another set of MZT experiments, Poehlman et al. utilized an exercise-induced 1000 kcal energy deficit using the same time periods and found a significant intra-pair correlation with FFM changes in the short-term trial, while long-term weight loss resulted in significant resemblance for both body weight reduction as well as fat mass.[7] The results of these experiments suggest some genetic influence in the presence of alterations in energy balance.

Studies of familial inheritance patterns of fat distribution suggest the presence of genetic components. Analysis of data from the Canada Fitness Survey notes that genetics accounts for a 40% of the variance noted in fat topography.[8] The Heritage Family Study demonstrated significant familial aggregation for truncal and extremity fat, skinfold, and WC.[9] Interestingly, the significance of this correlation did not hold when these families were subjected to 20-week exercise training, where the variability in body fat changes increased.

Over the past decade, much attention has been focused on the role of excess intra-abdominal visceral adipose tissue (VAT) as it relates to increased disease risk. Men are more prone to upper body or android obesity throughout their lifespan. Typically, women deposit excess fat in the lower body hip, thigh, and buttock region, resulting in a gynoid pattern of overweight and obesity. However, at the time of peri- and postmenopause, women begin shape shifting, preferentially depositing excess fat in the VAT compartment and assuming a more android body habitus. Both men and women experience some increase in VAT with age regardless whether they are lean or obese.[10] Using CT to evaluate abdominal fat, the Quebec Family Study and the Heritage Family Study noted consistent heritabilities of 42%–70%.[11,12] It is implied from these studies that there are genetic characteristics influencing the propensity of individuals to store or draw from specific fat depots. This gene effect, when combined with a multifactorial constellation of environmental influences, helps explain an individual's typical phenotype and body fat distribution.

AGE, RACE, AND ETHNICITY

In describing the evolution of a woman's body composition over her lifetime, it is important to acknowledge her racial and ethnic background, as both significantly impact on any variability observed. Racial characteristics refer to the presence of a biologically distinct group with common genetic inheritance. Ethnicity relates to factors that involve culture, ancestry, language, beliefs, habits, and lifestyle behaviors. Because there is often considerable genetic and cultural overlap, the term racial–ethnic will be used to describe differences seen between demographic groupings.

From infancy to the age of 3 years, there are negligible differences in FFM between males and females.[13–15] From the age of 3 years until adolescence, males carry less water in their FFM, as well as more protein and bone mineral. This maintains until adolescence and young adulthood at which time males significantly increase muscle mass and bone mineral content. The average FFM of young adult females is approximately 70% of the mean value for adult males. Racial–ethnic comparisons from childhood through age 19 years indicate that differences in FFM between American white, black, and Mexican American females are small.[16]

Goulding measured regional fat distribution using DXA in a population of predominantly American white males and females from ages 5 through 29 years.[17] Sexual dimorphism in fat patterning was noted in prepubertal children, with girls exhibiting less waist fat and higher hip circumferences than boys. These differences were magnified as the children transition through adolescence and early adulthood, leading to an increase in waist fat especially in males.[18]

Sex differences in FM are negligible until the age of 6 years at which time females accrue more FM, reaching a plateau about the age of 13–15 years, just as males begin their dramatic increase in FFM and bone mineral. By the age of 19 years, females have about 1.5 times the FM of males.[19] On the other hand, from infancy through early childhood, females in general carry a higher BF percent than males. Although males do increase FM somewhat throughout childhood, FM then declines with adolescence, reaching its lowest point by age 17 years, and then gradually increases throughout adulthood.

Using DXA technology, Ellis found that throughout childhood and adolescence, American black females tended to have greater muscle mass as well as bone mineral content. Mexican American females trended toward higher FM and BF percentage. In comparison, American white females had slightly larger muscle mass and similar bone mineral content as Mexican Americans, but less FM and BF percentage.[20] Similar findings were noted by Chumlea et al. from their analysis of bioimpedance data.[21]

VAT and subcutaneous adipose tissue (SAT) regions were quantified with CT by Goran et al. who found negligible sex differences in VAT and SAT from infancy through adolescence, although SAT showed more variation than VAT.[22] The data that do exist suggest that VAT begins to accumulate later in adolescence and continues to increase throughout

adulthood, more so in males. SAT increases throughout adulthood until the age of 60 years when it declines in both sexes. There are no discernable racial–ethnic differences between American blacks and whites in VAT and SAT growth patterns.[23] Throughout the lifespan, adult males have more VAT than females. However, postmenopausal females tend to gain more VAT.[10] An analysis of VAT and SAT using multislice MRI comparing Japanese and American whites revealed that Asian American females have slightly less total adipose tissue and SAT, but more VAT than American white females.[24] Overall, general patterns of sex differences in body composition changes tended to be the same across racial–ethnic groups, with variances in the magnitude of such differences.

FEMALE SEX HORMONES

The relationship between hormones and body composition is powerful and complex. As observed throughout childhood, growth hormone (GH) stimulates the transformation of preadipocytes into fully differentiated adipocytes.[25,26] Once a girl reaches puberty, GH secretion is further stimulated by female sex hormones resulting in increased overall growth, enhanced FFM, and relative reduction in FM. The presence of higher levels of VAT obesity is associated with lower GH levels.[27] Interestingly, GH levels are restored after weight reduction, suggesting that the reduction in GH is secondary and not the cause of the obesity.[28] This phenomenon may also help explain why, as a woman passes through middle age and beyond, and her FM increases (especially VAT) and FFM decreases, her GH is also low.[28] Further, increased levels of cortisol caused by age-related dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, combined with the lower levels of GH and thus decreased lipolysis, contribute to the increase in VAT as well.

Female sex hormones influence body composition throughout a woman's lifetime. In premenopausal women, gluteal–femoral adipocyte enlargement is associated with an increase in the fat storage enzyme, lipoprotein lipase (LPL), as well as a low sensitivity to lipolysis.[29] In late pregnancy and during lactation, this pattern is reversed allowing release of lipids from this fat depot as energy to fuel the mother's increased caloric requirements during breastfeeding.

Women produce much less testosterone than men, and the effects of this androgen may be quite different than that noted in men. In males, testosterone deficiency is associated with an increase in VAT while administration of testosterone markedly decreases VAT mass. Male VAT is characterized by a higher density of androgen receptors (AR) than that found in SAT.[30] In women, elevated testosterone levels are associated with the polycystic ovarian syndrome which is characterized by an increase in VAT, associated with hypertension, type 2 diabetes, and hyperlipidemia. Estrogen, on the other hand, appears to function like male testosterone. Until menopause, estrogen appears to down regulate the AR density in adipose tissue apparently protecting against adipose deposition in truncal SAT as well as VAT.[31]

The BioCycle Study investigated the influence of adiposity on sex hormone patterns across the menstrual cycle in premenopausal normal-weight and obese women with regular menstrual cycles.[32]Adiposity was measured by DXA. Compared with normal weight women, obese women were noted to have lower levels of progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and higher free E2 across the cycle. Women with central adiposity (increased amounts of VAT) averaged lower levels of total E2, FSH, with FSH and LH peaks occurring later in the menstrual cycle.

TABLE 26.1
Methodological Considerations in the Study of Hormonal Replacement Therapy and Body Composition

- Age at initiation of HRT
- Initial anthropometrics (weight, WC, BMI, FM, %BF, FFM, VAT, SAT)
- Type of HRT: single or combined (estrogen, progesterone, testosterone)
- Dosage of HRT
- Changes in type and/or dose
- Duration of HRT
- Compliance with HRT
- Preexisting medical conditions (metabolic syndrome)
- Presence of acute or chronic stress
- Medications (hypoglycemics, antidepressants)
- Weight management history (weight cycling, bariatric surgery)
- Quality of dietary intake and any changes during HRT
- Level of physical activity and any changes during HRT

WC, Waist circumference; BMI, body mass index; FM, fat mass; BF, body fat; FFM, fat-free mass; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

There are a variety of methodological considerations that significantly impact upon the study and interpretation of data involving the relationship between hormonal replacement therapy (HRT) and body composition. Table 26.1 provides a summary of key factors that must be addressed as investigations proceed. This list is further enhanced by emerging research shedding light upon new mechanisms of action of female sex hormones' effect on body weight, composition, and fat distribution. It is for these reasons that the current literature is inconclusive regarding the effect of HRT on a woman's body composition. This is evidenced by the following studies.

In early clinical experiments, postmenopausal women were administered estrogen replacement, and there appeared to be a shift from abdominal to premenopausal adipose gluteofemoral adipose deposition.[33] Estrogen replacement therapy decreased VAT accumulation somewhat.[34] However, when Blackman et al. conducted a randomized placebo-controlled study of estrogen replacement therapy with and without GH, and with GH alone, he found no effect of HRT alone on either FFM or FM.[35] In postmenopausal women, the reduction in estrogen levels and relative increase in androgens favors fat partitioning from the periphery to VAT. Gower conducted a longitudinal study of body fat distribution among postmenopausal women either on or off HRT.[36] CT and DXA were utilized to analyze VAT, SAT, and total adiposity. Sex hormones were assessed. Over 2 years, both cohorts experienced

a 10% increase in VAT. The HRT users were found to have an inverse relationship between estradiol levels and VAT.

In another experiment, Sites found that conjugated estrogens plus medroxyprogesterone acetate had no effect on body composition or body fat distribution but reduced insulin sensitivity. The decreased insulin sensitivity reversed after discontinuation of the HRT.[37] A *Cochrane Database of Systematic Reviews* analyzed 27 randomized, placebo, or no-treatment controlled trials describing the effect of HRT on body weight or fat distribution and found no evidence of an effect of unopposed estrogen or combined estrogen with progesterone on the menopause-related increase in body weight or BMI. There was insufficient evidence to enable examination of the effect of HRT on FM or skinfold thickness.[38] Onur evaluated the effects of a spectrum of HRT options including oral and transdermal forms of administration on postmenopausal women and found that all HRT types reduced WC most notably in women with a WC >35 in. Body weight and BMI did not change significantly suggesting a shift in fat distribution.[39]

More recently, Clegg and colleagues discovered that estrogens regulate body weight, energy expenditure, and fat distribution through estrogen receptor α (ERα) located on two distinct hypothalamic neurons: steroidogenic factor 1 and proopiomelanocortin.[40] These findings may lead to new targeted estrogen replacement therapies in which estrogen is delivered to the brain, obviating disease risks associated with whole-body estrogen delivery, including breast cancer and stroke.

GLUCOCORTICOIDS

Glucocorticoid receptors (GR) are found in human fat tissue with a higher density noted in VAT as compared to SAT.[41] When hypercortisolemia exists, there is a reduction in GR density in the various adipose tissue compartments that maintains this same rank order.[42] The hallmark of Cushing's syndrome is the presence of excess cortisol secretion and the associated insulin resistance which leads to a marked decrease in FFM and increase in VAT. The combination of cortisol and insulin is critical to increasing LPL activity and inhibiting lipolysis as well as GH secretion.[43] The interplay between these hormones leads to an increase in VAT as well as the presence of the metabolic syndrome, including type 2 diabetes, hyperlipidemia, and hypertension.

The relationship between chronic or episodic stress-induced elevations of cortisol and central obesity has been noted by numerous studies. In a study of prepubertal Hispanic girls, the presence of a high cortisol awakening response (CAR) as measured by salivary cortisol, a marker for psychological stress, was highly associated with the presence of both increased VAT and SAT, determined by multislice MRI.[44] In studying premenopausal women, Epel and colleagues found that those noting the highest levels of stress demonstrated overeating of dense calories, and accumulation of VAT leading to central obesity and higher BMI.[45]

This effect apparently increases in magnitude with the aging process, in which there is a decline in the resilience of the HPA resulting in longer exposure to higher levels of cortisol. This, combined with decreasing GH as well as estrogen, leads to a further tendency to increase VAT and thus central obesity.

ADIPOKINE INFLUENCES

Leptin is both a cytokine as well as a pleiotropic hormone with multiple effects including endocrine regulation, as well as reproduction and immune function. Adipocytes secrete the hormone leptin, which, through receptors located in the arcuate nucleus, regulate FM through alterations in energy expenditure as well as appetite. Decreases in FM result in lower leptin levels which then stimulate increased appetite and decreased energy expenditure restoring FM to normal levels.[46] Studies have shown that fasting and the use of very low calorie dieting reduces leptin levels. This makes adherence to such regimens difficult if not impossible. Although leptin administration in normal obese women does not produce weight reduction, it may instead have utility in restoring leptin to normal levels to support weight maintenance.

Beginning at puberty, women have higher levels of plasma leptin than men, while premenopausal women have higher levels than postmenopausal.[47] The etiology may be due in part to some measure of leptin resistance as well as the influence of female sex hormones. It has been postulated that obesity may occur in part to a leptin-resistant state. Leptin insufficiency is a rare syndrome leading to serious obesity beginning in childhood. It does respond to exogenous leptin administration reducing but not completely correcting obesity. As a woman ages, her leptin levels decline more rapidly than men accounting in part for a woman's increase in FM postmenopausally.

Levels of another adipokine, adiponectin, are inversely associated with adipose tissue mass and have a negative correlation with FM throughout the lifespan.[48–50] As well, adiponectin levels in women were found be higher than men, and, like men, to be inversely correlated with leptin levels.[51] Adiponectin levels increase with age in both men and women, when compared to younger people with similar anthropometrics. Since estrogen in women and testosterone in men lower adiponectin, it is presumed that the age-related phenomenon may be affected by sex hormone status. There may also be an ethnic influence. A study of Hispanic and African American men and women found that the inverse association of VAT with adiponectin was strongest in the latter, suggesting a possible racial–ethnic effect as it relates to central obesity.[52] Adiponectin exerts its metabolic effects on muscle tissue by increasing the combustion of free fatty acids while decreasing total triglyceride content.[53] In contrast to leptin, adiponectin levels rise after weight loss which is also associated with improvements in serum lipids and insulin sensitivity.[54]

BODY COMPOSITION AND DISEASE

The relationship between body composition and disease in women is confounded by significant methodological issues, including the use of indirect measures of body composition as well as biological, environmental, lifestyle habits, preexisting medical conditions, hormonal status, use or disuse of

HRT, and changes in an individual's anthropometrics over time. For purposes of this chapter, the discussion of disease risk as it relates to body composition will be limited to a group of disease states relevant to women's health.

In analysis of the relationship between body fat distribution and breast cancer incidence in premenopausal women participating in the Nurses' Health Study II, researchers found no correlation between body fat and the overall incidence of breast cancer in this cohort. However, WC, hip circumference, and waist-to-hip ratio were associated with an increased risk of ER-negative breast cancer.[55] For postmenopausal women, obesity appears to increase the risk of breast cancer.[56] It has been estimated that for every 10 kg increase in overall weight in postmenopausal women, there is a 6%–7% increase in the risk for breast cancer.[57] Further, it appears that the increased risk for breast cancer is more likely due to increases in weight over time.[58] The increased risk of breast cancer in postmenopausal women, especially noted in those with central obesity, may be related to the presence of insulin resistance, hyperinsulinemia, as well as high levels of estrogens and androgens.[59]

Ovarian cancer is the fourth most frequent cause of cancer death in women and the most lethal of the gynecological tumors in women from North America. The influence of body composition on risk of ovarian cancer has been inconsistent and inconclusive. Holman and colleagues examined the relationship between the risk of ovarian cancer, BMI, height, and weight in a cohort of Chinese women and found a significant correlation between high BMI and body weight 5 years prior to diagnosis but not at time of diagnosis.[60] Yet Møller et al. found no increased risk of ovarian cancer in a cohort of obese Danish women.[61] Higher BMI in young women may be associated with an increased risk of premenopausal ovarian cancer.[62]

Obesity increases the risk of colon cancer. Studies have noted that increased obesity-related hazard ratios for colon cancer were similar for men and women and also proved to be the same in multiracial–ethnic studies as well.[63,64] Weijenberg and colleagues examined the relationship between body size and the incidence of colorectal cancer among 120,852 men and women aged 55–69 years in the Netherlands Cohort Study. They found that in women, a large waist size coupled with a low physical activity level significantly increased the risk of distal and proximal tumors.[65] It is postulated that the higher levels of leptin associated with obesity may contribute to the growth of colon epithelial cells, as leptin receptors are typically found in colon cancer cell lines.[66]

Obesity is a well-established risk factor for type 2 diabetes, prompting some to refer to this pairing as "diabesity." The majority of women with type 2 diabetes are obese. Thirty-four percent of U.S. adults are obese and over 11% of men and women over the age of 20 years have type 2 diabetes.[67] Location of increased adiposity, primarily visceral fat, is more important than total adipose tissue mass. Increased VAT associated with an increased WC is associated with the metabolic syndrome, type 2 diabetes, and increased cardiovascular disease. Fox et al. assessed patterns of abdominal obesity in the Framingham cohort (N = 3348, 48% women, average age 52 years) using multidetector CT and found that 30% of both women and men had high SAT, while 44% of women had high VAT compared to 42% men. Further, the prevalence of the metabolic syndrome (elevated triglycerides, low HDL cholesterol, hypertension) was higher in women and men who had relatively more VAT than SAT.[68] An analysis of the relationship between body fat distribution and risk of type 2 diabetes in participants of the Nurses' Health Study demonstrated that BMI, WHR, and WC are powerful independent predictors of type 2 diabetes in U.S. women.[69]

Increased risk for coronary disease is associated with the metabolic syndrome which, as has been presented, is correlated with the presence of central obesity. Obesity was found to be a significant independent predictor of increased risk for coronary heart disease in a 20-year follow-up of over 88,393 women aged 34–59 years in the Nurses' Health Study.[70] In another prospective study of U.S. women aged 30–55 years, researchers found that even mild to moderate overweight significantly increased the risk for heart disease.[71] There is strong evidence that the presence of obesity and weight gain significantly increase the risk for coronary heart disease in women diagnosed with type 2 diabetes.[72]

MEASUREMENT OF BODY COMPOSITION

It is evident from current data that in order to optimize disease prevention and treatment, clinicians should monitor not only body weight but also body composition and body fat distribution. Although more emphasis has been placed on the relationship between adiposity and disease, it is also important to be aware that muscle is an integral component of body composition. Although not associated with metabolic disease per se, maintaining optimal endurance, strength, flexibility and balance is essential to avoid disabilities and frailty. The issue of muscular integrity will be addressed later in this chapter.

Table 26.2 outlines the basic body composition tools available to clinicians as well as fitness professionals and research scientists. What follows is a simple blueprint for

TABLE 26.2
Body Composition Measurement Clinical and Research Tools

Clinical use
Body weight scale
Girth measurements
Bioelectric impedance
Research or professional use
Skinfold testing
Hydrostatic weighing
Dual-energy x-ray absorptiometry (DXA)
Whole-body air-displacement plethysmography (BodPod)
Magnetic resonance imaging (MRI)
Computed tomography (CT)

understanding the benefits and limitations of using each measurement modality.

One of the first attempts to diagnose obesity was done by associating body weight with height. This event occurred with the creation of actuarial tables from the Metropolitan Life Insurance Company.[73] The standardized body weights were based upon data derived from young healthy white males who could afford life insurance. Extrapolations were made for female body weight. Moreover, the tables were based upon the subjective observation of an individual's frame. Despite the limitations, these tables were utilized as the accepted template for many years until it became clear that total body weight was but one part of a larger body composition equation.

A commonly used anthropometric measure to detect total body adiposity is the body mass index (BMI) defined as body weight in kilograms divided by height in meters squared. A host of epidemiological studies have demonstrated the strong association between BMI >30 kg/m^2 and increased morbidity and mortality.[74] There are limitations to the application of BMI, especially in individuals whose BMI is ≤30 kg/m^2 because total weight does not distinguish between FM and FFM. This works two ways. People who carry higher than average amounts of muscle mass and/or have increased bone density but normal to low FM may be erroneously diagnosed as overweight or obese. Conversely, individuals who are of normal weight and BMI but have lower than average muscle mass and higher than average FM, a condition referred to as sarcopenic overweight or obesity, would be counted as normal. BMI, therefore, has low sensitivity for the diagnosis of obesity. Sex and racial–ethnic differences exist, further complicating the precise detection and diagnosis of obesity.[75] Shah and Braverman have shown that these limitations lead to a significant under estimation of obesity prevalence, especially in older women.[76] Despite these limitations, it is recommended that clinicians add this measurement as one more element in their body composition equation as it does have a high specificity in detecting obesity.

Bioelectric impedance (BIA) technology is now accessible for clinicians as well as consumers. Impedance is measured through the use of a small, alternating, single-frequency current passing between points of contact measuring body tissues based upon their water and dissolved electrolyte content, noting that fat and bone are generally nonconductive. Total FFM is calculated based upon the estimate of total body water.[76] Using BIA, consumers as well as clinicians can monitor body weight as well as FM, body fat percentage, and FFM. The simplest consumer BIA scale measures body weight and body fat percentage. More expensive models include FFM as well as total body water and the regional distribution of FM and FFM. Clinicians can purchase these commercial BIA devices, which yield higher levels of accuracy and sensitivity. Level of hydration is important as dehydration results in an overestimate of body fat. BIA provides a measurement of total body fat and does not account for location of body fat.

Body fat norms for women based upon the *American College of Sports Medicine's Health-Related Physical Fitness Assessment Manual* are presented in Table 26.3.[77]

Combining BMI with a measurement of total body weight and body fat as well as appropriate girth measurements provides the clinician with a more complete picture of an individual's body composition. WC is a simple yet powerful way to assess central obesity, as it correlates well with intra-abdominal imaging and is highly associated with coronary vascular disease risk, morbidity, and mortality.[78,79] The only equipment needed is a cloth or flexible metal tape measure. The girth or abdominal circumference is the critical measurement as it is directly related to disease risk. Measure the narrowest part of the waist. This is often difficult to determine due to the presence of excess abdominal adiposity. If this occurs, take the measurement at the midpoint between the lowest rib and the top of the iliac crest. Other options include taking consistent measurements at the level of the umbilicus. In women, the goal is to achieve a girth of between 28.5 and 35 in. as the risk for disease and the metabolic syndrome increases with increasing girth size.[80]

Fitness professionals use BIA devices as well as skinfold measurements in assessing body composition. Skinfold testing should always be performed by a certified fitness professional using a calibrated skinfold caliper and ideally done by the same person each time. Body fat is estimated by skinfold thickness using between 3 and 12 anatomic sites. The mean of

TABLE 26.3
ACSM Body Composition (% Body Fat) for Women

		Age				
Percentile	**Fitness Category**	**20–29**	**30–39**	**40–49**	**50–59**	**60+**
90	Well above average	14.5–18.9	15.5–19.9	18.5–23.4	21.6–26.5	21.1–27.4
70	Above average	19–22	20–23	23.5–26.3	26.6–30	27.5–30.8
50	Average	22.1–25.3	23.1–26.9	26.4–30	30.1–33.4	30.9–34.2
30	Below average	25.4–32	27–32.7	30.1–34.9	33.5–37.8	34.3–39.2
10	Well below average	32.1	32.8	35	37.9	39.3

Source: *American College of Sports Medicine's Health-Related Physical Fitness Assessment Manual*, 2nd Edn., 2008, p. 59.

[a] Data provided by the Institute for Aerobics Research, Dallas, TX, 1994. Study population for the data set was predominately white and college educated.

two measurements is typically taken. Skinfold measurements do not measure body fat percentage, but offer an estimate of FM. Limitations to the use of this modality include morbid obesity, significant weight loss resulting in substantial excess subcutaneous skin, and the elderly who typically present with age-related muscular atrophy, loss of fat mass, and excess skinfolds.[81]

Recognized as the "gold standard" for the measurement of the two-compartment (FM and FFM) model, underwater or hydrostatic weighing requires a specialized stainless steel tank (or pool) usually located at a university research setting. When done correctly, body density is measured and body fat percentage can be calculated. Limitations include an underestimation of body fat in individuals with increased bone density and increased musculature, an overestimation of body fat in osteoporotic persons and the inability to measure young children, frail elderly and those with cardiovascular or pulmonary disease, including the obese.[82]

DXA has classically been used to study bone demineralization and to monitor osteoporosis. This technology can provide a comprehensive breakdown of FFM, fat tissue mass, and bone mineral content. The individual is scanned with photons generated by two low-dose x-rays at different energy levels. The body tissues' absorption of the photons at each level is measured. DXA scanning not only can provide a quantifiable assessment of the three body composition compartments but can also distinguish each by anatomical region. DXA cannot distinguish between VAT and SAT. Although DXA-derived abdominal fat assessments may underestimate CT-generated measurements, the DXA data still correlate well with that of CT.[83] Generally, DXA technology is accurate and reliable. It is still inaccessible for most consumers as insurance does not cover this service.

Although whole-body air-displacement plethysmography has been in use for many years, only recently has a practical, commercial device, the BodPod, been made available. This tool is expensive and is used primarily by research institutions, although the BodPod measurements have been made available to consumers on a fee-for-service basis. The BodPod measurement is as accurate as hydrostatic weighing, using air instead of water, and is more accessible to individuals for whom underwater weighing is not possible.[84]

MRI uses a powerful magnetic field, radio frequency pulses, and a computer to stimulate water and fat molecules in the body, producing detailed pictures of organs, soft tissues, bone, and virtually all other internal body structures. MRI does not use oxidizing radiation and is safer than CT scans and x-rays. CT scanning produces cross-sectional images of the body that can then be processed into 3D images. Specialized CT scans highlight fat depots and can provide a ratio of VAT to SAT. Both MRI and CT imaging provide the most reliable data on VAT depots.[85]

WOMEN'S BODY COMPOSITION AND EXERCISE

Optimizing body composition throughout a woman's lifespan yields multiple rewards. First, muscular strength enhances physical independence and the ability to perform activities of daily living as well as enjoy recreational pursuits. It also helps to prevent the frailty and sarcopenia associated with the aging process. Frailty in particular is linked to early mortality and increases exponentially with age throughout the adult lifespan. A 12 year study of 14,713 people, 54% of whom were women, found that at all ages, people who were relatively fit had a lower mortality and used fewer medical care services.[86] Sarcopenic changes are associated with age-related changes in body composition, inflammation, and alterations in hormonal balance.[87]

Second, maintaining an active lifestyle preserves bone health and can reduce the risk of osteoporosis and osteoporosis-related fractures. Children and adolescents who exercise show a higher bone accrual compared to sedentary peers.[88] In a *Cochrane Database of Systematic Reviews* of exercise interventions in the prevention of bone loss and fractures in postmenopausal women, an important effect of exercise on bone density was noted.[89]

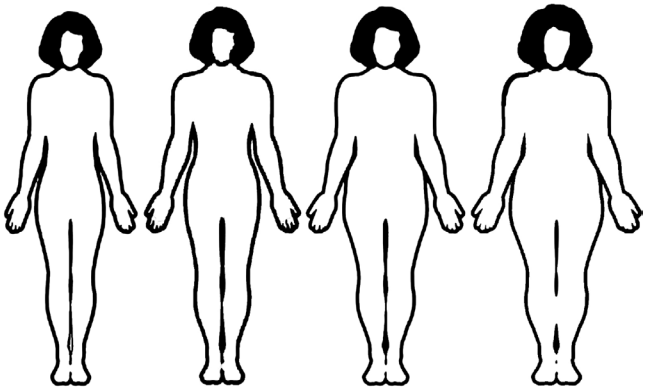
Third, by incorporating more activity into daily life, successful long-term weight management is possible as well as disease prevention. Sedentary behavior is a critical factor in the accrual of excess body fat from childhood throughout adulthood.[90] This increased adiposity, especially VAT, is associated with a spectrum of chronic diseases including type 2 diabetes, dyslipidemia, coronary vascular disease, and hypertension as well as increased mortality.[91,92]

Historically, women approached weight reduction by manipulating dietary intake with little or no regard to altering energy expenditure as well. Over time, this strategy has failed. In 1996, the Surgeon General issued a report summarizing relationships between physical activity and health.[93] In it, regular physical activity was shown to be an effective method to reduce and control excess body fat, especially in combination with a healthy diet. Given that there is no optimal diet for everyone, the report also recommended the people seek out a registered dietitian who can provide individualized dietary guidance.

A host of studies have shown that the most effective strategy for promoting weight loss is a combination of diet modification as well as regular physical activity.[94] Changes in the quality and quantity of food intake are responsible for initial weight loss, but regular physical activity helps by both supporting weight maintenance as well as preventing weight regain.[95,96] This two-pronged approach has been applied to chronic diseases such as type 2 diabetes in which weight management through lifestyle modification (e.g., healthy nutrition and regular physical activity) is now recognized as the "gold standard" for effective and sustainable weight reduction.[97]

More recently, researchers are focusing on alterations in body composition as well as markers of health and fitness during weight loss trials. Kreider et al. at Texas A&M University compared the efficacy of a structured diet and exercise (SDE) program vs. a meal replacement–based (MPB) diet in which obese female participants were only given verbal encouragement to increase activity.[98] Both groups underwent a 10 week weight loss phase followed by a 24 week maintenance period.

TABLE 26.4
Body Composition Variance with Identical Body Weight and BMI

	40 Year Old 5'4" 140 lb Female BMI 24			
	Figure 1 Athlete	Figure 2 Recently Weight Reduced, Regular Exercise, Healthy Nutrition	Figure 3 Recently Weight Reduced, Sporadic Exercise, Poor Nutrition	Figure 4 Chronic, Yo-Yo Dieter, No Exercise
				
Dress size	6	8	10	12
Waist circumference	↓	↓	↑	↑
Body fat%	↓	↓	↑	↑
Fat mass	↓	↓	↑	↑
Lean body mass	↑	↑	↓	↓

Results showed that daily energy intake was relatively the same, but while the MPB group did minimal activity, the SDE women engaged in moderate to vigorous activities. As compared to the MPB group, the SDE women lost more body weight, reduced FM as documented by BIA, decreased WC, and saw improvement in maximal aerobic capacity and strength.

Table 26.4 provides a simple model to illustrate Kreider's findings and to emphasize the importance of monitoring body composition during weight loss. This model is by no means inclusive of all factors related to alterations in body composition, but presents a basic template with which to understand the need to incorporate body composition assessments in clinical practice.

Despite identical age, height, and weight, the four women depicted have different body compositions and thus dissimilar sizes and WC. Clearly the amount of LBM and FM noted in athletes is dependent upon their sport, but for purposes of this model, it is assumed that the Figure 1 athlete might be one with greater muscularity such as a triathlete, and thus represents the woman with the least body fat, smallest WC, and maximal muscle mass.

At the other end of the spectrum is Figure 4, a woman representing a more typical scenario of weight cycling through periods of chronic caloric restriction with no exercise followed by compensatory overeating and weight regain. This pattern of "yo-yo" dieting without exercise has been found to have variable effects on body composition but no significant effect on mortality.[99] Factors affecting outcome on body composition in women who weight cycle include the motivation for initiation of the cycle (intentional vs. unintentional weight reduction), type of dietary intervention used (level of caloric restriction), duration of program, quantity of weight lost and regained, and frequency of cycling. In this model, it is assumed that the sedentary chronic dieter is not building muscle mass and is, as she ages, losing muscle.[100] Adults who do not engage in regular strength training lose on average 4–6 lb of muscle tissue per decade, further thwarting efforts to shed excess weight.[101] In addition, as previously noted, increasing WC is associated with increased disease risk. Thus, her already widened girth increases her future disease risk. As a result, the inactive yo-yo dieter carries the highest load of fat and, compared to the other women, average to below normal LBM.

The ideal body composition goal is represented by Figure 2, the woman noted to have recently undergone a weight reduction program utilizing regular exercise and a healthy diet. This strategy is supported by data provided by the National Weight Control Registry, a cohort of over 6000 people, primarily women, who have successfully lost weight and maintained that weight for an average of 5.5 years.[102–104] And finally, Figure 3 represents a woman who has also recently reduced weight, but is inconsistent with a healthy diet and exercise, another common pattern. Her anthropometric and body composition indices fall between the ideal scenario and the inactive dieter.

Important to note is that all of the women have the same normal BMI, yet their sizes, girth, and body composition are quite dissimilar, once again repeating the limitations presented by monitoring only body weight and BMI. It is important that clinicians and the women they guide understand that dieting alone is a failed strategy. Further, a healthy diet and exercise are *both* critical to achieve effective and sustainable weight loss and maintenance and that monitoring body composition is key to optimizing fat loss and muscle optimization.

The exercise prescription to achieve and maintain a woman's optimal body composition involves three components:

1. *Regular aerobic or cardio exercise*: Consistent with the recommendations of the Physical Activity Guidelines for Americans and the ACSM, women should strive to achieve 5 days or more per week of 30–60 min of moderate-intensity physical activity, or 3 days or more per week of 20–30 min of vigorous activity, or ideally a combination of both.[91,105] Studies now support the inclusion of high-intensity interval training for optimal weight reduction and maintenance in women.[106,107] Of note, participants of the National Weight Control Registry engage in high levels of physical activity, with more than one half of the members expending 2000 kcal/week (200 min/week of moderate-intensity exercise, the most common of which is walking). Exercise can be broken up throughout the day and ideally these sessions include higher levels of effort similar to short-burst training.[108]
2. *Strength training*: The age-related reduction in muscle mass previously noted is a major reason for the 2%–3% per decade reduction in resting metabolic rate observed in adults.[109,110] Current ACSM Strength Training Guidelines call for 2 or 3 nonconsecutive training days per week, 2–4 sets of each exercise with 8–10 repetitions, or 1 set with 12–15 repetitions, with 8–10 exercises for the major muscles.[91] The benefits of strength training include increased FFM, decreased FM, increased resting metabolism, improved cardiovascular fitness and metabolic profile, increased glucose uptake, increased bone mineral density, and increased muscular strength and functional performance.[111] Ideally, a woman is guided by a certified fitness professional when she begins her strength training.
3. *Activities of daily living*: Becoming active throughout the day is an integral component of healthy lifestyle. This includes time spent at work as well as in home and leisure.[112] Aggressive efforts are needed to enlighten both clinicians and consumers about the hazards of sedentary lifestyle habits.[113] Increased activities of daily living in combination with structured aerobic and strength training sessions is the ideal prescription to maintain optimal body composition.

CONCLUSION

The case has been made that one critical component of health and well-being is the need to optimize body composition throughout a woman's life. Increasing physical activity, in concert with a healthy dietary intake, is crucial to achieving this goal. It is imperative that clinicians actively engage in a meaningful dialogue with women and be prepared to offer effective suggestions as well as connections with the appropriate certified fitness experts, nutrition professionals, and community resources.

In the clinical setting, practitioners have not traditionally prescribed exercise nor have they placed significant emphasis on the need to change lifestyle habits to prevent and treat disease. Happily, a new trend is emerging. According to 2010 data from the CDC's National Health Interview Survey, one in three adults who had consulted a physician within 12 months were advised to engage in physical activity as part of their health management strategy.[114] This represents a 10% increase in physician-derived exercise promotion between 2000 and 2010. This advice doubled for consumers aged 85 years and above. Physicians were most likely to discuss physical activity with those who were overweight and obese. As well, the presence of a medical condition such as hypertension, diabetes, or heart disease prompted more physicians to suggest incorporating physical activity into daily life habits.

New resources are now available to assist clinicians in their efforts to convey the importance of physical activity in daily life. In 2007, ACSM launched what has transformed into a global multiorganizational supported campaign called Exercise is Medicine. Their vision statement notes:

> To make physical activity and exercise a standard part of a global disease prevention and treatment medical paradigm. For physical activity to be considered by all health care providers as a vital sign in every patient visit, and that patients are effectively counseled and referred as to their physical activity and health needs, thus leading to overall improvement in the public's health and long-term reduction in health care cost.[115]

The website www.exerciseismedicine.org provides clinicians and consumers alike with practical tools to help understand the invaluable role of physical activity in disease prevention, treatment, and the enhancement of quality of life.

Women seeking guidance as they strive to build a strong body, maintain a healthy weight, and mentally embrace the joy and challenge of their life journey look to form a powerful and productive partnership with health and wellness professionals. Lifestyle medicine is predicated on the belief that lifestyle habits and choices are central to disease prevention, treatment, and quality of life. Optimizing body composition provides an excellent opportunity for the practitioner–consumer partnership to transform this belief into a life-saving reality.

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27 Health and Wellness Coaching Skills for Lasting Change

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CONTENTS

Introduction 344
Epidemiology 344
It's Getting Harder to Develop and Sustain Healthful Behaviors 344
Genetics 344
Healthful Behaviors Can Change Our Genes 344
Each Patient Is Unique 345
Risk Factors 346
What Makes Lifestyle Change Even More Difficult? 346
Psychology of Positive Lifestyle Change 346
Mindful Attention 347
Self-Acceptance 347
Autonomous Motivation 347
Self-Efficacy 348
Identify and Deploy Strengths and Talents, Especially Those Used in Other Life Domains Such as Work 348
Develop Positive Emotions That Enhance Resilience, Reframing Setbacks as Opportunities 348
Adopt the Mind-Set of a Scientist, Experimenting with a Variety of Approaches 349
Design Behavioral Goals to Be Engaging and Realistic 349
Process of Changing Mind-Set and Behavior 349
Develop and Implement Plan for Change—Vision and Goals 349
Coaching Conversations That Elicit New Perspectives and Insights Lead to New Actions 349
Accountability 350
Referrals 350
Prevention and Treatment—Coaching Interventions 350
Physician Using Coaching Skills 350
Gap in Medical Education and Training 350
Walk the Walk 350
Evidence for Use of Coaching Skills by Physicians 351
Expert and Coach Approaches 351
Health and Wellness Coaches 352
Coaching Scenarios 355
Diane, a 30 Year Old Woman Who Is Overweight, Prepregnancy 355
Coaching Tips for Physicians: Applying the Five-Step Cycle 355
Coach's Process—Deploying the Five Forces of Sustainable Change 355
Shirley, a 40-Year-Old with Type 2 Diabetes 355
Coaching Tips for Physicians: Applying the Five-Step Cycle 356
Coach's Process—Deploying the Five Forces of Sustainable Change 356
Audrey, a 55-Year-Old with Breast Cancer 356
Coaching Tips for Physicians: Applying the Five-Step Cycle 356
Coach's Process—Deploying the Five Forces of Sustainable Change 357
Rachel, a 65-Year-Old with Heart Disease 357
Coaching Tips for Physicians: Applying the Five-Step Cycle 357
Coach's Process—Deploying the Five Forces of Sustainable Change 358
Appendix A: 12 Coaching Competencies 358
References 359

INTRODUCTION

Health care providers know that a healthy lifestyle is essential to optimal health, but they do not know how to enable patients to adopt new healthy habits and abandon old harmful ones. Medicine was beautifully designed to manage acute medical emergencies and conditions, but it is not as well suited to helping patients manage a lifelong journey to sustain health-promoting behaviors. In many cases, patients need to master new life skills—how to develop a personal formula for health and vitality and how to become confident in their ability to implement, sustain, and adjust that formula over a lifetime. Most patients do not believe that they are capable of mastering these life skills.[1] Many patients have never even considered these life skills as important, and some patients probably have never even contemplated them at all. In fact, the patients facing bariatric surgery face the greatest doubts in this arena.[2]

Professional health and wellness coaches are emerging as an expert competency designed to help people become personally responsible, self-motivated, confident, and fully engaged in leading a healthy lifestyle.

EPIDEMIOLOGY

It's Getting Harder to Develop and Sustain Healthful Behaviors

Over the past 10 years, American adults have been consistent with their lifestyle behaviors, and that does not bode well for their health status. According to the CDC's Behavior Risk Factor Surveillance System, the numbers are holding steady for the statistics from 2001 to 2009 surveys of Americans consuming five fruits and vegetables a day and the number of Americans who engage in moderate-intensity exercise for 30 min or engage in vigorous-intensity exercise for 20 min a day or 5 or more days in the week.[3] Less than one quarter of American adults get the phytonutrients and healthy ingredients of five or more fruits and vegetables per day, and only half of Americans engage in the recommended level of physical activity known to produce optimal health benefits. Thus, it is not surprising that well below half of Americans fall in the normal weight category by body mass index (BMI), only 35% in 2010 decreasing from 42% in 2000.

Interestingly, the overweight category was ~36% in 2000 and 2010, but the obese category gained in girth with 20.1% of Americans obese in 2000 and 27% obese in 2010. In terms of diabetes, in 2010 the survey shows that 8.7% of American adults had been told by a physician that they had diabetes compared to 6% of Americans in 2000. It looks as if things are getting worse, not better.

What are we doing to get us into this predicament? According to a report by the United States Department of Agriculture, Center for Nutrition Policy and Promotion, about two-thirds of all adults reported that on average they had watched 2 h of TV or videos per day or more in the past 30 days. Not only that but about a quarter of Americans supplement this sedentary activity with two or more hours of computer time outside of work. Close to three quarters of Americans reported that, over the past 30 days, they had not walked or bicycled as a form of commuting to work or school or running errands.[4]

What accounts for the current trend of lifestyles full of sedentary behavior as well as fat-filled, sugary snacks and over scheduling of everyone from age 1 to 70 years? With the spread of fast food and supersized portions, Americans received a double blow of reduced quality of food and increased quantity of food. Other factors stacked up against a healthy lifestyle include the following:

1. The trend away from cooking at home
2. The wide availability of processed white carbohydrates which hijack our brain's reward centers
3. The invasion of technology into personal lives—stealing away opportunities to unplug, recharge, and rest
4. The common long commute, mixed with long hours of work, serious responsibilities of raising families, and the intense pressure to advance career for social status and/or financial reward
5. The confusion that patients feel as a result of being bombarded by the latest fad diet, diet supplement, exercise regimen, or the newest exercise equipment for strong abdominal muscles

In addition to all these factors, a recent survey from the nonprofit International Food Information Council (IFIC) found that concerns about weight and weight loss are at an all-time low. With the U.S. economy in trouble, a high unemployment rate, and global unrest, people are worried about money and security. Oddly, at a time when there is an increased emphasis on health and wellness, more and more concrete evidence in favor of fruits and vegetables as well as physical activity, plus more and more obesity and diabetes, Americans are not following the guidelines of a healthy lifestyle. David Katz, MD MPH, founding Director of the Yale University Prevention Research Center in New Haven, CT, surmised, "I think there is a certain element of burnout." He also emphasized a critical point, "We have not yet done a nearly good enough job empowering people to make them feel like they really can get to the prize—the prize being sustainable weight loss, their weight controlled without being hungry and miserable for the rest of your life."[5]

Now is the time to heed the words of wisdom from Ralph Waldo Emerson, "The first wealth is health," and put stock into our health by addressing the things we can control like how physically active we are, what we put into our mouths, and what we schedule or not schedule into our daily lives.

GENETICS

Healthful Behaviors Can Change Our Genes

What is responsible for our health and our lifestyle choices? Nature or nurture? Or both? More and more evidence is mounting in support of a combination of both nature and

nurture as the answer. As we have come to accept that certain people carry a specific gene that puts them at risk for breast cancer, ovarian cancer, or colon cancer, we have also realized that the environment can play a key role in whether these genes are activated. For example, if people smoke, they are putting themselves at risk for lung cancer as cigarette smoke is a known carcinogen. Similarly, drinking alcohol to excess will put someone at greater risk for liver cancer. On the other hand, if people with a family history of heart disease engage in healthful behaviors such as a diet of healthful fats and no *trans*-fats, low in sugar, low in salt, yet high in fruits and vegetables, nuts, and lean protein; exercise regularly at least for a half an hour 5 days of the week; don't smoke; and drink only one glass of red wine a day, then they mitigate their increased risk of a heart attack by their behaviors.

Epigenetics is the study of the impact of environmental factors on our genes' behavior. How our lifestyles affect the expression of our genes has long been of interest to scientists and researchers, but it was not until about 10 years ago that this new field emerged and has grown exponentially along with the research—there are epigenetic studies on prostate cancer, lymphoma, autoimmunity, diabetes, atherosclerosis, fetal alcohol syndrome, rheumatic diseases, schizophrenia, nephritic syndrome, and Alzheimer's disease, to name a few.

Benjamin Tycko and John Ashkenas in the *Journal of Clinical Investigations* wrote an interesting overview of epigenetics in 2000.

> The adjective "epigenetic" has been used to describe many types of biological processes, but with the evolution of epigenetics into a sub-discipline of molecular biology, its meaning has become quite focused. Although the term is sometimes used more broadly, epigenetic effects are usually taken to encompass changes in the genetic material—the genomic DNA and chromatin—that alter gene expression in a manner that is heritable during somatic cell divisions (and sometimes even in germline transmission), but that is nonmutational and therefore fundamentally reversible.[6]

Looking at epigenetics at the microscopic and macroscopic level will help put it in focus. Microscopically, there are chemical "marks" on the DNA that are not part of the actual DNA coding sequence of A (adenosine), T (thiamine), G (guanine), C (cytosine). These marks are methylations on the tips of the DNA or acetylations/deacetylations of histones (proteins that the DNA winds around to make chromatin). Some of these marks suppress DNA expression and some of the marks enhance its expression. In other words, these marks are like switches that can turn the DNA on or off. Thus, they can help control the expression of our genes or the behavior of our genes, not our genes themselves. That is why it is epi (above) genetics.

Lifestyle choices can influence our genes. Studies of identical twin studies help demonstrate this point. In these studies, one identical twin has developed cancer or heart disease and the other has not. Two individuals can share the exact same DNA code, but they do not have the same DNA expression. An interesting study in mice helps demonstrate this further. Mice and humans have a gene called agouti. The sequence of the gene is the same in all mice. However, its genetic expression differs. For example, if the agouti gene is unmethylated, then the mouse is fat and yellow. If that gene is methylated, then the mouse is brown and thin. Amazingly, if researchers fed a yellow, fat female mouse a diet rich in methionine, then most of its pups were born brown and skinny, and they remained that way throughout their life span. Nutrients known to affect the human epigenome include methionine, folic acid, vitamin B12, and vitamin B6. Dietary sources of methionine include sesame seeds, Brazil nuts, fish, peppers, and spinach. Sources of folic acid include leafy vegetables, sunflower seeds, baker's yeast, and liver. Vitamin B12 is found in meat, liver, shellfish, and milk. Meats, whole grain products, vegetables, and nuts are good sources of vitamin B6.[7]

There is also evidence that exercise plays a role in epigenetics. In a study of rats, it was demonstrated that regular exercise affects the demethylation of DNA and the acetylation of histones. Also, exercise affects the transcription of an important protein in the regulation of brain-derived neurotrophic factor (BDNF) that is heavily involved in the learning process for rats.[8]

The study of epigenetics is fascinating and especially pertinent to lifestyle change efforts as it strengthens the case for a healthy diet and exercise to help people reach their optimal wellness. Randy Jirtle studies epigenetics at Duke University Medical Center and he has said, "The thing I love about epigenetics is that you have the potential to alter your destiny."[9]

Each Patient Is Unique

In addition to unique genetics and epigenetics, each person is unique with respect to dietary history and preferences, diet trials and tribulations, and exercising habits or lack of exercising. More and more information on dietary allergies emphasizes the unique differences in our systems. Dr. Mark Hyman's book, Ultrametabolism, encourages people to evaluate how their bodies function when fueled by certain foods and nutrients. He recommends an elimination diet, eliminating common allergens such as dairy, gluten, caffeine, and sugar. By eliminating all of the allergens, you can start with a clean slate and then add them back on one by one to see how you feel. Some people are gluten sensitive and others are not. Some are lactose intolerant and cannot eat dairy. This approach backs up the theory that there needs to be an individualized approach to nutrition counseling in order for it to be effective.

People also have their own exercise preferences. Some people love to jog and have been doing so since they were teenagers. Those same people are not necessarily swimmers. Other people love cycling or spinning. Disability or pain, such as knee pain from osteoarthritis, might limit the exercise options for some clients. Team sports like basketball or soccer might be the best recommendation for an exercise routine. Zumba (a form of exercise dance which started in Latin America) has taken off among women as a fun, musical

experience that doesn't feel like exercise. Preferences depend on the person, their past experience with sports, and their current interests.

When it comes to providing information, just as children have different learning styles, some adults are visual learners who can benefit from graphs and pictures while others are auditory learners who rely on lectures and conversations to consolidate information. Knowing your patient and his or her learning style helps to adapt your approach so that your efforts will be effective and efficient.

When working with patients on behavior change, as well as on the delivery of expert knowledge and guidelines, it is important to approach each patient as a unique individual, supporting his/her journey to find the formula which best fits his/her genetics, history, capacity, and way of life.

RISK FACTORS

What Makes Lifestyle Change Even More Difficult?

There are various mental health barriers to sustainable behavior change that people need to overcome in order to reap the benefits of good health. Certain conditions such as attention deficit disorder (ADD), depression, and addiction make it even harder to adopt healthy lifestyles. Other high hurdles include physical disability and chronic pain. Although these health conditions add complexity to adopting and following a healthy lifestyle, they can be overcome when addressed specifically and strategies are built in specifically for each condition. For many, the first priority in these cases is managing the condition to put stability and balance in place before tackling healthy lifestyles. For some, the enhanced energy and confidence gained from a new, healthy behavior can improve the motivation for tackling the medical condition.

Another risk factor for an unhealthy lifestyle is socioeconomic status. Patients with low income cannot afford to shop at farmer's markets, upscale grocery stores such as Whole Foods, most of which do not accept food stamps. On $40 budget a week for food, it is often difficult and overwhelming to plan for fresh produce at every meal. Along with low socioeconomic status, a low education level adds to the difficulty because if a person does not know the dangers of sugar and partially hydrogenated fats, then they are not likely to avoid them. In addition, fitness apparel, sneakers, gym equipment, and gym memberships are additional expenses. These are important barriers, but there are solutions on an individual and societal level. For individuals, frozen fruits and vegetables are often cheaper, readily available at all grocery stores, and a good alternative to fresh produce. At the societal level, educating people about the importance of donating healthful foods to the food pantries is a great place to start. There are nonprofit organizations that work to educate people in the low socioeconomic classes about healthful food choices and the importance of physical activity. You do not have to be a member of a gym, sporting fashionable athletic wear, to enjoy physical activity. Walking is an accessible and effective form of exercise and 15 min a day can have a significant impact on your health and longevity. In a large study of over 400,000 people in Taiwan, it was demonstrated that those subjects who exercised 15 min a day had a 14% reduced risk of all-cause mortality and a life expectancy 3 years longer than subjects who were not active.[10]

Also, the library is a wonderful resource for all. Computers are free. Books are free. DVDs are free. All of which can be useful to people whose finances are limited.

Weak family system support is another risk factor for unhealthy lifestyles. When family members are unhealthy, whether they are overweight, smokers, junk food junkies, or sedentary, it is often a challenge to spread your wings and take the path less traveled. Aligning with friends who share the same priorities for health can help. If there is no one immediately available, free online support group sites can fill this gap. Social support for change is a key ingredient. What else is important?

PSYCHOLOGY OF POSITIVE LIFESTYLE CHANGE

Now that we have recapped the large-scale health care crisis of unhealthy lifestyles and described the need for people to take action to improve their genes and the additional challenges faced by those who struggle most, the good news is that the scientific study of how humans change behavior, and the important ingredients which enable sustainable change, is evolving rapidly in the fields of psychology and neuroscience.

Social and behavioral psychologists pioneered the field over the past few decades, joined by positive psychologists in the late 1990s, focusing on (1) what enables the adoption of behaviors shown to improve physical and mental health, such as exercise, healthful nutrition, weight and stress management, and mindfulness practices; (2) what behaviors lead to positive mental health or flourishing; and (3) whether and how mental flourishing improves physical health.

Psychologists are now joined by neuroscientists who are exploring the biological processes of neuroplasticity, which some call self-directed neuroplasticity, the generation of new neural connections and integrated brain-wide networks which undergird the formation of new habits, and the cognitive and emotional mind-sets needed to sustain them.

Coaching is a human relationship designed to facilitate positive and sustainable change. Prior to more fully exploring how coaching competencies can be used by physicians and health care providers, including the evidence for coaching outcomes to date, this section presents and integrates a set of robust, evidence-based theories that make up the foundation of core coaching competencies. The presentation uses a conversational style to assist the reader to more readily put the concepts into practice in discussions with patients and addresses the development of five domains, which are the basis of 12 coaching competencies, summarized in Appendix A:

1. Mindful attention
2. Self-acceptance
3. Autonomous motivation
4. Self-efficacy
5. Process of change of mind-set and behavior

Mindful Attention

Change begins with a mindful focus on a need and/or desire for a positive change. Focused attention may be triggered and supported by a wide variety of inputs—for example, a physician's diagnosis, prodding by a spouse or friend, observing a respected role model, new information reported in the media, a state of low vitality or energy, an annual trigger (get fit for summer, back to school, or new year, new you), or a health crisis—perhaps personal or someone close.

While many triggers can be a catalyst to start, they do not necessarily lead to the full focus needed for lasting change. Given finite brain resources to attend to change and challenge, including stress and adverse events, expanding self-awareness of personal health competes with other life foci which can appear more urgent or pressing. Psychologist Jon Kabat Zinn and physician David Ludwig conclude in their paper on Mindfulness in Medicine in *JAMA* in 2008:

> The current age has been referred to as one of "continuous partial attention." E-mail, cell phones, and other technology invade nearly every moment of waking life. Economic pressures demand ever-increasing productivity, even as time to enjoy the fruits of labor declines. These factors adversely affect the health care system overall and diminish the patient-physician relationship. In this context, mindfulness may hold promise as a potential way to help prevent and treat disease, increase ability to cope with pain and chronic illness, reduce stress in patients and practitioners, foster compassion, improve quality of care and reduce medical errors. High-quality, mechanism-oriented studies and randomized controlled trials of mindfulness in medicine are needed.[11]

A calm coaching conversation can provide mindful, focused attention to personal health and enhance self-awareness by quieting a client's emotional frenzy for a short time, tuning out distractions, and enabling a curious and insight-generating inquiry into "what's really going on here?"[12]

In the *Handbook of Primary Care Psychology*, Carson and Langer describe the cognitive flexibility of mindfulness, vital in self-managing a process of changing behavior: (1) the ability to view both objects and situations from multiple perspectives and (2) the ability to shift perspectives depending upon context.[13]

Not only is it helpful to patients but physicians who completed an intensive mindfulness training experienced sustained improvements in well-being, burnout, and attitudes toward care of patients.[14]

Coaching competency: Facilitate a calm, mindful focus of attention on a patient's state of health and well-being which expands self-awareness of deficits and awakens the desire for possible benefits of positive change.

Self-Acceptance

One of the benefits of mindfulness is that it helps people get out of a rigid mind-set, expand their perspectives on themselves, and come to accept themselves as well as take control and responsibility for changing their future course.[13] For patients who realize that their past and present lifestyles are damaging their health, over-ruminating on negative self-judgments ("what a loser I am") is a potent source of negativity. Negative emotions have been shown to narrow the brain's focus and attention, decrease open-mindedness, and impair creativity, problem solving, as well as strategic thinking. Feeling badly about past behaviors restricts the brain's resources for problem solving and change even before first steps are taken.[15]

Empathy is also a potent tool in fostering self-acceptance. Physician empathy has been shown to improve patient outcomes.[16] A mindful, nonjudgmental, and empathetic coaching dynamic helps patients to appreciate how self-judgment is holding them back, to choose to let go of the weight of self-judgment, and to affirm the lessons of the past, so they are more positive about proceeding to make change. A coach's empathy and nonjudgment fosters a client's self-empathy and self-acceptance.

Coaching competency: Empathize with a patient's circumstances, show acceptance, and foster a nonjudgmental and affirmative perspective ("let's appreciate and learn from the past and move forward to build a better future").

Autonomous Motivation

Once the groundwork of a mindful focus and self-acceptance have been laid, we can turn our attention to helping patients find the motivation and drive to succeed in the process of change. The most respected theory of human motivation is self-determination theory (SDT), developed by psychologists Edward Deci and Richard Ryan at the University of Rochester over 40 years of study. Deci and Ryan have identified three primary human drives honed by our evolutionary biology: autonomy, competence, and human connection. They have explored various types of external and autonomous motivation, and identified the type of motivation which leads to sustainable change.[17] As they summarize in 2008 in *European Health Psychologist*, SDT argues that

> developing a sense of autonomy and competence are critical to the processes of internalization and integration (of motivation), through which a person comes to self-regulate and sustain behaviors conducive to health and well being …. When patients have their psychological needs for autonomy, competence, and relatedness supported in the process of their health care, they experience more volitional engagement in treatment and maintain outcomes better over time. This pattern of findings appears to hold for broad lifestyle changes such as smoking cessation or dietary regulation, as well as discrete behaviors such as the adherent use of medications.[18]

Autonomy is the first of the three core human drives; we are wired to want to march to our own drummers and dislike being told what to do. Not just toddlers and teenagers, even adults resist being told what to do, including their physician's recommendations. They resist and rebel even when resistance is not in their best interest. People (all ages) perform best when they are free to make an autonomous choice.

This is good news because people also assume personal responsibility for their health when they act autonomously.

To support autonomy, it is important to "get out of sails and get into fishing" by open questions, undistracted listening, and reflecting to clarify and demonstrate listening, with an open, mindful, and curious mind-set, rather than preaching and prescribing which shuts down autonomy and can elicit resistance. Imagine your patients and clients sitting in the driver's seat, holding the steering wheel. Resist the urge to grab the steering wheel. This is a simple metaphor for an autonomy-supporting relationship. We explore the contrast of the expert approach and coach approach further in the next section on physicians applying coaching skills.

Coaching competency: Encourage autonomy, putting patients in the driver's seat and yourself in the passenger seat, by undistracted listening, open-minded inquiry, refraining from mindless advice giving, and helping patients to make choices by brainstorming a few options to select from.

Deci and Ryan have identified two types of motivation—external motivation ("I exercise because my doctor told me to") and autonomous motivation ("I choose to exercise because I want to"). External motivation comes in two forms—an external source such as a boss, spouse, or authority figure or "internalized" external motivation when one has swallowed the external rules (e.g., eat less and exercise more) whole, without digestion and connection to a positive desire for what's good for oneself. This internalized external force turns into an inner critic who might say something along the lines of "I should exercise. I'm a failure because I don't exercise."

There are also two types of autonomous motivation—intrinsic motivation, related to present engagement ("I go to yoga classes because I have fun and enjoy the challenge; I do it for its own sake") and internal regulation, related to one's identify and future self ("I choose to exercise because I am convinced that it's good for me, helping me live the life I value now and in the future"). Future-focused internal regulation is the form of motivation that enables sustained behavior change.

Psychologist Barbara Fredrickson has shown that people are more likely to persist in developing new habits if they start noticing benefits that they value early, within a short period such as 2 weeks, which likely enhances internal motivation. Hence it's important to help clients identify new habits which may yield a benefit quickly, or motivation may drop off.[15]

Coaching competency: Help patients find health behaviors that are intrinsically motivating (enjoyed for their own sake) and/or find internal motivation (articulating and valuing future personal benefit) for a health behavior, for example., it will allow them to make a difference in the world or do more of things they treasure most, now and in the future. Help patients select behaviors which have the potential to enhance autonomous motivation quickly.

Self-Efficacy

> Whether you think you can, or think you can't, you are right.
>
> **Henry Ford**

Self-efficacy, one's belief in one's ability to be successful, is a codependent companion of motivation: both are essential for successful change. Ryan et al. assert that the desire for "competence" is the core human drive behind self-efficacy.[18] A robust source of motivation fades quickly if confidence in succeeding is inadequate. Fortunately, there are many roads to building self-efficacy, beyond cultivating autonomous motivation, which include the following.

Identify and Deploy Strengths and Talents, Especially Those Used in Other Life Domains Such as Work

Only one-third of adults can describe their strengths (Linley et al. 2010) and are more focused on their weaknesses and how to overcome them. In addition to an informal survey of friends, colleagues, and family members, there are a variety of validated strengths assessments, including www.viacharacter.org, www.strengthsfinder.com, and www.strengths2020.com, which identify top character strengths and talents. Applying top character strengths in novel ways in support of health goals can be an unexploited opportunity.[20]

Coaching competency: Help clients identify personal strengths and talents and brainstorm ways to deploy strengths in the pursuit of lifestyle change and better health.

Develop Positive Emotions That Enhance Resilience, Reframing Setbacks as Opportunities

Barbara Fredrickson has shown that a main mediator of resilience is the level of positive emotions summoned in a time of stress or adversity. The level of negative emotions is not a determining factor; people with high levels of negativity are resilient if they have high levels of positivity. Hence, higher levels of positive emotions predict higher levels of resilience.[21]

Marcial Losada and Barbara Fredrickson determined a positivity "tipping point" of 3:1 positive to negative emotions, above which people are on an upward spiral—resilient, adapting well to adversity, and having the capacity to change, and below which people are stuck and languish. Positive emotions have an immediate positive impact on brain function, increasing openness, creativity, and strategic thinking. In addition to psychological resilience, they also deliver other cumulative effects over time, improving memory, reducing pain, and improving relationships and health.[22]

Losada identified the 3:1 tipping point by developing a nonlinear mathematical model of team dynamics. Fredrickson validated the tipping point for individuals, which also correlated with Gottman's research on marriages (5:1 ratio needed for successful marriages). Fredrickson's research suggests that 80% of American adults are below the 3:1 tipping point, making lifestyle change a significant challenge, and positivity an important domain for personal development.

Domains for cultivating positive emotions are plentiful. Time orientation is one useful way to think about ways to improve positivity. Positive emotions related to the past that can be developed include forgiveness, appreciation and gratitude, and finding silver linings as well as lessons in negative

experiences. Present-oriented sources of positivity include mindfulness (improves focus, reduces negativity, and fosters positivity), savoring of small pleasures including caring relationships, and engaging one's strengths in meaningful activities. Future-oriented positive emotions emerge from cultivating an inspiring vision, as well as improving hope, and optimism.

Coaching competency: Cultivate positive emotions by starting sessions with positive topics—experiences, lessons, successes, strengths, which improves brain function for more challenging topics. Unpack and harvest positive topics at the close of sessions.

Adopt the Mind-Set of a Scientist, Experimenting with a Variety of Approaches

The field of hope psychology has shown that success increases with higher levels of hope, and has focused on what builds hope, which includes setting goals and identifying multiple pathways to reach them.[23] There are a multitude of ways to engage in exercise, eating healthful foods, developing mindfulness and positivity, and managing weight and stress. It's important to adopt a "scientist" mind-set and test or experiment with several options in order to find and settle on a good fit, and even better a personal formula of —three to four behaviors that work together synergistically to deliver desired results.

Coaching competency: Help clients brainstorm on various paths to reach goals so that they appreciate that if one path doesn't work, one or more other paths are possible, which increases hope and confidence.

Design Behavioral Goals to Be Engaging and Realistic

While goal-setting researchers have taught us that ambitious goals are more engaging and lead to higher performance than more modest goals,[24] a moderating factor is their impact on confidence. Too challenging goals can lead to stress and anxiety, damage confidence, and arrest interest in continuation. It's important to find the right balance of "stretch" which is engaging and doesn't jeopardize confidence. For example, at the beginning of a change process, people often commit to too ambitious goals (common for New Year's resolutions), setting them up for failure. Thus it is important to negotiate more realistic goals at the outset and reserve the ambition for a motivational vision statement that has an indefinite end point. There is great power in succeeding at small goals because it builds self-efficacy and keeps motivation high.

Rating confidence on a scale of 1–10 (10 is the maximum score) and defining how to increase confidence can also improve results. Designing one's environment to be supportive (e.g., removing processed foods from kitchen shelves or keeping running shoes under an office desk) and soliciting social support from family, friends, and colleagues (requesting encouragement, reminders, or help) are strategies to improve confidence.

Coaching competency: Help clients select goals and develop strategies, including environmental and social support, which enhance confidence.

Process of Changing Mind-Set and Behavior

Now that we have cultivated mindfulness, self-acceptance, and developed autonomous motivation and self-efficacy, we have the foundation needed for a successful change process. Lasting change depends upon both a lasting change of mind-set (I love being fit and don't want to go back to my old sedentary ways) as well as lasting behavior change (I consistently do four 30 min workouts weekly).[25]

While we do not have brain images of developing neuronal networks that support sustainable habits, one can imagine an extensive network supporting new habits which emerges when a mind-set of greater mindfulness, self-awareness, heartfelt motivation, positivity, confidence, and resilience develops over a period of weeks and months. Following are the important features, identified by psychologists, of a successful change process.

Develop and Implement Plan for Change—Vision and Goals

We addressed in the section on autonomous motivation the use of a vision statement as a means to summarize the basis for a client's internal motivation (I want to be fit and healthy in order to have the vitality I need to be my best at home and work).

Setting goals and implementing action lists are a process by which clients can move toward their motivational visions. If lifestyle change is the desired outcome, it is wise to help clients set specific behavioral goals—such as "I will be consistently walking for 30 min four times per week by 3 months from now" rather than vague goals of outcomes "I will improve fitness by walking regularly."

Confirmation of small details (what, when, where, how) and backup plans leads to more success. Creating SMART goals is one of the keys to success with behavior change. SMART goals are specific, measurable, action oriented, realistic, and time sensitive.[26]

Coaching competency: Help clients define motivational vision statements and specific behavioral goals to provide structure for pursuing lifestyle change.

Coaching Conversations That Elicit New Perspectives and Insights Lead to New Actions

Coaching sessions or brief discussions at their best generate or catalyze small shifts in mind-set as clients adopt new perspectives, question their assumptions, and find new meanings for their experiences. A surprise question or observation can open a client's mind and lead to a new insight that likely initiates new neuronal connections, the beginnings of the neuroplasticity needed to support lasting change. Nonjudgmental harvests of lessons from recent goal performance, particularly setbacks and challenges, are rich ground for new insights. There are no "failures" in this process, only opportunities to grow and learn.

Coaching competency: Alternate open questions and reflections to generate new insights and perspectives that support new behaviors. Acknowledge and unpack new insights and perspectives to help them stick.

Accountability

New habits are formed by much practice and repetition until they are well supported by new neuronal pathways and networks and become more automatic. It takes weeks and months of experimenting, practicing, developing skills, gaining knowledge and insights, bouncing back from setbacks, and recharging motivation as well as confidence, for lasting change. The limiting factor may be the pace at which the brain can lay down a robust, lasting network.

In the early stages of change, accountability between a client and physician and/or coach, as well as with other social supporters, is a key success factor. Goal-setting theorists, Latham and Locke, note that people perform better when they commit to others that they will succeed.[25] A commitment to a coach or physician provides valuable accountability in the early stages of change.[27]

We see examples of people seeking "extreme" accountability when they choose to go on reality TV shows and share their journeys with a large audience. There are many methods of scheduling and follow-up to choose from—reminders, written progress reports, coaching sessions, phone/e-mail check-ins, and behavioral "apps."

Coaching competency: Help clients select and build in methods for commitment and accountability, decide on level of goal ambition (bold or baby steps) and behavioral goal time frames which will work best (3 months, 1 year, beyond).

Referrals

During the change process, clients will need to learn, acquiring both knowledge and skills, to become confident and competent. A physician and coach can facilitate referrals "just-in-time," just at the moment needed to avoid distraction or overwhelm, to sound informational sources (e.g., Mayo Clinic website) and other professionals for particular skills, including how to exercise, how to cook and shop for food, how to develop mindfulness and positivity, and how to manage sleep, stress, and weight. If clients have mental health conditions such as depression or anxiety, referrals to therapists may be critical before or alongside a change process.[26]

Coaching competency: Help clients find resources to support gaining of knowledge and learning of skills just-in-time to enhance motivation, confidence, self-awareness, and new insights, and support their goal attainment.

PREVENTION AND TREATMENT—COACHING INTERVENTIONS

Physician Using Coaching Skills

Gap in Medical Education and Training

Our current medical education system falls short—counseling on healthful lifestyle behaviors such as physical activity, nutrition, and weight management is not routinely taught in medical school core curricula and clinical training, which focuses on the knowledge and tools for diagnosing and treating disease. In fact, the literature reveals that since 1975 physicians have been wondering, "Will physicians of the future be able to prescribe exercise?."[28] Thirty years later, medical school deans where polled about exercise prescription competence of medical students. The Deans reported that only 10% or their graduates were able to prescribe exercise.[29] Internal Medicine residents reported a lack of confidence in exercise prescription counseling, and only one-third of the residents were able to list three ways to integrate physical activity into the patient's daily life, to identify the personal exercise stages of change, and to calculate their own target heart rate.[30]

Helping patients uncover their motivation to change behavior is a key part of counseling patients and there is little time spent on this topic in medical schools. It has also been noted that personal trainers and group exercise instructors rely on motivation, but they receive little specific education in this area.[31]

Training medical students and health care professionals how to effectively counsel patients on lifestyle issues such as exercise and diet has never been more critical. In 2011, the U.S. Preventive Services Task Force (USPSTF) reviewed the medical literature in this area and reported:

> Thus, the current literature, while much improved over the past, may still be insufficient to unequivocally define for the clinician what does and does not work across all primary care behavioral counseling interventions. However, given the prevalence and health impact of unhealthy behaviors, clinicians may still use the time and resources readily available to them to reinforce the importance of healthy behaviors with their patients.

Walk the Walk

The first thing that physicians can do to help themselves and their patients is to "walk the walk." In a study by Abramson et al., it was demonstrated that physicians who perform aerobic exercise counsel patients on aerobic exercise and physicians who perform strength training counsel patients on strength training.[32] If providers are comfortable with the activity and familiar with it on a personal level, then they are more likely to discuss it with their patients. Physician Erika Frank and colleagues looked specifically at women physicians and their counseling and personal exercise habits. Her study demonstrated that 96% of women physicians reported engaging in exercise but that only 49% of them reached the levels of activity recommended by the American College of Sports Medicine (ACSM). In addition, this study showed that women physicians who met the ACSM guidelines were more likely to counsel on exercise, to counsel with confidence, and to be trained in counseling.[33] Given the obesity epidemic in our country, it is time for all health care providers to take the lead and model healthy lifestyles.

By "walking the walk," health care providers can then do something that takes minimal time (30 s) in the office with the patient, and the effects are motivating and inspiring. That something is called self-disclosure. Frank et al. conducted a study at Emory University and discovered that physicians who spent an additional half a minute disclosing information

about their own personal dietary and exercise practices during an office visit and also had an apple and a bike helmet on their desks were more motivating and more believable regarding exercise and diet than physicians who did not disclose their personal practices or have an apple and helmet on their desks.[34] To be motivating and believable, the health care provider does not have to be in "perfect shape." They just need to be working on sustaining a healthy lifestyle with regular exercise and a balanced diet. Striving for health is not something a physician does for his patients only but he must do it for himself also.

Evidence for Use of Coaching Skills by Physicians

There is encouraging evidence in the current literature that counseling on lifestyle behaviors works. Grandes et al. demonstrated that when family physicians provide advice and an exercise prescription to patients, those patients increased their minutes of moderate and vigorous activity per week at a 6-month follow-up significantly more than those patients in a control group who received standard care.[35]

Teasing out what approach works well in counseling was the subject of another study by Hillsdon et al.[36] In this study, two approaches of counseling patients on physical activity were compared to a control. Each approach took 30 min. One approach involved negotiating and collaborating with the patient on the subject of exercise and the other approach involved advising, warning, and educating the patient on exercise benefits, dangers of sedentary behavior, and physical activity guidelines. When comparing the results of their efforts by examining the minutes of walking accumulated per week, the patients who received the negotiation and collaboration counseling walked significantly more minutes than a no-intervention control at follow-up. Patients who received the advising and warning counseling had no significant difference in minutes accumulated walking per week at follow-up when compared to patients in the control.

Thus, if a physician is going to spend time counseling a patient on physical activity, the best use of this time would be to put on a collaborative hat, ask patients questions about their physical activity habits, likes, and desires, engage them in a brief discussion, and then cocreate a plan for increasing physical activity.

Motivational interviewing has been demonstrated to have beneficial effects on patient health. For example, in a randomized controlled study by Watkins et al., stroke patients were placed in two groups; one that received usual care in a stroke unit and the other group received usual care plus four individual, weekly sessions of motivational interviewing. Twelve months after the intervention, the stroke patients in the intervention group had improved mood and reduced mortality.[37]

Additional support for the use of motivational interviewing by primary care physicians comes from an observational study published in the *American Journal of Preventive Medicine*. In this study by Pollak et al., 41 primary care physicians and 461 of their overweight or obese patients were the subjects. Physicians were observed during their office visits with these patients. Physicians were rated on their use of motivational interviewing techniques and specifically reflective statements. The results showed that patients who saw physicians who had the highest scores on the global Motivational Interviewing-Spirit score had greater weight loss (1.6 kg greater) than those patients who were seen by physicians with lower scores on this motivational interviewing assessment.[38]

A study by Hojat et al. demonstrated that physicians' empathy is also associated with positive clinical outcomes for diabetic patients.[16] In the study, 891 diabetic patients and 29 family physicians were studied. The hemoglobin A1C and LDL-C were obtained for each patient, and a Jefferson Scale of Empathy score was calculated for each physician. Patients of physicians with high empathy scores were significantly more likely to have good control of hemoglobin A1C and LDL-C than patients of physicians with low empathy scores. This study serves to underline the importance of empathy in the physician–patient relationship.

Expert and Coach Approaches

Most health professionals are trained in what is known as the "expert approach," which works well with acute situations, medical emergencies, and sick visits. However, when dealing with "chronic" behavior change, the "coach approach," using collaboration and negotiation, can yield better results as various studies have reported. There are several key differences in the two approaches. In the expert approach, the health care provider shares his or her knowledge and gives "mini lectures" to educate patients. In the coach approach, the provider checks in with the patient to discover what the patient knows and understands and then asks permission to share information that is directly pertinent to the patient's problem. In the expert approach, the provider listens, but is often doing more than one thing, such as writing down the history while continuing to ask closed ended questions provided by checklists in medical care systems.

In the coach approach, the provider listens and concentrates solely on what the patient is saying and the emotions he or she is conveying at that moment, not thinking about the next sentence he is going to say or the next question he is going to ask. More often than not, in the expert approach, a problem requires quick response and an immediate solution from the provider. In contrast, in the coach approach, a problem is an opportunity to learn more about a patient, his desires, needs, and barriers. A roadblock on a behavior change journey requires creative brainstorming and collaboration in order to cocreate a viable approach for getting around the roadblock.

When providers are in the expert mode, they shoulder responsibility for the patient, the diagnosis, the treatment, and the cure. When providers are in the coach mode, they realize that the patient is ultimately responsible for their daily actions, steps, and strategies. It is up to the patient to change. The provider cannot "make" a patient abandon one behavior and adopt another, but he can help and guide a patient by collaborating, negotiating, motivating, brainstorming, and

empowering. This takes time. The expert is often looking to solve a problem in a 15 min visit whereas the coach realizes that behavior change takes time—weeks to months, and a year or two to demonstrate sustainability. The coach prepares for the marathon, not the sprint.

Moving from the expert approach to the coach approach can be a challenge, especially in the area of sharing our knowledge and asking permission. Sometimes it seems as if it is more time efficient simply to blurt out our recommendations and insist on compliance after warning patients of the dangers of their current behaviors. However, this approach often elicits resistance because it steps on a patient's autonomy and does not help the patient to move forward. Spending time, 5 or 10 min, asking open-ended questions, and cocreating the next steps forward to optimal health is a more efficient use of time.

Coaching skills for physicians: Utilizing a five-step cycle will help the expert transition into the coach approach. Be empathetic—Align motivation—Build confidence—Set SMART goals—Set Accountability plan—Be empathetic.

This is a simple cycle to focus on when you are dealing with behavior change.[39]

Step 1: Empathy involves truly connecting with and understanding a patient's emotions and calls for a mindful approach to patient care. In the medical literature, there are several studies that demonstrate the positive effects of empathy on the patient encounter from increased patient satisfaction, better adherence to recommendations, improved collection of clinical data, and a more therapeutic physician–patient relationship (Coulehan et al.). In order to feel and express empathy, a physician needs to listen attentively and patiently. Thinking about the review of systems or the pertinent lab value is not part of listening mindfully or being fully present for the patient. Mindfully listening means sitting and looking into the patient's eyes, face to face, not working at the computer, not taking notes, not examining the patient as he or she tells her or his story. Reflecting back what was said and restating it is a powerful way of letting the patient know that you were paying careful attention and you understood the situation. These reflections are ways to express empathy.

Step 2: Motivation plays a crucial role in behavior change. Motivators are similar to the corner pieces of a puzzle; they hold everything else together. Tapping into a patient's internal motivating forces is the only way to make these motivators work. Telling a patient that they have diabetes and they have to lose weight, in essence making their diagnosis of diabetes his or her motivator might not work because the patient might not understand the disease process or the sequelae. People are more motivated by ideas that they themselves think of rather than ideas given to them. It is hard to know what motivates people without asking. Thus, asking patients questions about what they value most in life can help patients put things in perspective and align their motivation for behavior change.

Step 3: Building confidence is key. This is one of the most important pieces of the behavior change puzzle. In order to help patients gain confidence, you need to focus on what is working well right now and what has worked well in the past. Inquiring about previous successes with behavior change will help the patient identify strengths that might be utilized with this current effort to adopt healthy lifestyles. Also, drawing on character strengths, celebrating them, and figuring out how they will help the patient achieve their goals will serve to increase confidence.

Step 4: Setting SMART goals that are specific, measurable, action oriented, realistic, and time sensitive is another critical part of the behavior change plan. Stating I will exercise more this week is good goal, but a SMART goal involves stating more details such as next week, I will walk for 30 min on Monday, Wednesday, and Friday at 7 a.m., before work. On Saturday and Sunday, I will take an hour walk mid morning with my husband. If it rains on any of those days, I will go to the local mall to walk. Working with patients to cocreate SMART goals is important and success with these goals will help empower patients. Success breeds success.

Step 5: Holding patients accountable for their goals is the only way to ensure that the goals are prioritized and that they get done or that they are at least attempted or experimented with. If a patient creates goals but no one ever checks up on them, then the patient might be more likely to avoid them or even forget about them as time goes by. A physician can have an office assistant to call the patient in a week to check-in. Check-ins can be e-mail check-ins as well. In fact, sending a postcard reminding them about their goals and asking them to contact the office is another way to keep accountability high. This is another area where physician and patient need to collaborate and find the system that works best for both of them.

Health and Wellness Coaches

Since 2000, a handful of commercial and academic coach training organizations for health professionals have trained more than 5000 health and wellness coaches who work in diverse settings—corporate wellness, health club, medical fitness facility, hospital, clinic, health plan, spa, and private practice in the United States and other countries. Health and wellness coaches typically become coaches as a second career, coming from diverse health backgrounds including medicine, nursing, exercise, nutrition, mental health, and complementary medicine.

In 2009, an Institute of Coaching was launched at McLean Hospital, an affiliate of Harvard Medical School, to fund and support coaching research and the translate and bridge the most robust theories and research into best coaching practices. Teams of health and wellness coaches are piloting coaching interventions for a variety of patient populations at several academic medical centers, including Duke, Vanderbilt, and University of Minnesota. Clinical applications include diabetes, cancer survivors, heart disease and cardiac rehabilitation, cardiovascular risk reduction, obesity, smoking cessation, chronic pain, and comorbid mental and physical conditions.

The groundwork for the professional health and wellness coach was developed and cultivated through the efforts of many leaders focused on changing the direction of patient care from disease-focused to one of patient empowerment, disease prevention, and wellness. The 2005 guidelines for the practice of health care in all settings, as mandated by both the Joint Commission on Accreditation of Health Care Organizations (JCAHO) and the Institute of Medicine (IOM) include[40]:

- Placing patients at the center of their health care
- Treating the patient as a whole person
- Shared decision making

In November 2011, Centers for Medicare and Medicaid announced that

> The evidence is adequate to conclude that intensive behavioral therapy for obesity, defined as a body mass index (BMI) ≥30 kg/m^2, is reasonable and necessary for the prevention or early detection of illness or disability and is appropriate for individuals entitled to benefits under Part A or enrolled under Part B and is recommended with a grade of A or B by the U.S. Preventive Services Task Force (USPSTF).[41]

Intensive behavioral therapy for obesity consists of the following:

1. Screening for obesity in adults using measurement of BMI calculated by dividing weight in kilograms by the square of height in meters (expressed in kg/m^2)
2. Dietary (nutritional) assessment
3. Intensive behavioral counseling and behavioral therapy to promote sustained weight loss through high-intensity interventions on diet and exercise

Government reimbursement of personal counseling sessions for obesity is a promising step forward and paves the way for coaching interventions based upon science-based coaching competencies.

While the research literature on coaching interventions in health care is limited, several randomized controlled studies support the use of coaching interventions to help treat and prevent disease. Clinical outcomes examining lab values as well as well-being and activity levels have demonstrated that coaching interventions can improve health and reduce depression scores.

Johns Hopkins University[42] investigated the effectiveness of two weight loss coaching interventions, one delivered remotely through telephone sessions, a study-specific website, and e-mails and another delivered through in-person coaching sessions, in 415 obese patients with at least one cardiovascular risk factor. Weight loss at 2 years was significantly greater in both intervention groups compared with the control group (self-directed weight loss). Weight loss of 5% or more occurred in 18.8%, 38.2%, and 41.4% of controls and those receiving remote and in-person support, respectively.

Lowering hemoglobin A1C levels among diabetics,[43] increasing diabetic patients' satisfaction with care,[44] reducing diabetes-related distress,[44] lowering cholesterol in cardiac patients,[45] increasing number of days per week or exercise,[46] increasing weight loss,[46] increasing consumption of fruits and vegetables in teenage girls,[47] lowering rehospitalization rates in pediatric asthmatic patients,[48] decreasing pain severity in cancer patients,[49] and increasing activity levels in the elderly[50] are among the outcomes demonstrated in these randomized controlled clinical trials (Table 27.1).

While coach training, coach backgrounds, and coaching protocols vary widely in these studies, shared features include multiple coaching sessions over 3 months or longer, in-person or by phone, collaborative goal setting and problem solving, and ongoing accountability. The alliance of the coach and patient shows potential in supporting sustainable lifestyle change, which needs to be confirmed in additional randomized studies.

To expand coaching research, it is critical to define standards for coaching competency, training, and education. To meet this need, a National Consortium for Credentialing of Health & Wellness Coaches[51] formed in 2010 and has grown to 75 organizations. The Consortium is committed to developing coaching competency and training and education standards for health and wellness coaches to support a collaborative coaching research endeavor. A further mission is to support the integration of coaching competencies into health professions, including the work of physicians as discussed earlier. The consortium's work is focused on job definition and tasks, scope of practice (including appropriate recommendations of other health professionals), and prior degrees, credentials, and coach training and education necessary to deliver a minimal standard level of competency demonstrated through a national certification process.

At a 2 day Summit of the National Consortium held in September 2010, a collective vision of the role of health and wellness coaches emerged:

1. Being a vehicle to create a paradigm shift to the "whole person"
2. Being a catalyst for change of the delivery of health care from dependency to empowerment
3. Empowering, inspiring, and transforming both clients and providers
4. Spanning the continuum of health: from the very sick to those pursuing increased health (primary prevention)
5. Becoming a routine and integrated part of the health care system and consumer wellness

While it will take many years for health and wellness coaches to be well established in health care and consumer wellness, good foundation blocks are in place and there is no reason to delay the dissemination of coaching skills wide and far.

Now let's explore coaching in action.

TABLE 27.1
Randomized Controlled Trials of Health and Wellness Coaching

Authors	Design	Subjects	Intervention	Results
Wolever et al.[43]	RCT comparing integrative health coaching with usual care (control)	56 patients with type 2 diabetes	Fourteen 30 min coaching sessions by telephone over 4 months	Significant reduction A1c levels among participants with to baseline values > or equal to 7% ($p = 0.03$)
Whittemore et al.[44]	Pilot RCT; nurse coach as usual care intervention group received a nurse coach intervention	53 women with type 2 diabetes	Six coaching sessions were delivered over 6 months	Intervention subjects had better diet self-management ($p = 0.002$), less diabetes-related distress ($p < 0.01$), better integration ($p < 0.031$), greater satisfaction with care ($p = 0.01$), and trends toward better exercise self-management ($p = 0.13$) and lower BMI ($p = 0.15$)
Vale et al.[45]	RCT; coach as usual care	792 patients with CVD	Five telephone coaching sessions were delivered for 6 months	Intervention subjects demonstrated greater decrease in total cholesterol ($p < 0.0001$), more weight loss ($p < 0.0001$), greater reduction in the intake ($p = 0.041$), and more walking activity ($p < 0.0001$)
Vale et al.[46]	RCT; COACH model as usual care	245 CHD patients	Six telephone coaching sessions were delivered for 6 months	Intervention subjects had significantly lower fasting total cholesterol ($p < 0.0001$) and LDL-C levels ($p < 0.0004$)
Edelman et al.[47]	RCT; personalized health plan and a health coach with a medical provider as usual care plus health report	154 patients with one or more CV risk factor	28 two-hour in-person group training sessions with biweekly 20–30 min individual telephone sessions for 10 months	Intervention subjects had significantly greater decrease in CHD risk ($p = 0.05$), greater increase in number of days of exercise per week ($p = 0.002$) and greater weight loss ($p = 0.54$)
Debar et al.[48]	RCT; group meetings and coaching as usual care	228 teenage girls	Annual visits, fitness center membership, biweekly team meetings, quarterly telephone sessions, and team meetings with parents, all of which are supported by a study website	Intervention on subjects had higher BMD in the spine ($p = 0.007$) and trochanter ($p = 0.03$) regions and greater consumption on of calcium ($p < 0.001$ and fruits and vegetables) ($p = 0.01$) for 2 years
Fisher et al.[49]	RCT; child and parent received coaching as usual care	191 children ages 2–8 years with diagnosis of asthma	Telephone and in-person visit with parent then biweekly telephone calls for 3 months, after which calls were monthly for the duration of the 2 year intervention	Intervention subjects had significantly lower rehospitalization rates ($p = 0.002$)
Oliver et al.[50]	RCT; individualized education and coaching as usual care group with additional education	87 cancer patients with moderate pain	20 min visit before visit with doctor	Intervention group experienced lower pain severity ($p = 0.014$)
Holland et al.[51]	RCT; nurse coaching as usual care	51 subjects with chronic health condition	Group classes on health topics and three 1 h exercise training sessions with 11 contact hours with the nurse health coach by telephone and e-mail for 12 months	Intervention subjects demonstrated increased minutes of weekly aerobic activity ($p = 0.001$) and increased minutes of weekly stretching ($p = 0.0008$)

Source: From Pegg FE, et al., *American Journal of Physical Medicine & Rehabilitation*, Lippincott Williams & Wilkins, New York, 90(12), 1074, Copyright 2011.
COACH, Coaching Patients on Achieving Cardiovascular Health; RCT, randomized controlled trials; BMI, body moss index; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; CV, cardiovascular; BMD, bone mineral density.

COACHING SCENARIOS

To bring to life the work of health and wellness coaches, and the use of coaching competencies by physicians, we present four coaching scenarios, and explore how the principles of coaching change can be applied.

Diane, a 30 Year Old Woman Who Is Overweight, Prepregnancy

Diane is a 30-year-old woman who has a busy law practice and is eagerly working to become a partner. She has never been a big exerciser and did not participate in team sports growing up. Diane has had a serious "sweet tooth" her whole life, especially for chocolate cake and cookies. Although she was never excessively heavy growing up, she always considered herself a large framed girl. Since her mother's fight with cancer that ended in a long drawn-out death, Diane has been noticing her pants getting tighter and has had to buy new suits for work. Disgusted with herself, she has tried several different diet plans without success.

Coaching Tips for Physicians: Applying the Five-Step Cycle

Empathy: When Diane is talking about her problems, listen intently and don't think about what you are going to say next. Show empathy with Diane's lack of exercise experience growing up and with her difficult time during her mother's battle with cancer. At this point, you could use self-disclosure and share with the patient that you, too, have a sweet tooth so you are familiar with the challenges or that you were not an avid exercisers growing up but now you take walks in the evening or whatever is true for you.

Motivation: Explore and validate Diane's heartfelt reasons to embark on changing her lifestyle. Ask her what has been motivating her to try different diets.

Confidence: Ask her about her confidence level for embarking on lifestyle change and brainstorm possible supports to improve her likelihood of success. Discuss her strengths noting that as a lawyer, she must be dedicated, clever, and good at handling detail. You can mention that she must have perseverance as she made it through law school, and creativity in order to build strong legal cases, and both of those traits will be useful when adopting healthy lifestyle changes.

SMART goals: Given that Diane reports feeling, "disgusted with herself" she might be ready to set a goal for herself. In fact, she might have been thinking about possible steps forward, toward adopting a healthy lifestyle. Ask if she is ready to set a goal and what she would want to tackle first. Don't assume that she wants to cut out sweets even though she mentioned that. Make sure that Diane sets a specific, measurable, action-oriented, and time-sensitive goal. If she is not ready to set a goal, then ask her to think about this and contact the office when she settles on one.

Accountability: Negotiate and cocreate a system of accountability that works for both of you. If Diane is having a follow-up visit soon, then you can use this time to check in on the goals. Depending on your office setup, you could have an assistant call the patient or e-mail the patient to check in after a week. It is important to set up the plan with the patient at the visit and document it. If you have pen and paper in your office, the patient can write down the plan and you can document it in the chart.

Coach's Process—Deploying the Five Forces of Sustainable Change

Mindful attention—Diane begins to appreciate how she puts the needs of her work and family ahead of her own and that it is worth exploring whether investing more in self-care would payoff with more energy and zest at work and in close relationships.

Self-acceptance—Diane starts to notice how her inner critic eats away at her confidence and energy and learns that she is far more focused on her deficiencies than her strengths. She experiments with "changing the channel" from beating herself up about her weight loss failures to savoring and harvesting her successes and accomplishments and enjoying her strengths in action.

Autonomous motivation—Diane discovers that vanity about her appearance isn't the motivator that she thought it would be. Instead she wants her clients and loved ones to see her "sparkling" eyes, warm smile, and confidence that shine through when she is good to herself.

Self-efficacy—Diane has noticed how organized and persistent she is in getting things done at work and starts to intentionally bring those talents to her exercise and meal planning. She finds two friends to provide mutual accountability and support and they swap stories on how they use their strengths in their self-care weekly.

Process of change of mind-set and behavior—Diane has posted her vision for herself, with bright eyes and smile, on her fridge and smartphone, and her coach has set up a text reminder of her vision statement to arrive Sunday evening when she wants a boost to start the next week. She starts to imagine herself as energetic and full of life, instead of letting herself get down about her weight. Funny, her cravings for sweets have dropped enormously and sticking to "no carbs after 5 p.m." has been a simple change which has allowed her to lose 2 lb/month without feeling deprived. This Diane can sustain!

Shirley, a 40-Year-Old with Type 2 Diabetes

Shirley is a 40-year-old woman with type 2 diabetes who is the mother of three children. With her busy schedule at home, she finds it hard to fit in any regular exercise, despite the fact that she was a college volleyball player and enjoys sports. Her children are 10, 8, and 6 years and are picky eaters, refusing to eat anything except pizza and mac and cheese. Eating their leftovers has become habit now. Shirley is trying to eat less but finds it difficult. Having type 2 diabetes is something that scares Shirley and she wants to lose weight but can't find the time to commit to healthy eating habits or regular exercise.

Coaching Tips for Physicians: Applying the Five-Step Cycle

Empathy: After listening intently to Shirley, you could nod and use a reflection such as, "It sounds like you are really busy with your three children and finding time to exercise is a real challenge right now."

Motivation: It appears that Shirley is scared about her diagnosis of diabetes. You could check in with her about this and find out if it is a motivator for her interest in exercise by saying, "I heard you say that your diagnosis of type 2 diabetes worries you. What would it take to help mitigate that fear?" Or, "I heard you say that you are trying to fit exercise into your life right now and you are trying to eat less. How would your life be different if you were able to accomplish both of these goals?"

Confidence: You can help build up Shirley's confidence by pointing out some strengths that you identified while she was telling you her history. For example, you might say,

> From what I heard today, you sound like a dedicated mother who is prioritizing her children. Being a dedicated mother takes great patience. I also learned that you were a competitive volleyball player, which takes long hours of practice as well as skill. These combined strengths of dedication, perseverance, and the ability to train for a competitive sport will all come in handy to help you achieve success in adopting healthy lifestyles.

SMART goals: Ask Shirley if she is currently working toward a specific goal in terms of eating less, which she mentioned was an overall goal. Depending on her answer, you can work to help her create a specific, measurable, action-oriented, realistic, and time-sensitive goal. If Shirley is not interested in creating a SMART goal around eating less, then check in with Shirley and see what is most important to her right now. Let her tell you what she would like to tackle first. Then, help her create a SMART goal for that.

Accountability: Negotiate and cocreate an accountability plan as with the first case.

Coach's Process—Deploying the Five Forces of Sustainable Change

Mindful attention—Shirley has learned how mindless, "asleep at the switch," she is around food and exercise, on automatic pilot, and not intentional or thoughtful about her decisions and choices. She has swallowed her kid's leftovers without a moment to stop and reconsider what would be best for her, and her days fly by without a thought of scheduling exercise and resetting her priorities.

Self-acceptance—Shirley awakens to notice how bothered she is that she doesn't have the athletic body and fitness she once had. Exercising makes her feel bad about what she has lost and so she dreads it. She begins to think about how her body has borne three healthy children and what a great accomplishment that is. She begins to be more at peace with herself. She notices how her frenzy spills over to her children and when she is more relaxed and less controlling her kids are less picky about what they eat.

Autonomous motivation—Shirley is concerned that her kids will develop a lifetime of bad eating habits and get diabetes like she does. She really wants to be a role model of great health and physical fitness and decides that setting an example is a better strategy then nagging.

Self-efficacy—To handle her constant state of frenzy, she begins to make a schedule for the next day before she goes to bed, and then she does 10 min of deep breathing meditation before breakfast and her kids get up to clear her mind of static. She also completes a character strength assessment (www.viacharacter.org) to find that love of learning and curiosity are strengths. She finds new DVD exercise programs to experiment with.

Process of change of mind-set and behavior—Shirley has set a goal to do four 30 min workouts/week and she tells her kids when and what and asks them at bedtime to remind her before they go to school, which they love to do. They remember on their own to ask her when they get home whether she did her workout. She also set a goal to eat two veggies and one fruit at dinner and finds new recipes to prepare them in interesting ways. Her kids are starting to ask about the veggies and fruit and even ask for some to try. Shirley is now starting to see herself and her kids as a family team and is starting to ask them to share what family wellness means to them, which has led to some cool new ideas for weekend outings.

Audrey, a 55-Year-Old with Breast Cancer

Audrey is a 55-year-old breast cancer survivor who is anxious to do everything in her power to remain healthy. She is currently overweight but is trying to change that by exercising 3–5 days a week. Since her diagnosis of breast cancer, she has tried to be careful with her diet, avoiding processed red meat and eating more fruits and vegetables. However, she loves ice cream and finds herself indulging in this guilty pleasure late at night.

Coaching Tips for Physicians: Applying the Five-Step Cycle

Empathy: Start by acknowledging how hard it is to lose weight. Then, you can reflect back that you heard Audrey say she is exercising 3–5 days a week and that she is adding more fruits and vegetables into her diet. After that, you can say that you sensed some disappointment and guilt when Audrey spoke about eating ice cream late at night. At that point, you can say something like it is sometimes hard to quit a habit, especially if it gives you pleasure.

Motivation: Tapping into Audrey's motivation to "do everything in her power to remain healthy" after her breast cancer treatment is a good place to start. By saying, "It sounds like you are already moving in a positive direction with your desire to remain healthy after your battle with breast cancer." What do you think will keep you focused and on track with this desire in the long run?

Confidence: By spending a moment congratulating Audrey on her exercise routine that she started, you can help empower Audrey to continue to tackle lifestyle behavior challenges in the future. You can ask her how she mustered up the energy and commitment to get that done. Then, you can move to her diet and congratulate her on the changes that she already made and ask her a similar question. How did she make that change happen? By having Audrey relay her successes in the area of exercise and diet, you can set her up for feeling confident to tackle more obstacles, like the ice cream that she mentioned.

SMART goals: Ask Audrey what goals she would like to commit to for the upcoming weeks. Again, do not assume or even suggest that she simply "stop eating the ice cream." See what she comes up with. Audrey brought up the ice cream and she knows it is a problem. If she wants to tackle this as her first goal, that is fine. If she chooses something else, follow her lead, as she may need another week or two before she tackles this "guilty pleasure." Make sure to help Audrey create specific, measurable, action-oriented, realistic, time-sensitive goals.

Accountability: Negotiate and cocreate an accountability plan as with previous cases.

Coach's Process—Deploying the Five Forces of Sustainable Change

Mindful attention—Audrey has started to notice how sad and low she feels at the end of the day and how she uses ice cream as medicine to make her feel better. She decides to save ice cream for celebrations and special occasions and enjoy it as a fun treat, not to anesthetize her sadness.

Self-acceptance—Audrey is starting to cultivate pride in how she handled her cancer treatment and healing process, keeping herself active in her relationships and volunteer work, instead of focusing on her extra weight, which is a common side effect of cancer treatment. She starts to see her extra weight as an opportunity to get healthier, rather than a burden.

Autonomous motivation—Audrey has learned how precious her life is, and how her days are not limitless, and she wants to live every day to its fullest, enjoying small pleasures and helping others in small and large ways. Even if being in good health does not extend her life, she wants to look back and say "I lived many of my best days after cancer."

Self-efficacy—Audrey comes up with three strategies to get her through the evenings when she finds her mood sliding downward and her motivation slipping—to relive past memories by talking to old friends, or pulling out old photo albums and reminiscing, to plan a fun outing or adventure, or going for a walk with a friend to get some fresh air. She taps into her character strength of kindness by making sure she does something nice for someone everyday and then reflects on the pleasure that gave before going to bed.

Process of change of mind-set and behavior—Audrey has begun to notice that she has some control over her mood, that if she acknowledges that she feels sad, and then shifts from sad thoughts to good ones about helping others, doing something fun in the future, or appreciating her past rich life, she notices her energy lift and her desire for ice cream to fade—much faster than she thought possible. She wakes up more energized and now briskly walks for 30 min when it's not raining hard immediately after breakfast. She is thinking that it might be a good idea to get a used treadmill for rainy days because the walks make the rest of her day go so much better and why miss out on rainy days.

Rachel, a 65-Year-Old with Heart Disease

Rachel is a 65-year-old woman with heart disease. She recently suffered a heart attack. Currently, she is in the obese category by BMI. Although her cardiologist insists that she stop eating red meat, ice cream, and butter, Rachel is not convinced that she wants to give up the foods that she loves and relies upon for sustenance and comfort. Since Rachel has been sedentary for over 30 years, she is not only hesitant to start an exercise program now but also scared that her physical activity will bring on another heart attack. Rachel feels that it is too late to change and does not think that losing a little weight will do much for her anyway.

Coaching Tips for Physicians: Applying the Five-Step Cycle

Empathy: First reflect what you heard, "It sounds like you have been through a lot with your recent heart attack, your cardiologist insisting that you stop eating some of the foods that you most enjoy, and your fear that exercising will bring on another heart attack." You can also reflect back her powerful statement, "I heard you say that you feel it is too late to change and you feel that losing a little weight will not do much anyway." By repeating Rachel's words, you are letting her know you were listening and that you care. She is more than likely expecting you to side with her cardiologist and give her another lecture on diet and exercise, and your response will surprise her.

Motivation: Rachel did talk about being afraid of another heart attack, and you can use this as a starting point. "You mentioned that you are afraid of another heart attack. What do you want to do to help reduce your risk of another heart attack?" Another tactic would be to ask, "How would your life be different if you felt confident and comfortable exercising, instead of fearful?"

Confidence: It sounds like Audrey has been beaten down. You can ask her, "What would it take for you to feel confident about your future health?" By emphasizing that Rachel is a survivor, you can help increase her confidence. "Rachel you are a survivor. You survived a heart attack. I bet you have been successful at many things in your life. Tell me about one of them."

SMART goals: See if Rachel is ready to set any goals during this visit. If she is not, you can ask her to think about a goal she would love to achieve by 3 months. Do not jump in and start setting weight loss goals, exercise goals, and diet goals, even if that is what you are first compelled to do. In Rachel's

case, a goal might be to investigate how to avoid another heart attack or research exercise and heart attacks. You could not set these goals for her, but if she says she has no idea what goals to strive for, you could ask permission to brainstorm together. These might be some ideas that you toss out to her and see if any of them catch her interest. Remember it is her agenda. You must honor her autonomy.

Accountability: Negotiate and cocreate an accountability plan as with previous cases.

Coach's Process—Deploying the Five Forces of Sustainable Change

Mindful attention—Rachel begins to notice how angry she is about having a heart attack and that the anger clouds her thinking and takes over her brain leading her to conclude that she can't possibly summon the resources to do healthy things. She's also angry at doctors who don't understand how hard it is for her to give up the things she loves. She decides that a few therapy sessions to explore, heal, and release her anger would be valuable.

Self-acceptance—Rachel begins to feel grateful that her heart attack has "cracked" open her shell and that she is more aware of how her emotions affect her physical stress and energy. She decides that she wants to transform the energy of her anger into something healthy and positive rather than keep it bottled up.

Autonomous motivation—Rachel decides that what she wants most is to feel calm and at peace and that will allow her to heal and create a new beginning.

Self-efficacy—Once Rachel sees how much power she has in her bottled up emotions, which she had turned inside, she decides to channel that energy outward into exercise. Amazingly not only is she making her heart stronger, but she is putting her emotions through a spin cycle and she feels calm at the end of her workout. Rachel prides herself on thinking out of the box and looks forward to the next challenge.

Process of change of mind-set and behavior—Rachel is setting small goals, 1 week at a time, and accomplishing more than she planned for—longer and more intense workouts than she committed to herself to do. She learns that if she focuses on a small goal each day and week, she is successful, feels proud of her success, and now is starting to reach out to others in her rehab class to see how she can help them learn what she has learned. She can't believe that she has become a devoted exerciser.

It is a privilege for physicians and coaches to be catalysts for people whose health is calling them to move toward a health-giving lifestyle. Each of them has their own story and journey; how satisfying it is to watch them outgrow their old selves and turn their health crises into an opportunity to learn, change, and thrive.

> Change is the handmaiden Nature requires to do her miracles with.
>
> **Mark Twain**

APPENDIX A: 12 COACHING COMPETENCIES

1. Facilitate a calm, mindful focus of attention on a patient's state of health and well-being which expands self-awareness of deficits and awakens the desire for possible benefits of positive change.
2. Empathize with a patient's circumstances, show acceptance, and foster a nonjudgmental and affirmative perspective ("let's appreciate and learn from the past and move forward to build a better future").
3. Encourage autonomy, put patients in the driver's seat and yourself in the passenger seat, by undistracted listening, open-minded inquiry, refraining from mindless advice giving, and helping patients to make choices by brainstorming a few options to select from.
4. Help patients find health behaviors that are intrinsically motivating (enjoyed for their own sake) and/or find internal motivation (articulating and valuing future personal benefit) for a health behavior, for example, it will allow them to make a difference in the world or do more of things they treasure most, now and in the future. Help patients select behaviors which have the potential to enhance autonomous motivation quickly.
5. Help clients identify personal strengths and talents, and brainstorm ways to deploy strengths in the pursuit of lifestyle change and better health.
6. Cultivate positive emotions by starting sessions with positive topics—experiences, lessons, successes, strengths, which improves brain function for more challenging topics. Unpack and harvest positive topics at the close of sessions.
7. Help clients brainstorm on various paths to reach goals so that they appreciate that if one path doesn't work, one or more other paths are possible, which increases hope and confidence.
8. Help clients select goals and develop strategies, including environmental and social support, which enhance confidence.
9. Help clients define motivational vision statements and specific behavioral goals to provide structure for pursuing lifestyle change.
10. Alternate open questions and reflections to generate new insights and perspectives that support new behaviors. Acknowledge and unpack new insights and perspectives to help them stick.
11. Help clients select and build in methods for commitment and accountability, decide on level of goal ambition (bold or baby steps) and behavioral goal time frames which will work best (3 months, 1 year, beyond).
12. Help clients find resources to support gaining of knowledge and learning of skills just-in-time to enhance motivation, confidence, self-awareness, and new insights, and support their goal attainment.

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Part VI

Men's Health

Craig Garfield, MD, MAPP

28 Perspectives on Men's Health

Craig Garfield, MD, MAPP

CONTENTS

Life Course Health Development and Men's Health 363
Preventive Health for Men across the Life Course 364
Adolescent Male Health 364
Fatherhood and Men's Health 364
Future Directions 366
References 367

The 2001 Institute of Medicine (IOM) report *Exploring the Biological Contributions to Human Health: Does Sex Matter?* notes that from the cellular to the societal level, gender matters in regards to health. According to the Centers for Disease Control and Prevention (CDC), men are at greater risk of death in every age group compared to women, with 1.6 times more mortality for all causes, 1.8 times for diseases of the heart, 1.4 times for cancers, and 2.4 times of for accidents.[1] While biological factors play a role in this gender gap, these are relatively small compared to the role of behavior.[2–4] Some of these behaviors—tobacco use, poor diet, physical inactivity, and alcohol consumption—represent the leading *actual* causes of death between 1990 and 2000 and are considered modifiable and preventable.[5] Yet men's participation in the health care system is noticeably lower than women's,[6] perhaps due to knowledge and help-seeking behaviors, gender beliefs, finances, or lack of unique health system attention.[2,7–16] Men from ages 18 to 44 years were 70% less likely to visit a physician in 2007 and 80% less likely to have a usual source of health care, as compared to women.[18] While the past decades have seen a necessary focus on understanding women's health and the creation of the Office of Women's Health (OWH) in the U.S. Department of Health and Human Services, no similar organization has been tasked with improving the health of men. Nevertheless, research on men's health has been increasing as the disparity in life expectancy has grown and as researchers, policy makers, and clinicians have realized the important contributions men make in the workplace, their families, and society.

Though male-specific cancers and sexual health receive much of the attention, conceptualization of men's health has expanded beyond this simple view. There has been increased attention to the reexamination of men's various roles throughout their life span and how this may affect opportunities to engage men with the health care system. Additionally, there has been a growing focus on the unique characteristics of men and their risk, protective, and help-seeking behaviors with attention paid to ways to engage men in maintaining their health and interacting with the health care system. In this chapter, we introduce a conceptualization of men's health that spans the life course and offers insights into when men's health interventions might prove most beneficial across the life span. Then we describe key preventive health steps for men to take along the life span in general and in adolescence in particular. Then we discuss a particular condition for men, namely fatherhood, and its impact on men's health and health behaviors. Finally, we provide suggested areas of future work that have the potential to fully optimize men's health.

LIFE COURSE HEALTH DEVELOPMENT AND MEN'S HEALTH

Research on health and behaviors over the life span has highlighted gateways and barriers to optimal health. The Life Course Health Development (LCHD) framework explains how health trajectories develop over a person's life, acknowledging the contributions of biopsychosocial and contextual determinants to health.[18] Halfon and Hochstein use this framework to suggest that a focus on early risk factors and protective factors leads to more effective preventive strategies and interventions to maximize health over time.[18] Lu and Halfon compliment the LCHD framework by further showing the importance of properly timed interventions on improving health outcomes along a developmental continuum.[19] The LCHD suggests that effective interventions or events that either lower risk or encourage protective behaviors provide the highest likelihood that an individual (or population) achieves his optimal trajectory over time (Figure 28.1).[20] This framework highlights the potential openings during a man's life to engage or reengage him with the health care system.

Some risk reduction strategies as related to men's health include avoiding smoking initiation and promoting cessation programs for those who have begun smoking, safe alcohol use, avoidance of illegal substance use, safe driving initiatives, and safe sex practices. Health-promoting strategies can include proper immunizations from childhood onward, appropriate health care encounters across the life span, weight surveillance and appropriate behaviors to maintain a healthy weight, and age appropriate health screenings such as for blood pressure, mental health disorders, and cancers

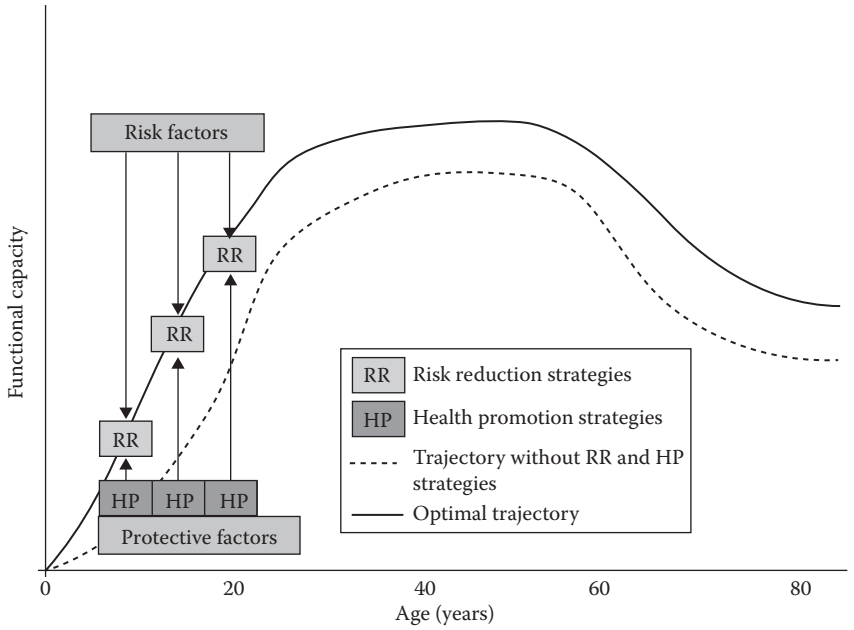


FIGURE 28.1 Maximizing functional capacity by risk reduction and health promotion over the life course.

(prostate, colon, etc.). Each of these behaviors can in turn shift the health trajectory curve toward optimization; the earlier the risk reduction occurs, the greater effect it has on the ultimate trajectory.

PREVENTIVE HEALTH FOR MEN ACROSS THE LIFE COURSE

The U.S. Preventive Services Task Force (USPSTF) recommendations for health care for men address many of the precursors or actual causes of death and comorbidities for men. These preventive measures are easily conducted by primary care providers and include (1) blood pressure measurement; (2) height, weight, and body mass index (BMI); (3) fasting lipid profile, (4) fasting glucose; (5) depression screening; (6) tobacco, alcohol, and other substance abuse and counseling; (7) injury prevention screening; and (8) provision of appropriate immunizations (Table 28.1).[21] While discussion of the specific attributes of the various screening tests in Table 28.1 is beyond the scope of this chapter, all the suggestions are recommended by the USPSTF review. The following suggestions are for screenings across the life span beginning at age 18 when young males leave pediatric care and enter young adulthood.

ADOLESCENT MALE HEALTH

Males going through adolescence have a unique set of developmental and health issues to consider. According to a 2008 IOM report,[22] most adolescents are considered healthy in terms of morbidity and mortality. However, adolescence is a time of transition when patterns of health behaviors, risk behaviors, identity issues, and relationship issues emerge as adolescents strive for independence and engage in experimentation. Adolescents need a safe, confidential, and accessible place to explore these issues and obtain reliable and confidential information. The IOM report outlines key requirements for quality adolescent health services, including (1) coordinating primary care; (2) focusing on disease prevention, health promotion, and behavioral health; (3) engaging the community; (4) maintaining confidentiality; and (5) preparing providers for the needs of young adults.

The adolescent stage in the life span is noted for several public health concerns that disproportionately affect young men, including homicides, suicide, motor vehicle crashes, substance use and abuse, smoking, and sexually transmitted illnesses. Accordingly, adolescent health is now one of the new objectives in the Healthy People 2020 framework. Table 28.2 lists a selection of these new objectives, their baseline incidence, the target goal for 2020, and the magnitude of the change expected.

Finally, there is promising research on interventions for adolescents that focus on positive youth development. The concept of resiliency, the ability of an individual to rise above obstacles, risks, and adversity in his environment and continuity to thrive and succeed, is receiving greater attention. Typical examples of resilient factors are supportive relationships with peers and others, social connectedness, and positive experiential opportunities.[23] Continued identification of those aspects of resiliency that pertain most to adolescent males and designing interventions to strengthen these factors hold great potential for improving adolescent male health.

FATHERHOOD AND MEN'S HEALTH

Becoming a father is a major transition for men with implications for motivations for change, altered life trajectories, psychological well-being, and roles in the family.[24–29] These changes may be "redefining," "jolting," or may result in "settling down."[24,26,30] Capitalizing on this developmental

TABLE 28.1
Suggested Screening Tests for Men Beginning at Age 18

Screening Test	Age 18–39	Age 40–49	Age 50–64	Age 65 and Above
Abdominal aortic aneurysm screening				Screen patients age 65–75 who have even smoked.
Blood pressure screening	Screen at least every 2 years if normal blood pressure is lower than 120/80.	Screen at least every 2 years if normal blood pressure is lower than 120/80.	Screen at least every 2 years if normal blood pressure is lower than 120/80.	Screen at least every 2 years if normal blood pressure is lower than 120/80.
	Screen once a year if blood pressure is between 120/80 and 139/89.	Screen once a year if blood pressure is between 120/80 and 139/89.	Screen once a year if blood pressure is between 120/80 and 139/89.	Screen once a year if blood pressure is between 120/80 and 139/89.
	Discuss treatment options with patients with blood pressure 140/90 or higher.	Discuss treatment options with patients with blood pressure 140/90 or higher.	Discuss treatment options with patients with blood pressure 140/90 or higher.	Discuss treatment options with patients with blood pressure 140/90 or higher.
Cholesterol screening	Starting at age 20 until age 35, obtain screening cholesterol test if patient is at increased risk for heart disease.	Check cholesterol regularly.	Check cholesterol regularly.	Check cholesterol regularly.
	Starting at age 35 and older, check cholesterol test regularly.			
Colorectal cancer screening (using fecal occult blood testing, sigmoidoscopy, or colonoscopy)			Beginning at age 50, screen for colorectal cancer.	Continue screening for colorectal cancer through age 75.
Diabetes screening	Screen for diabetes if blood pressure is higher than 135/80 or if on hypertension medication.	Screen for diabetes if blood pressure is higher than 135/80 or if on hypertension medication.	Screen for diabetes if blood pressure is higher than 135/80 or if on hypertension medication.	Screen for diabetes if blood pressure is higher than 135/80 or if on hypertension medication.
HIV test	Discuss risk with patient and test for HIV if patient at risk for HIV.	Discuss risk with patient and test for HIV if patient at risk for HIV.	Discuss risk with patient and test for HIV if patient at risk for HIV.	Discuss risk with patient and test for HIV if patient at risk for HIV.
Syphilis screening	Discuss risk with patients and test for syphilis if patient is at increased risk.	Discuss risk with patients and test for syphilis if patient is at increased risk.	Discuss risk with patients and test for syphilis if patient is at increased risk.	Discuss risk with patients and test for syphilis if patient is at increased risk.

TABLE 28.2
Selected Baseline and Target Adolescent Health Objectives in Healthy People 2020

Objective	Current Baseline	Target Goal by 2020	% Change
Adolescent wellness checkup	68.7%	75.6%	10% increase
After-school activities	82.5%	90.8%	10% increase
Adolescent–adult connection to discuss serious problems	75.7%	83.3%	10% increase
Graduate high school after 4 years	74.9%	82.4%	10% increase
School absenteeism due to illness or injury	14.6%	13.1%	10% decrease
Exposure to illegal drugs on school property	22.7%	20.4%	10% increase
Student safety at school as perceived by parents	86.4%	95%	10% increase
Serious violent incidents in public schools	17.2%	15.5%	10% decrease
Youth perpetration of, and victimization by, crime	444.0/100,000 adolescents	399.6/100,000 adolescents	10% improvement

event as men reconsider their responsibilities to their family and child may be beneficial for engaging men with the health care system and their own health promotion.

The health benefits of becoming a father are debatable and complicated by the fact that they have primarily been studied vis-à-vis the health benefits of being married. Men who are fathers and married have more proactive health beliefs related to health behaviors and outcomes compared to single men,[31] may gain health benefits from increased monitoring of health behaviors,[32,33] and derive psychological benefits through social support.[34,35] In the Panel Study of Income Dynamics, researchers found lower mortality risk in husbands with more children over a 20-year period compared to married men with fewer or no children.[36] Evidence from a sibling and twin model found among mostly married men that becoming a father after very young adulthood is associated with fewer chronic illnesses.[37] Alternatively, becoming a father could potentially be detrimental to male health. Approximately 5%–7% of new fathers screen positive for depression around the time of their partner's pregnancy.[38–40] Qualitative research describes the father-to-be as often unprepared, anxious, and experiencing role strain.[41] Another study of men during the first year of the transition to fatherhood found no significant changes in mental health but did find a significant decrease in general health,[42] while others report neither benefits nor risks.[43,44]

Hormone alterations also occur in expectant and new fathers and may have health implications for men.[45] Paternal cortisol increases in late pregnancy and during the labor process and then decreases postnatally, perhaps in relation to baby stimuli and cues. Prolactin increases in fathers prior to birth and is associated with greater responsiveness to baby cries and "pregnancy symptoms" in fathers.[45] The noted drop in men's testosterone during the postnatal period associated with greater paternal responsiveness may benefit men's overall health by decreasing high testosterone atherosclerotic and insulin sensitivity activity.[46,47] Finally, anticipation of a child appears to have both biological and behavior implications for men. In two observational studies, men and their pregnant partners were found to reduce smoking and drinking during the pregnancy with recent findings supporting the postnatal hospital stay as a successful venue for introducing a smoking cessation intervention.[48]

Changes in the mental health of men around the time of the birth of their children is another area of discovery in regards to men's health and fatherhood. Similar to the growing awareness and acknowledgement of the mental health of mothers in the peripartum, paternal perinatal depression is receiving attention for its effects on the father, his partner, and their children. Estimates of paternal depression within the first year of a child's life range from 7% to 10%.[49,50] An IOM report estimates that 4.3% of men with a child under 18 years had a major depressive disorder within the last 12 months.[51] This mental disorder has major ramifications for children, as it has been associated with decreased paternal warmth in parenting; increased parental conflict, hostility, and rejection; and lower psychosocial functioning in children.[52–54] Most of the current research focuses on the effect of paternal depression on the child; future work needs to examine the effect and natural history of paternal depression on the father's health and well-being.

While research in the area of fathering and its effect on men's physical and mental health expands, the current state of research suggests that becoming a father is a key period along the life course holds promise for interventions, supports, and further conceptualization of how this life altering event can be used to improve risk reduction, support positive health behaviors, and ultimately shift men's health trajectory.

FUTURE DIRECTIONS

There remains much to be learned in understanding and improving men's health. Future improvements will come from a variety of sources. First, improvements at the local level may have a particularly enduring effect on men's health. Ultimately, it is the relationship that men have with their health care provider that has the potential to prevent disease and improve their health. Men need to feel welcome, confident, and trusting of their health care provider. There are a number of successful ways to create a male-friendly health care practice. The creation of male-friendly healt hcare services helps men to identify a medical home, initiate, and continue to receive care. Developing health care programs or facilities especially designed for men that make use of gender-sensitive clinical practices is a growing trend within the health care industry.[2,15,16] Some of the approaches used to create a male-friendly practice include creating a welcoming office environment for men, striving to promote the use of health services via presentations and education, and encouraging clinicians to effectively engage men during the health care encounter (see Table 28.3).[55]

The second source for improvements is in the area of research. Researchers who focus on men's health must continue to expand and improve our conceptualization of men's health. This includes incorporating and accounting for protective and risk factors that contribute to men's health, as well as applying a life course perspective. Future research also must focus on the health of men in particular subgroups, such as immigrants, African American, Hispanic, Native American, Asian, and gay men. While there are many overlapping similarities in these groups, each possess unique challenges and opportunities that have an impact on men's health. Measures taken to include these subgroups in research and outcomes will improve our understanding of men's health.

Finally, men's health would benefit from greater involvement from public policy makers. Debate already exists around the creation of a center synonymous to the OWH called the Office of Men's Health (OMH). This government entity would be tasked with championing men's health across research, policy, and clinical care domains. With men generally poor participants in the health care system and with a dwindling life expectancy compared to women, an OMH could be a useful proponent of men's health during the ongoing health care reform discussions.

TABLE 28.3
Recommendations for Creating Male-Friendly Practices

General Topics	Suggested Clinical Practices
Welcoming health care setting	• Use administrative procedures that provide more anonymity (e.g., writing down reasons for visits) • Have men's interest magazines available • Make Internet access available • Provide health education materials targeting men's health issues • Gather feedback from male patients about the waiting room and how to improve it
Promoting service utilization	• Conduct outreach presentations where men routinely gather • Extend operating hours in the evening and on weekends due to men's work schedules • Use marketing strategies that appeal to men's characteristics • Collaborate with other agencies, key community figures, and women to get men into the health care system • Use direct mailings to promote knowledge of certain health risks and available services for male patients
Clinician–patient interactions	• Spend more time with men to inquire about health concerns • Affirm men for seeking help • Encourage health-promoting behaviors as ways to maintain independent, successful functioning • Provide education about relevant health issues (e.g., self-examinations, changing risky health behaviors) • Promote active involvement during health care visits

Taken together or separately, at the local practitioner level or the population level of researcher and policy makers, increased focus and attention to men's health has the potential to improve our understanding of men's health needs and to ultimately improve men's health outcomes across the life span.

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29 Addressing Men's Mental Health through a Strength-Based Approach

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CONTENTS

Gender Theories and Mental Health Outcomes 370
Shifting Clinical Orientations and Practices 371
Strength-Based Approaches: A Brief Review of the Literature 373
Strength-Based Approaches and Lifestyle Medicine 373
Men and Masculinity Strength-Based Approach 373
Case Description 373
Overview and Application of MMSBA 374
Phase 1: Establishing Patient–Practitioner Relationship 374
Phase 2: Shifting the Clinical Focus to Strengths and Men's Issues 375
Phase 3: Implementing an Action Plan 377
Conclusions 379
References 380

In the early 1990s a new subfield emerged in psychology, which was termed the psychology of men and masculinity. The emergence of this subfield was perplexing to some in the psychology field because so much of psychological research, theory, and practice had historically been focused on men. However, the psychology of men and masculinity was new because it recognized an important limitation in the psychological history of men; namely, men were never considered gendered individuals. The new psychology of men and masculinity pays a debt of gratitude to the feminist movement of the 1960s and 1970s in the United States and to the psychology of women for bringing much needed attention to the gendered identity of people [1]. A recent search of the term of "masculinity" in Psych Info (the predominant research database among psychologists) further illustrates that masculinity was understudied although men were often the focus of previous research. A search from 1860 to 1990 revealed 485 results while a search from 1990 to 2011 revealed 1163 results, which indicated a substantial increase in research focused on the gender norms and identity of men. A similar search of PubMed resulted in 351 hits for "masculinity" between 1800 and 1990 and 504 hits between 1990 and 2011. The study of masculinity is a multidisciplinary effort involving a wide range of disciplines, such as history and sociology to economics and medicine [2–5].

The new psychology of men sought to examine masculinity identities, how men responded to the changing roles of women (e.g., more women in the workforce and in education), and how men's identities and roles related to their health and well-being. A key assertion among the founding scholars of the new psychology of men and masculinity is that gender is recognized to have a biological basis, but the expressions of masculinity and femininity are not innate, biological traits but rather social constructions that are taught, learned, reinforced, and performed by individuals [6]. Both males and females are socialized to fit certain molds that can be both beneficial and detrimental to their health and well-being. Boys and men have been socialized to adhere to such masculine norms as being tough, aggressive, competitive, dominant, independent, stoic, and self-reliant, which is typically referred to as traditional masculinity [7,8]. The gender role socialization process is multilayered, longitudinal, and occurring across systems [9]. For example, a young boy may be taught to be tough and aggressive by his father (family system), which is then positively reinforced by a football coach when the boy becomes an adolescent (social system), but may become detrimental when the boy becomes an adult and cannot express emotions and vulnerability in romantic relationships (relationship system). Although not exhaustive, the example highlights the potential rewards of gender socialization (e.g., parental approval, athletic achievement) as well as the potential drawbacks (e.g., relationship difficulties).

Although there are many definitions of masculinity, this chapter espouses the definition of masculinity as a set of socially constructed characteristics and behaviors that men adopt in order to remain congruent with societal, cultural, and contextual expectations [10]. Terms and concepts used in this chapter are included and summarized in Table 29.1. The expression of masculinity can vary from man to man, from groups of men to groups of men, across cultures, ethnicities,

TABLE 29.1
Terms and Definitions

Common Terms	Definitions
Psychology of men and masculinity	A subcategory in the field of psychology emerging in the early 1990s. Refers to a psychology that considers male identities, how men respond to changing roles of women, and how male roles and identities relate to their health and well-being.
Masculinity	Social constructions about what a man should be that are taught and reinforced.
Masculine norm	The way men are expected to behave, think, and act according to social and cultural views of men.
Traditional masculinity (norms, roles)	Posits that men should be tough, self-reliant, stoic, independent, and take care of their business.
Gender role socialization	The way males and females are taught to be and to act. This can be rigid and limiting and have a negative effect on the lives of males and females.
Gender role strain	Posits that gender role norms are constantly being violated because they lack consistency and are contradictory. Violators of gender role norms are condemned especially if they are males.
Gender role stress	Subjective feelings of intense demands to uphold gender role norms and expectations, causing cognitive distress and emotional conflict.
Gender role conflict	A conflict between how an individual is socialized according to the individual's gender and how that individual wishes to live.
Toxic masculinity	Constellation of socially regressive male traits that serve to foster domination, the devaluation of women, homophobia, and wanton violence [34].
Positive masculinity	Positive qualities of traditional masculinity that can be used to promote the well-being of men.
Possible masculinity	A type of masculinity that encourages men to create goals and aspire to the ideal self. Possible masculinity places an emphasis on individuality of each male and the ability of men to use strengths they already have to reach their goals.
Gender competence	An ongoing process in which personal awareness and biases regarding gender are examined and challenged and more knowledge is sought about gender and gender roles.

geographies, income statuses, and sexual orientations. It is beyond the scope of this chapter to describe all the different expressions of masculinity. This chapter focuses primarily on the expression of masculinity in the United States among adult, heterosexual men. Readers are directed to additional readings for a more nuanced understanding of masculinity across different subgroups and cultures (International populations of men [11]; gay men [12]; African American men [13]; Asian men [14]; Mexican American men [15]).

GENDER THEORIES AND MENTAL HEALTH OUTCOMES

Early scholarship in the 1980s [10] was able to identify and explain the struggle that many men were experiencing during that time and continue to experience in modernity. Many men struggle with a feeling of dissatisfaction from trying to live up to the traditional masculinity ideals that they were taught. When they attempt to deviate from traditional masculinity norms, they often feel pulled back "into the box" by societal pressure (e.g., bullying). In other words, many men do not want to adhere to traditional norms of masculinity, which they consider inflexible, but they adopt some or most of those norms because of external pressure or reinforcement. This struggle is defined as gender role strain [16]. For example, an adolescent male may internally desire to be a high-school cheerleader. However, he recognizes that all of the cheerleaders at his school and on television are females. Further, he clearly learned from his parents and friends that boys are positively reinforced for playing certain sports, but that cheerleading is not one. If the boy tries out for the cheerleading team, an expected outcome might be bullying by his peers. The boy, then, may suppresses his desire to be a cheerleader. As a result of gender role strain, some men may experience dissatisfaction, guilt, anger, and other psychological distress.

In addition to feeling strained, some men experience gender role stress, which is defined as men's subjective feelings of pressure to uphold gender norms and expectations that result in cognitive distress and emotional conflict [17–19]. The negative effects of stress and the importance of using stress management skills on an individual's lifestyle and health behaviors are likely well known to readers of this chapter [20,21]. Specifically related to men, gender role stress has been associated with aggressive behavior, intimate partner violence, feelings of anger, and severity of posttraumatic stress disorder symptoms [18,19,22,23].

Gender role conflict theory, another prominent theory in the new psychology of men and masculinity, sheds additional light on men's adherence to traditional masculinity roles [24]. According to O'Neil [25], gender role conflict "is defined as a psychological state in which socialized gender roles have negative consequences for the person or others." Gender role conflict occurs when a man rigidly adheres to gender roles that restrict their potential to be the man of their choosing [24]. As men experience their socialization and become afraid of exhibiting femininity, gender role conflict can take the form of six predominant patterns: (1) restrictive emotionality, (2) health care problems, (3) obsession with achievement and success, (4) restrictive sexual and affectionate behavior, (5) socialized control, power, and competition issues, and (6) homophobia in men's interpersonal, career, family, and

health lives [25]. Men's gender role conflict has been found to correlate with depression, anxiety, stress, feelings of shame, an inability to put words to feelings (i.e., alexithymia), use of unhealthy coping strategies, alcohol and substance abuse, and low self-esteem [25,26].

Indeed, a consistent finding in research over the years has found a strong association between rigid and restrictive adherence to traditional masculinity and negative health outcomes among men, such as a decreased ability to express emotions and to seek help [27–29]. Additional theoretical and empirical support has been found for the connection between many mental health issues (e.g., depression, anxiety, substance abuse, relationship conflicts, stress) and a man's conformity or nonconformity to masculine norms [30,31]. In a landmark study in 2000, Courtenay [32] connected 30 negative health behaviors (e.g., sunscreen use, wearing seat belts, and substance abuse) to behavioral factors, such as gender socialization, among men. The result of this research has been preliminary conclusions that there are "toxic" aspects of or a "dark side" to traditional masculinity [33]. Taken to the extreme, "toxic masculinity" refers to an exaggerated set of male traits that promote violence, devalue women and individuals of sexual minority orientations [34]. Based on the culmination of this body of research, it is easy to take an essentialist perspective and conclude that traditional masculinity is always negative. Therefore, it is important to recognize that traditional masculinity per se is not associated with negative mental health outcomes, but the rigid, restrictive, sexist enactment of stereotypical male roles [35].

In a contrarian response to the empirical findings linking traditional masculinity to negative outcomes, some scholars have begun to examine the positive aspects of traditional masculinity [36]. The term "positive masculinity" has been coined in order to refer to qualities of traditional masculine roles that are positive and can be used to better the lives of men. Research on positive masculinity is scarce and primarily theoretical. The primary theoretical assertion behind positive masculinity is that traditional masculinity norms such as self-reliance, risk-taking behaviors, and a male relational style can be more positive than previously thought [36]. These behaviors can be used to promote an understanding of men that is not based on a comparison using the standards by which females are measured. Rather, Kiselica and Englar-Carlson [37] assert that traditionally oriented men possess a list of strengths that should be recognized and valued as a starting point to interventions: male relational style, male ways of caring, self-reliance, generative fathering, fraternal organizations of service, worker–provider tradition, male courage, daring and risk taking, humor, and heroism.

More currently, scholars and health practitioners are beginning to merge the different threads in the scholarship by recognizing the negative outcomes associated with the toxic aspects of masculinity and acknowledging the positive aspects of traditional masculinity. The next step has been to encourage men to be flexible with their roles and take a more balanced perspective to masculine norm adoption. For example, men are choosing to be "stay-at-home dads" at an increasing rate and finding satisfaction with this nontraditional role in their families [38]. The assumption is that many men may improve their health and the health of their families and communities if they adhere less rigidly to traditional masculinity norms and feel free to assume nontraditional roles and identities.

"Possible masculinity" is a recently developed construct that, like positive masculinity, tries to shed a more positive light on men's attitudes, norms, and behaviors [39]. However, possible masculinity does not universally endorse the positive aspects of traditional masculinity and tries to align men's behaviors to what society currently needs from men to promote healthy communities (e.g., nonviolent conflict resolution, appropriate emotional expression, fostering of egalitarian relationships). To start, possible masculinity asks men to identify their aspirational goals and encourages men to aspire to the ideal self that they establish. In other words, possible masculinity, in theory, is different for each individual man and reflects his self-defined characteristics of a man that contribute to the well-being of himself and others. Further, possible masculinity has room for both traditional and nontraditional aspects of masculinity in a man's aspirational self. By having future goals in mind, men have been shown to be better prepared to identify obstacles to their goals and what is necessary to overcome these obstacles [39]. This in turn can be applied to men's psychological health because men are encouraged to take responsibility for their actions and aspire to a more positive ideal self. Research on possible masculinity is nascent as the concept arose from counseling men, but the construct has potential to help men lead healthier lives.

SHIFTING CLINICAL ORIENTATIONS AND PRACTICES

A troubling outcome of men's socialization is that many men do not seek help from health professionals for their concerns. Many men are less likely to seek psychological help for fear of appearing emotionally unstable, vulnerable, and weak when they were taught to be strong and handle their problems independently. In a study focused on men and depression, researchers found many reasons why men do not seek help for depression such as the need to look good "at all costs" and to maintain the appearance of being in control [40]. However, men's socialization only tells half of the story. The other half of men's lack of help seeking stems from a lack of training, responsiveness, and cultural sensitivity from health practitioners despite literature that details the study of men and masculinity as an important multicultural competency [41,42]. As a result, health practitioners can approach men in an awkward, ineffective manner, which may help explain why men have been found to spend less time with their physicians; receive less overall information, explanations, and advice about health care issues; and receive less instruction on how to conduct self-examinations [43].

The proceeding research that will be outlined in this section has been conducted with mental health professionals in mind; however, the findings and recommendations have practical implications for all health professionals who provide clinical services to men. One of the first characteristics health practitioners notice about their patients is gender, which comes with underlying assumptions and expectations [44]. Robertson and Fitzgerald [45] found that mental health therapists viewed their patients as more pathological if they did not conform to traditional and stereotyped gender norms. Counselor's initial assessment with a group of female and male patients revealed that women were more likely to be described as "vulnerable," and male patients were often portrayed as "stuck" and "difficult," which perhaps illustrates gender stereotyping in therapeutic interactions [44].

Although not always the case, the practitioner's gender may factor into biases and assumptions that arise in the treatment of male patients. Some research has found that female counselors are more likely to emphasize the emotional expression of male patients, compared to male counselors [44]. The emphasis on emotions may be incongruent with many men, especially men who have been socialized to be stoic and would typically avoid mental health interventions because of the perception that counseling is all about talking about feelings. Holly Sweet [46], a female psychologist in private practice, has written that female counselors must be mindful of the values of therapy, such as connecting with another and being emotionally open and expressive because these values and expectations put males at a disadvantage when entering therapy. Sweet continued by making two important recommendations for female practitioners that work with male patients. First, female counselors should become aware of male gender role socialization and the challenges men face, which would reduce negative interactions with male patients in health interventions [46]. Second, female practitioners should increase their self-awareness of how their personal gender norms may minimize their ability to be sympathetic and understanding of male issues.

Male health practitioners have also been found to have biases in their interventions with male patients. For example, male counselors have been found to be more likely to have empathy for male patients who express emotions that are typical of male roles (e.g., anger) while reporting negative attitudes toward male patients that expressed non-stereotypical emotions (e.g., sadness) [47]. In addition, Cottone et al. [48] found that male patients paired with male therapists were less likely to continue treatment after the initial intake, suggesting that there was some aspect of the help-seeking experience and/or gender dyad that influenced treatment duration. Male practitioners are susceptible to the same socialization of their male patients, which may result in avoiding appropriate emotional exploration or reinforcing dissatisfying, straining, or stressful masculine roles [49].

Overall, the gender of the health practitioner is not as important as the health practitioner's self-awareness of their gender socialization, awareness of how their gender socialization may affect their interventions with male patients, and commitment to offer services that are congruent with the diversity of male patients. In the counseling psychology literature, treatment outcomes for male patients (i.e., psychological well-being) have been shown to be contingent upon the gender competence of the practitioner [50]. It is helpful for both male and female practitioners to think about ways in which gender roles have impacted their lives in order to gain a greater appreciation for the dynamic ways in which gender may play a role in a male patient's presenting concerns [41,46]. Awareness of male gender norms and expectations allows for a less biased interpretation of the patient and decreases the likelihood of the health practitioner reenacting negative interpersonal experiences the male patient has experienced previously.

Researchers have begun to identify ways to engage men in help seeking. In a study focused on men and depression, researchers found that the best way to help men who are depressed but unwilling to seek help is through redefining help seeking in male-oriented language [51]. Brochures about mental health distributed to men used terms such as "mental health consultant" instead of counselor and "strategy for attacking," rather than therapy. They also reframed counseling as a team effort and cost-effective and help seeking as a sign of strength rather than weakness. The results of this study found that men had improved attitudes about help seeking [51]. Efforts such as these highlight the need to shift the orientation of clinical practice. Clinical efforts should be congruent with men's attitudes, beliefs, and behaviors of masculinity and a health setting should be a welcoming place for men to have their health concerns addressed in a careful, male-friendly manner. In a recent literature review of masculinity and men's health, Garfield et al. [52] posit a set of male-friendly recommendations for health practitioners: (1) provide a welcoming health setting such as having men's interest magazines and Internet in the waiting room, (2) promote service use by having extended evening hours and conducting outreach workshops at male gathering places, and (3) enhance clinician–patient interactions by encouraging help seeking, educating about self-examinations, and being conscientious about spending an appropriate amount of time with male patients.

Implementation of male-friendly practices can enhance a practitioner's clinical effectiveness with male patients. In particular, clinical efforts with men would benefit from beginning with and focusing on strengths instead deficits [37]. An ideal model to approaching men's health is integrative and accounts for positive masculinity as well as possible masculinity and all other self-defined strengths of men. It is necessary to shift away from a deficit model of clinical intervention and toward a strength-based approach. A strength-based approach is more encouraging to men seeking help for mental health concerns and allows health practitioners to convey a sense of respect, welcome, and congruence with their male patients. In order to enhance health practitioners'

competence and effectiveness in their interventions with men, an outline of a strength-based approach in conjunction with an overview of male socialization is provided.

STRENGTH-BASED APPROACHES: A BRIEF REVIEW OF THE LITERATURE

A strength-based approach to mental health interventions began to emerge in the 1990s and overlaps with positive psychology [53]. Strength-based approaches and positive psychology interventions are a shift from a sole focus on problems and weaknesses to treatment methods and intentional activities that aim to enhance strengths, positive feelings, behaviors, and cognitions [54,55]. Using a strength-based approach involves considering and examining strengths, resources, and other positives of the patient throughout the treatment process, although this does not exclude problems from being discussed as well [56,57]. Rather, strengths and problems should be understood in an integrated manner that provides a holistic conceptualization of the patient [57]. In fact, strength-based approaches are considered easy to integrate with many other treatment approaches and practitioner worldviews [54,57,58].

The major differentiation between a strength-based approach and other approaches is that in a strength-based approach, strengths are seen as what allows the patient to make positive changes [58]. Remedial interventions often require patients to do something new while a strength-based approach aims to capitalize on things that patients are already doing well that can contribute to improvements and well-being [56]. The exploration and enhancement of strengths, resources, and assets foster resiliency, which may allow for the prevention of future problems rather than remediation and management of existing problems [59]. Yet, health practitioners working from different approaches with patients may already rely upon patient strengths to facilitate recovery even if they do not discuss or emphasize strengths [58]. Viewing a patient from a strength-based focus creates an optimistic conceptualization among health practitioners, which may facilitate a better patient–practitioner relationship and enhance patient motivation to change [56,58,59]. In a recent meta-analysis, Sin and Lymbomirsky [55] found strong empirical support for a wide range of positive psychology interventions that enhance well-being and decrease depressive symptoms. Examples of interventions included setting positive goals, personal strengths activities, and goal training to name just a few [55].

STRENGTH-BASED APPROACHES AND LIFESTYLE MEDICINE

Health practitioners aligning with a lifestyle medicine approach to interventions may find a strength-based approach to be a good fit with their clinical practice and professional identity. Unlike traditional medicine that works from a remedial medical model and heavily relies on medications for treatment, lifestyle medicine aims to prevent the problem from happening by emphasizing changing the behavior of the individual. This is done through the use of lifestyle changes such as exercising, quitting smoking, and changing the diet of the patient. Behavioral changes such as eating healthy, exercising, and watching intake of sodium can lower blood pressure and in turn prevent medical problems [60].

The focus on prevention is what links lifestyle medicine and strength-based approaches to men's health. Both lifestyle medicine and strength-based approaches first assess what the problem is and then use the individual's strengths and resources to tackle the problem [60]. Similar to strength-based approaches, lifestyle medicine uses the individual's strength of being able to change and adapt as a preventative measure against the development of medical problems [61]. By using the individual's strengths, both practices use something that is already available and inexpensive. However, due to the fact that both lifestyle medicine and the strength-based approach are reliant on the individual and not medication, they may take time to become effective. Lowering blood pressure without medication through dietary changes and exercise may take months, but in the long run it costs the individual less in medication and has more global beneficial impact on the individual's health [62]. By focusing on changing behavior to better the health of an individual, lifestyle medicine poses the risk of fewer negative side effects than many medications [63]. Both lifestyle medicine and strength-based approaches value educating and empowering the patient through transparent clinical care. An informed patient is better equipped to deal with medical, psychological, physical, and mental health problems that may arise.

MEN AND MASCULINITY STRENGTH-BASED APPROACH

The following section provides a case description of a fictional male patient. The steps of the strength-based approach and its application to the case example is provided in order to detail a concrete example for health practitioners on how to use the approach in their clinical practice with men. Though this case describes a mental health encounter, the steps and advice contained within are equally applicable for general medical issues. However, the men and masculinity strength-based approach (MMSBA) should not be considered as the first line of treatment for patients with more severe psychopathology such as bipolar disorder, posttraumatic stress disorder, or schizophrenia, which require more specialized services. However, the MMSBA can be integrated with treatments that address severe psychopathology.

CASE DESCRIPTION

Mike is a 32-year-old man who presents for treatment on his own accord because he is concerned that he has been having outbursts of anger lately. He feels out of control of these outbursts and this is unsettling to him. Mike reports that these

outbursts started about 5 weeks ago when he was passed over for a promotion at his job where he works at a factory. Mike reports dissatisfaction with his job and the desire for a better paying job so that he can support his family. Mike is married and has two children. Mike's daughter is 2 years old and his son is 6 years old. Currently, his wife is a paralegal and makes more money than Mike.

Mike was raised in a family with a stay-at-home mother and a father who was a factory worker. In Mike's lower middle-class neighborhood, higher education was viewed suspiciously and the general sentiment was that people went on to higher education to avoid doing "real work." Mike appears to have retained some of this sentiment, and he never pursued education beyond high school. Mike does express the desire to have a "better job," but he does not have a clear idea of what this job would be. Mike expresses that he is "fine with my wife working because it is important to her to have a career, but I'd rather the family not be financially dependent upon her working."

Mike coaches a soccer team in the same league that his son plays in, but not his son's team. Mike explains that this is because he wants to be involved with his son's activities without the risk of pressuring his son or pushing him too hard. Mike plays friendly games of soccer in the backyard with his son but refrains from trying to coach him during these games. Mike enjoys taking his daughter for walks and "making music" with her on toy instruments. Currently, Mike's son is in kindergarten and Mike's daughter attends an early preschool program 2 days a week and stays at her maternal grandparent's house during the other times when Mike and his wife are working.

Mike describes his relationship with his wife as good except for the recent outbursts of anger. Mike and his wife communicate well about their children and relationship, though Mike says that he has some difficulty talking to his wife about frustrations at work. Mike and his wife share household tasks according to their preference for doing certain tasks and what they have decided are fair arrangements. For example, Mike's wife enjoys cooking and Mike does not, so Mike's wife makes meals and Mike does kitchen chores such as washing dishes. Mike takes on the responsibility of bath time for the children, and Mike's wife takes the kids to school and grandparents' house and picks them up in the afternoon. In addition to activities with his family, Mike reports that he enjoys listening to music and attending concerts, hiking, and traveling.

OVERVIEW AND APPLICATION OF MMSBA

There are 10 steps to our strength-based approach with men separated into three phases. It is important to note that the steps do not need to be followed in the exact order set forth in this chapter; rather, there are times to "retrace" to previous steps or to implement overlapping steps at one intervention point. The steps are likely to be implemented over approximately—two to four sessions. A brief listing and overview of the steps are included in Table 29.2.

TABLE 29.2
Overview of the Men and Masculinity Strength-Based Approach

Phase 1: Steps 1–3
Focuses on establishment of a rapport and a healthy clinical relationship with the patient
- Step 1—Establish rapport with the patient.
- Step 2—Give the patient the opportunity to discuss what has brought him to therapy.
- Step 3—Discuss the strengths and resources the patient has.

Phase 2: Steps 4–6
Focuses on identification of patient's strengths and integration of new psychology of men and masculinity
- Step 4—Help the patient identify his strengths.
- Step 5—Assess the patient's level of gender role adherence while providing the patient with necessary information.
- Step 6—Introduce possible masculinity into therapy.

Phase 3: Steps 7–10
Focuses on helping the patient engage in new behaviors and move toward concrete behavioral change
- Step 7—Work with the patient to create an action plan.
- Step 8—Discuss potential barriers to implementation of the action plan.
- Step 9—Discuss strengths and resources the patient has that can help overcome barriers to the action plan.
- Step 10—Schedule a follow-up meeting with the patient to discuss patient's progress with the action plan.

Phase 1: Establishing Patient–Practitioner Relationship

Phase 1 is the initial phase. The goals of phase 1 are to establish a healthy clinical relationship, identify the patient's presenting concerns, and to identify the patient's strengths and resources. Step 1 is establishing rapport and a healthy, clinical relationship with the patient. A clinical relationship is built on trust and safety while serving as the foundation for the following intervention steps. Utilization of basic helping skills in this step such as active listening, summarizing, clarifying, paraphrasing the patient's disclosures, and ensuring that the patient feels heard and understood are useful. It is also important that the practitioner maintains a nonjudgmental attitude toward the patient and exhibits genuineness [64].

With Mike, it may also be helpful to draw from research that suggests that men respond more to cognitive-oriented interventions in the initial stages of treatment instead of emotion-based interventions [65]. It is important to validate Mike's help seeking and reframe help seeking as a strength instead of a sign of weakness. Specifically, a practitioner can say, "I'm glad you came to consult with me today Mike. It's a real sign of strength that you noticed something is off with you and you want to fix it." Asking Mike about soccer, perhaps if he is a fan of a local Major League Soccer team or a World Cup team, could also help build rapport based on his interests in soccer.

Step 2 entails giving the patient an opportunity to discuss his presenting problems. The goal of step 2 is to discuss the patient's presenting problems while addressing resistance or defensiveness to talking about strengths [66]. People typically

expect that mental health interventions involve discussing problems and may be resistant to talking about strengths without first expressing their problems and concerns. The approach assumes that talking about strengths first would be confusing to patients and may lead to resistance and/or defensiveness from patients. When meeting with Mike, engage in an open discussion about his anger. Acknowledge that outbursts of anger are troubling, which validates his concerns. As a practitioner, you can also explore the anger outbursts in more detail by asking some open-ended questions such as "what triggers the outbursts of anger?" "Have you had difficulty with anger in the past?" "What do you do when you're angry (e.g., yell, punch a wall, berate yourself)?" These questions help to assess history with the problem, current coping mechanisms, and common patterns and antecedents to the problem. In addition to gathering pertinent information about the problem, the questions foster insight and reflection from the patient.

Mike reported that his anger is mostly triggered by "issues at work," primarily that he was passed over for a promotion that he felt he earned. Mike rarely expresses anger at work, but on a few rare occasions, he has snapped at coworkers, which has resulted in complaints to management and social avoidance from coworkers. In general, Mike described "sucking things up, finishing the day" and then "blowing up at home, later in the day." Mike described himself as normally quiet, having a good sense of humor, outgoing and never really angry, not like he is now. Mike admitted that he does not cope well with this new anger, which is why he is seeking help. He has punched his bedroom wall, making —two to three holes. He reports yelling at his wife as well. Mike has insight that this is not healthy for himself or his relationship with his wife.

Step 3 is the important process of shifting the orientation away from the patient's presenting concerns (i.e., their deficits, problems) to strengths. The goal of step 3 is to educate the patient about the process of the strength-based approach and answer any questions from patients. A critical part of the successful implementation of this step is being very transparent. It is important to tell the patient that you are going to tell them about how you work with patients and that your approach involves focusing on the strengths of patients. Practitioners should tell patients why focusing on strengths is important and integral to your approach. For example, a practitioner can say, "I work with all kinds of people, with all kinds of problems. I find that a common link between people and solutions to their problems is their strengths. Therefore, I spend a lot of time with patients identifying strengths and figuring out how patients can use their strengths in ways that lead to health and well-being." Practitioners should invite questions from patients about the strength-based approach and also be prepared to clarify any patient confusion.

Phase 2: Shifting the Clinical Focus to Strengths and Men's Issues

Phase 2 is the second phase of the steps of the strength-based approach. The goals of phase 2 are to shift the focus onto patient's strengths and resources and to integrate concepts from the new psychology of men into the process. Phases 1 and 2 could be completed in —one to two sessions depending on the pace and clinical judgment of the health practitioner. Additional time may be needed if formal assessments are utilized, which would require administering, scoring, and discussing the results with the patient. Discussing formal assessments should not be rushed.

Step 4 is strength identification. The goal of this step is to have the patient identify their own strengths. However, patients may not be comfortable talking about their strengths, or may be clouded by their mental health concern (e.g., a depressed patient may be less inclined to discuss their strengths because of their depression). In these instances, a practitioner can start the process by taking a more active role in identifying patient strengths. The identification of patient strengths can be a very informal or formal process. For example, a practitioner can simply ask the patient, "What are your strengths?" or "Tell me all the things that you do really well." Strength identification can also utilize formal measures and tests. For example, Dr. Martin Seligman from the University of Pennsylvania, the founder of the current positive psychology movement, operates a free website [67]. The website hosts several measures. A specific assessment, the Brief Strengths Test, measures 24 character strengths of an individual. The Brief Strengths Test is self-administered and takes approximately 5–15 min to complete. The output of the Brief Strengths Test provides the test taker with a ranking of their strengths.

When asked about his strengths in an informal manner, Mike answered that he is a hard worker, family man, cares about his children, athletic and fit, knows his way around a factory, and is a loving husband. The practitioner can identify additional strengths, such as that Mike does not push his son too hard in athletics but maintains involvement through coaching and practicing with his son. In addition to individual strengths, a practitioner should ask Mike about community and cultural strengths. Mike discussed having supportive parents and that he belongs to a group of "soccer dads" who all coach youth soccer, play a weekly pickup game together, and meet after the game at a local coffee shop to talk about life, family, children, work, and sports. Mike brightened up when he discussed the "soccer dads" and described them all as "good guys, good men." When asked more about this group, Mike described that the group can play soccer together and "bust each other's chops" but also discuss "really important things." It appeared that Mike was implying that this group of men could be vulnerable with each other and that this was refreshing and supportive. When this interpretation was presented to Mike, he agreed and added, "At the factory, it's all business, it is actually work and my mentality. Have to kind of keep a poker face all day. With the soccer guys, I can let my guard down, relax more."

After Mike discusses both his individual and community strengths, the practitioner validates those strengths and emphasizes the importance of Mike recognizing his strengths. This may also be a good time to note any discrepancies

between Mike's strengths and presenting problems (i.e., anger outbursts). Noting discrepancies is a clinical judgment based on the practitioner's assessment of the therapeutic relationship and appropriate timing of such an intervention. For example, a practitioner could say, "Ok Mike, I heard you say at the beginning of our time together that you get angry and you take out your anger on your wife by yelling at her even though she doesn't necessarily deserve it. Yet, I also heard you describe yourself as a family man and good husband. There seems to be a discrepancy here." Noting a discrepancy may lead to further exploration of the problems and strengths as well as helping Mike see how he can use his strengths of being a good husband and family man to change his presenting problems of angry outbursts. In other words, Mike should be aware that a good husband does not yell at his wife. The strength that is present in Mike but needs to be enhanced is being a good husband.

Step 5 entails assessing the patient's level of gender role adherence while providing the patient with necessary information. An additional goal of step 5 is to educate the patient about positive masculinity. This step is significant because many health professionals are not trained in the new psychology of men and masculinity, but assessing a man's gender role conflict and masculine identity is a cultural competency that will nourish the treatment process. Conceptualizing men's mental health through gender role socialization, gender norms, and masculinity contributes to a greater understanding of the etiology of mental health concerns. Similar to strength identification in step 4, assessment of masculine identity and gender role conflict can be done in an informal or formal manner.

Informally, a practitioner can ask Mike, "Some men don't like to ask for directions and are kind of stoic. Other men aren't like that, they don't mind wearing pink shirts and are less macho. How would you describe yourself as a man?" In response to this question, Mike reported that he was raised in a traditional home and that his father taught him to be tough, work hard, and to look other men in the eye and give them a firm handshake. Yet, he makes a point to show affection toward his children, stating that "they know that I love them." However, Mike also reported that he is not "too much of a touchy, feeling guy" but that his meetings with his soccer dads often end in a "group hug kind of thing." Asked to clarify, Mike described that all of the soccer dads wrap up their time at the coffee shop by going around and giving "man hugs" to each other. Mike further explained, "I guess it's situational for me. At work, in the factory, I'm gruff, stoic, and tough. That's how I have to be there. I guess that's traditional masculinity, more macho, but everyone acts like that there. But at home, with my kids, I hug and kiss them, tell them that I love them. I get lost all of the time, I have to ask for directions or I wouldn't get anywhere. And with my soccer friends, we are more emotional with each other, we give each other hugs. My dad would never do with his friends, but I feel comfortable doing that."

Overall, Mike was articulate in describing his masculinity identity and the complexity involved in describing his identity. However, more formal assessments may aid men who are less articulate or do not have a high level of insight. A useful assessment text for masculinity is the Conformity to Masculine Norms Inventory (CMNI) [31], which is a 94-item measure with 11 subscales that represent distinct masculine norms that are predominant in the United States. The 11 subscales are Winning, Emotional Control, Risk Taking, Violence, Dominance, Play Boy, Self-Reliance, Primacy of Work, Power Over Women, Disdain for Homosexuals, and Pursuit of Status. The scale is estimated to take about 10–15 min to complete. The items are answered on a 4-point scale (0 = strongly disagree; 3 = strongly disagree), with a calculated total score and scores for each subscale. The transformed total score (mean = 50; SD = 10) produces four categorical ranges of extreme conformity (above 60), moderate conformity (50–60), moderate nonconformity (40–49), and extreme nonconformity (39 and below). The total score can be used as an overall assessment and the subscales can be mined for detailed exploration. A clinical benefit of the CMNI is that it measures masculinity norms, which can then be explored with the patient to determine if conforming to the endorsed norms is healthy and positive for the patient or harmful and negative to the patient. Potential stress from not conforming to masculine norms can be explored as well [31].

The CMNI taps into masculinity roles and norms. Therefore, step 5 may also be a good place for psychoeducation about male socialization in relation to Mike's presenting concerns. For example, Mike is expressing anger, which is considered one of the few acceptable emotions for men to express. Mike may be feeling depressed, anxious, or shame because of work issues, but men are socialized to hide those emotions. Mike identified the antecedent of his anger outbursts at work as the lack of a promotion that he felt he deserved. Men are socialized to compete and succeed, especially in the business/career domain of life. Thus, Mike may perceive a lack of promotion as failing to succeed in an area that he is expected to succeed in. Taken deeper, Mike may feel that he is failing as a man if he is not able to achieve at work. Mike learned from his parents that the father works and is the "breadwinner" and the mother stays at home and cares for children. Mike and his wife appear more coparental and are in a dual career family structure, but Mike may be feeling ashamed or devalued that his wife makes more money than him and that his identity as a breadwinner is diminished in his family.

Male socialization does not necessarily lead to pathology. Introducing the concept of positive masculinity may allow him to view traditional masculinity as a source of strength. A practitioner could say, "Some men have difficulty being macho all the time. There can be positives and strengths found in traditional masculinity. What aspects of traditional masculinity are of value to you?" With Mike, it is clear that he exhibits generative fathering (e.g., actively involved in children's lives), males relational styles (e.g., soccer with other dads), and worker/provider tradition [37]. The practitioner should validate these positive aspects of traditional

masculinity and perhaps ask how those strengths can help to fix the angry outbursts that Mike has reported.

The goal of step 6 is to help the patient engage in possible masculinity by identifying goals, aspirations, and addressing any incongruence between the patient's adherence to male roles and aspirational self. In this step, there is a shift toward being aware of their possible masculinity as many men feel restricted by their gender role socialization. It is important to note that possible masculinity can be explored with men who fall along the masculine ideology continuum.

Possible masculinity is a broader concept that also tries to help men identify strengths in masculinity. A practitioner works from this broad stance, asking a man, "What kind of man do you want to be in the future? What aspirations and ideals are you striving to achieve as a man?" The key assumption with possible masculinity is that there is incongruence between how men are acting in the present versus how men want to be in the future. The typical pattern of incongruence, especially in clinical settings, is that men are dissatisfied with their current actions and have more admirable and positive future goals for themselves. One of the goals of possible masculinity is to facilitate men taking responsibility for the incongruence.

Mike has been able to identify his strengths as well as other positive aspects of traditional masculinity and the socialization that he is familiar with from his parents. Yet, Mike also recognizes that the angry outbursts "are not me, not who I want to be." When asked what kind of man that he wants to be, Mike explained, "I want to be a true leader, I want to handle my emotions and anger in a direct manner. I want to be an employee at work that can be counted on not just to do my job but to train others, manage others, lead a team. I also want to be a guy that can express my emotions in an appropriate manner and to not take them out on my wife." The next possible masculinity question is to ask Mike what is keeping him from achieving those ideals and goals. The intent of the question is to have Mike look inward, take responsibility, and express an internal locus of control and change.

Phase 3: Implementing an Action Plan

Phase 3 is the third and final phase of the MMSBA. The goal of phase 3 is to help the patient engage in new behaviors and move toward behavioral change. Steps 7–9 of phase 3 are likely to require one session. Phase 3 and the corresponding steps (7–10) are aligned with a behavioral approach to interventions, with a debt owed to scholarship written on the behavioral activation technique [68]. A key theoretical underpinning of behavioral activation is that a negative mood is related to disengagement from positive reinforcement [69]. Therefore, increasing positive moods and emotions entails re-engaging behaviors that increase positive reinforcement for the patient [70].

Step 7 is action planning. The action plan should focus on having the patient identify concrete behaviors to engage in that will enhance their current strengths, be a source of positive reinforcement, and help them meet their future-oriented goals identified in step 6. It is important for the practitioner to allow the patient to arrive at their own action items while also monitoring to ensure that the action items are indeed behaviors.

In order to introduce this important step to Mike, the practitioner is advised to discuss the importance of transforming thoughts, feelings, and goals into a plan that can be implemented. For example, a practitioner can say, "Mike, you have done a great job of seeking help, articulating your concerns, engaging in self-reflection on your strengths and the type of man you want to become. The next step is to help you to take some concrete behaviors that will help you to reach your goals. It is important to engage in new behaviors, not just talk about engaging in new behaviors." The health practitioner can then ask Mike what behaviors would he like to exhibit in the next week or two that will help him become more congruent with the type of man he wants to be. It is important to set an actual date for the completion of the behaviors and to have Mike schedule the behaviors.

Mike stated that he has two behaviors that he wants to implement in the next week. First, Mike reported that he wants to schedule a meeting with his boss at work in order to discuss his future at the company and how he can be better positioned in the future when promotions are available. The second behavior that Mike wants to engage in is to apologize to his wife for his angry outbursts and to communicate to her that his outbursts, although directed at her, are not caused by her but by his inability to manage his anger related to work issues and stress. Mike reported that he can talk to his boss after the mid-week department meeting and that he can talk to his wife tonight after the children go to bed. Both times and days were recorded on the action plan: Wednesday, 11:00 a.m. and Monday, 9:00 p.m., respectively. Mike's behavioral plan appears to be appropriate; therefore, the health practitioner should ask Mike what strengths that he can draw upon to help him exhibit these behaviors. Mike reported that his strengths of being a hard worker and loving husband (as identified in step 4) will help him talk to his boss and wife. As a practitioner, it is helpful to validate these strengths while also identifying other strengths such as using his ability to be emotionally open with his soccer dads group to be emotionally vulnerable with his wife. Second, the health practitioner can explore with Mike what new strengths may be developed as the result of him implementing his new plan. Mike explained that he may develop assertiveness skills as he talks to his boss and the strengths of open, honest communication as he talks with his wife.

The goal of step 8 is to identify potential barriers to the execution of the action plan. Therefore, the health practitioner and patient brainstorm potential barriers. Many barriers often prevent patients from taking the needed, yet difficult step of implementing their plan. Exploring potential barriers is a proactive step that helps patients gain awareness of the change process. Specifically related to men, gender socialization often entails pressure, punishment, and reinforcement

that maintain unhealthy and destructive behavior. Therefore, health practitioners are encouraged to ask their male patients about any perceived social and cultural barriers related to being a man that would impede the action plan. A health practitioner could ask a male patient, "I know men face a great deal of pressure to conform to a certain idea of manhood. What messages about masculinity and manhood have you noticed that may keep you from following through on your action plan?"

In addition to social and cultural barriers, men often have self-imposed barriers to positive change. Previous experience with exploring possible masculinity with male patients resulted in patients regularly taking responsibility for not reaching their aspirational goals of manhood. This represents a significant shift as many men often become defensive or deflect responsibility when prompted to identify their negative behavior and consider making changes in their lives. A health practitioner should view a man taking responsibility for the role they play in holding themselves back as a positive moment in the intervention.

Mike was asked about potential barriers and he quickly responded that he is a very stubborn person. As a result, admitting a mistake to his wife will be difficult. Mike also acknowledged that he is fearful and anxious about approaching his boss at work. Mike feared that he could get fired or will "say the wrong things." Mike's fears are valid and the health practitioner should review the pros and cons to Mike talking to his boss in order for him to make an informed decision of sound judgment.

In response to the question concerning masculinity barriers, Mike reported that talking to his boss about his future with the company will be a big departure from other men at the factory and what his father taught him. Mike explained that men should let the quality of their work do the talking, yet he was also raised to speak up for himself and to not get walked over. Therefore, Mike expressed conflicting messages about masculinity: should he stay quiet and hope that his boss recognizes his work or should he assert himself and alert his boss to the merits of his work? Mike should ultimately arrive at the answer to this question with the health practitioner facilitating exploration rather than offering direct advice.

Step 9 provides a complement to step 8 by asking the patient to brainstorm potential supports and any additional strengths that will help to overcome the identified barriers in step 8. The goal of step 9 includes identifying supports as well as an explicit conversation about how to access those supports. Given men's lack of help seeking, step 9 is a good opportunity to reinforce the idea that help seeking is a sign of strength, not weakness, and that it is okay for men to seek additional support. A simple question to ask a male patient while implementing step 9 is "What or who will help you overcome those barriers?"

When these questions were asked of Mike, Mike reported that he can talk to his wife more openly and comfortably when they are engaged in an activity together, such as walking. Mike described that he will arrange for a babysitter and ask his wife to go for a walk tonight after the children go to bed. He believes that doing something active helps him to open up more rather than just sitting and talking face to face. In terms of talking with his boss, Mike reported that he needs to develop a script on what he wants to communicate to his boss instead of speaking off the cuff. In particular, Mike wants to clearly communicate his contributions to the company and his desire to assume more of a leadership position. Mike also wanted to obtain feedback from his boss on his current performance and what he needs to do in order to earn a promotion. Mike reported that he will feel more confident if he practices the script before the meeting. Mike also stated that he has a good friend from the soccer dads group who is in the business field and would be a great sounding board for Mike to practice the script with and receive some feedback. Mike affirmed that he would seek the help of this friend. The health practitioner can validate and encourage Mike's use of the identified supports.

Step 10 is the final step and involves scheduling and having a follow-up meeting with the patient, with the goal of assessing how the patient progressed or is progressing through the action plan. To recap, steps 1–6 are expected to take about 1–2 sessions while steps 7–9 are expected to take about 1 session. Yet, some patients may work quickly, thus only needing 1 session to get through steps 1–9. Therefore, 1–3 sessions have occurred before the follow-up meeting. The follow-up meeting is intended to check-in with the patients about their progress implementing the action plan. A simple way to start this meeting is to ask the patients if they were able to do the behaviors that they listed on their action plan. A patient could answer with an array of answers, ranging from "yes, I completed the action plan" to "no, I avoided doing all of the behaviors on the action plan." Based on the patient's progress, the follow-up meeting can serve additional purposes. For patients you completed the plan, the follow-up meeting can be used to offer praise and positive reinforcement as well as to assess how the implementation of the plan went for the patient. For example, a health practitioner can say, "wow, that is great that you completed the plan. How did everything go?" For patients who avoided some or all of the plan, assessing what prevented them from doing so is appropriate. It is important not to shame patients or make them feel like they failed. Rather, it is valuable information for future interventions if the patient does not complete the action plan. The follow-up meeting can serve as a point of reevaluation, further exploration, and a recommitment to action and progress. The health practitioner can help patients discuss how the steps in this model can be used in the future to manage problems.

Mike returned for the follow-up meeting. When asked about his progress, Mike reported that he had a mixed bag of results. First, Mike explained that he could not find a babysitter and therefore could not go for a walk with his wife to apologize on the scheduled day. Instead, Mike waited until the weekend when the children were with his in-laws for the afternoon. Mike reported that he was very nervous and talked

about everything else (e.g., the weather, soccer) before finally getting around to apologizing to his wife. Mike expressed relief that he finally was able to apologize and that his wife accepted his apology. At this point, a health practitioner can offer praise and positive reinforcement with Mike, such as "great job Mike, I am glad you took this big risk and things worked out!"

Mike's face shifted to a look of embarrassment when asked if he talked with his boss. Mike reported that he did not talk to his boss as his anxiety increased and his fears of losing his job acted as barriers. The health practitioner should empathize with the difficulty of the task, "I understand that it is a very difficult thing to do, talking with your boss. It is a big risk." The health practitioner and Mike can try several new directions in the intervention. For example, Mike can set a new, intermediate goal to lead up to the previous bigger goal of talking to his boss. Breaking the big goal into smaller tasks may help Mike gradually build his confidence and decrease his anxiety and fears. Starting with drafting the script may be a good intermediate goal to focus on first. Mike and the health practitioner can also reexamine the pros and cons of the original task. Perhaps, Mike has concluded that the cons and the risks of possibly losing his job are too high and he wants to drop the task from the action plan. On the other hand, Mike may recognize that the pros of asserting himself and dealing with the work problem that is at the root of the anger outbursts outweigh the cons. At this point in the intervention, the health practitioner can remind Mike of the connection between the goal and his presenting concerns of anger by asking, "You seemed to have a lot of anger related to work, your boss, and being passed over for a promotion. Does not talking to your boss increase or decrease your anger?" The clinical assumption is that Mike's anger is increased by not talking to his boss and that talking to his boss, despite the risks, will help him manage his anger more positively. Finally, the follow-up meeting can re-explore how Mike's strengths can help him in this process or what are some new strengths that he needs to develop to help facilitate meeting his goals. Mike may need to schedule additional appointments or require a referral to a more appropriate health provider.

CONCLUSIONS

With the new surge in research focusing on masculinity, health practitioners are called upon to utilize this scholarship to better understand the positive and negative effects of male gender socialization, norms, and roles to men's health and well-being. Accounting for gender role socialization, gender norms, and masculinity contributes to a more thorough conceptualization of men's mental health concerns and more efficacious interventions. Masculinity is a changing construct dependent upon the current social and cultural norms, expectations, attitudes, and behaviors. Although the dominant (i.e., hegemonic) masculinity expression in the United States has historically been to value strength, toughness, competitiveness, success, stoicism and men as breadwinners, shifts seem to be occurring. Some men are emphasizing equal participation in household tasks and many fathers are striving to be more involved and coparental in childcare [71,72]. Ultimately, health practitioners are encouraged to challenge those norms that detract from positive help seeking and health behaviors among men.

Each particular male patient likely expresses their masculinity differently, with varying effects on their health and well-being [73]. Therefore, starting interventions from a strength-based perspective may allow health practitioners to build a stronger clinical relationship as male patients' unique strengths are recognized and used in the intervention process. Health practitioners need to be comfortable affirming or challenging aspects of predominant and marginal masculinity norms depending on the patient's presenting concerns and treatment goals. Often, health practitioner comfort with the continuum of masculinity expression is enhanced through self-reflection and awareness of one's own assumptions, biases, and beliefs about men, masculinity, and gender roles [39].

Focusing on the culture in which one's masculinity was created and reinforced helps health practitioners to understand the individual differences among many subgroups of men, who may present with additional cultural beliefs about masculinity and gender roles. A strength-based approach is also culturally sensitive as strengths are culturally dependent and defined. Clinicians are encouraged to always question their assumptions of what is considered a strength or weakness, considering what is seen as a strength in one culture may be considered a weakness in another [58,59]. Cultural competency has the potential to frame treatment and conceptualization in terms of deficits such as oppression, victimization, and discrimination [73]. Focusing on strengths is a positive way to integrate culture into interventions without focusing on the aspects of a patient's culture that impact the patient negatively [59]. Rather, patients can discuss culturally specific strengths that have helped them develop a positive identity, buffer against stress, and rise above challenges [59,74].

The MMSBA is a new, integrative model of intervention. The MMSBA takes into account male socialization and puts the focus of intervention on men's strengths rather than deficits. As such, the MMSBA is an exciting and promising approach to mental health interventions with men. Although research is beginning to support the use of strength-based approaches, the MMSBA lacks empirical support. Therefore, using the MMSBA in conjunction with, rather than as a complete replacement for, other empirically supported and evidence-based treatments (e.g., cognitive behavior therapy) is a useful approach. The MMSBA is considered to be most suitable for male patients with such mental health concerns as adjustment issues, adjustment disorders, and moderate psychopathology such as depression and anxiety.

Although the MMSBA was designed with mental health in mind, it is a broad enough approach to apply to other health concerns and lifestyle medical situations. For example, presenting concerns such as initiating an exercise program and eating a healthier diet have been situated within a

gendered context [52]. As a result, health practitioners could easily draw upon the 10 steps of the MMSBA to facilitate the adoption of healthier lifestyle decisions with male patients.

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30 Promoting Nutrition in Men's Health

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CONTENTS

Masculinity and Men's Health 383
Men, Food, and Health 384
Promoting Nutrition in Men's Health 386
References 388

Men's health promotion is important since men are, generally, less interested in self-care and healthy living. A focus on diet is especially important since mens' food choices are traditionally more restricted and less healthy than their female counterparts. In this chapter, we will explore why men are typically disinclined to pursue healthy lifestyles and, in particular, why healthy eating poses such challenges for many men. The role of masculinity will be discussed, since many researchers suggest that gender identity is crucial in understanding mens' (and womens') health practices. We will then proceed to explore some recommendations for enhancing mens' engagement with healthy eating.

MASCULINITY AND MEN'S HEALTH

Men on average die 4 years younger than women, outnumber women in mortality statistics for most major illnesses, and generally lead unhealthier lives (e.g., drink more alcohol, eat less fruit and vegetables, exercise less) in the United Kingdom, United States, and Europe [1–3]. This "crisis" in men's health has attracted a lot of media attention in recent years, with various calls to explain the problem(s) and offer solutions. In the midst of debates about cause and effects, most attention has been directed at "masculinity." As early as 1978, for example, Harrison directly implicated masculinity in his influential paper entitled "Warning, the male sex role may be dangerous to your health," while a later review paper by the leading men's health researcher [4] and activist Will Courtenay in 2000 developed this argument, suggesting that disinterest in healthy living was bound up with masculine identity performance [5]. So, for example, men may be more concerned with appearing tough, independent, and unemotional than considering health advice, with help seeking viewed as weak and emasculating. But what exactly is this thing called masculinity, and how does it affect nutritional behaviors?

Over the years, social scientists have attempted to define and measure masculinity (and femininity). Originally, theorists tied biological sex to gender attributes such that "masculinity" was deemed exclusive to men and femininity tied to women—deviations from this pattern were judged problematic, if not pathological [6]. Later sex role theories, however, disrupted the connection between biological sex and gender such that men and women could display both masculine and feminine attributes. For example, on the Bem Sex Role Inventory (1974), one could score highly on both masculine and feminine dimensions ("androgynous"), low on both ("undifferentiated"), or high on one and low on the other ("sex-typed male/female")—regardless of biological sex [7]. In the past 20 or so years, however, theories of gender have moved on, and we now have a wide-ranging and developing literature on men and masculinity on which we can draw to help us understand men's (un)healthy behaviors.

The most influential and debated theoretical work on masculinity has been generated by Connell and colleagues [8,9], responsible for the term "hegemonic masculinity." Briefly, the concept refers to dominant constructions of masculinity which influence men's identities and practices, including health practices. For example, in most Western cultures men are assumed to be emotionally and physically strong, independent, and prone to risk taking [10]. Such attributes have been associated with unhealthy practices: men are less likely to admit to pain or seek medical advice compared to women, which leads to delays in receiving treatment and often serious health consequences such as advanced cancer or heart disease [11]. Men are also more likely to eat restricted meat-based diets and large portions [12]. While only few men such as celebrated sportsmen or musicians can ever (if at all) attain hegemonic status, all men are "complicit" in supporting hegemonic ideals through their practices, whether it be weight training, promiscuity, or eating unhealthy foods. Connell's analysis also explains that hegemonic masculinity is maintained via practices which oppress women (e.g., domestic violence) and other, "subordinated" and "marginalized" men (e.g., homophobic abuse). Such practices clearly have impact on the health of men, and women.

As a consequence of Connell and colleagues work, most researchers in gender studies now refer to *masculinities* in the plural to suggest many facets, that is, there is no one single masculinity factor which can stand for masculinity once and for all. A quick free association to the term masculinity will undoubtedly throw up many different characteristics, preferences, and roles, such as "strong," "rational," "active," "independent," "achievement oriented," interested

in sport, breadwinner, and leader. But these associated ideals and practices are not simply a matter of individual choice, since masculinities are validated in relation to other people and wider social contexts. For example, it is not enough to believe yourself to be a brave man—this is something that must be demonstrated to others in meaningful situations. In other words, masculinities can be thought as "socially constructed," that is, presented and negotiated during social interaction and subject to prevailing social influences and constraints. For example, a man's capacity to become a modern involved father will in part be limited by work patterns, financial pressures, and community norms about fatherhood. Similarly, a man's inclination toward eating healthier, "feminized" foods such as salad, vegetables, and fruit will be shaped to some extent by gendered expectations emanating from peers, family, and work colleagues.

In addition to being conceptualized as multifaceted and socially embedded, masculinity is conventionally considered to be defined in opposition to femininity. So, if femininity is defined as emotional, masculinity is unemotional or rational; if femininity is defined as weak, masculinity is strong; if femininity is defined as relational/dependent, masculinity is defined as autonomous/self-reliant; and so on. In an early study with male university students on modern masculinity, for example, participants preferred to talk about themselves indirectly, in terms of what they are not, which amounted to a critique of women as neurotic, demanding, and inferior—and a implicit construction of men as rational, relaxed, and superior [13]. However, for men today it is increasingly difficult to ignore changing gender relations and societal forces which, for example, place expectations on men to become healthier, more interested in their appearance, and more emotionally articulate. And so in the realm of health, men are being asked—by media, health services, significant others—to consider what they eat, how much/little exercise they do, their weekly level of alcohol consumption, and so on. It is no longer viable to disregard health concerns since modern societies are so "healthist" [14] that those who refuse to engage in healthy living risk being stigmatized as irrational, immoral, and unfit—we can highlight the critical attitudes to smokers, those deemed clinically obese, and binge drinkers (see also Ref. [15]). Old fashioned definitions of masculinity which rely on an irresponsible, cavalier approach to health are increasingly difficult to sustain, so men are now called upon to reconcile being masculine with being healthy. What research with men has demonstrated here is that men will draw upon a discourse of balance or moderation, a rational position where both health and gender concerns can be accommodated:

> It's like the smoking, I told you about that. I gave up when the second one [baby] was born … I thought I have got to be serious about this and I stopped … eventually. I still like to go on the lash [drinking alcohol] on a Saturday night. You've got to really, I mean you have got to have a good time some time, but not all the time. In moderation, if you know what I mean (Robertson and Williams [16], p. 364).

Robertson [17] articulates this challenge with reference to a dilemma between control and release, a "don't care/should care" dichotomy. This health-aware climate means, of course, that men are now encouraged to reflect on what they eat with a view to making their diets more nutritious—a project which only women (predominantly) have been concerned with until recently.

MEN, FOOD, AND HEALTH

In most Western societies, women have traditionally been socialized into roles and activities revolving around food—shopping, preparation, and distribution to loved ones—which have been linked to conventionally powerful feminized identities such as mother and wife [20,21]. Men, on the other hand, have been designated as consumers of food, ignorant of the cost or nutritious value of food [22,23], and removed from the kitchen environment [24]. As well, women have typically been positioned as knowledgeable about food and interested in healthy diets (albeit informed with feminized ideals of thinness), whereas men have largely been defined in terms of narrow food preferences usually involving red meat and large portions [25]. Indeed, it is only relatively recently that the area of men, food, and health has attracted the attention of academic researchers; traditionally, research on food has centered on women, with a particular focus on body image issues [16].

There are some statistics comparing the sexes on nutrition matters. We know, for example, that men generally consume less fruit, vegetables, and fish than women and eat more high calorie items than women [26]. Other research has found that men are not terribly interested in the health aspects of food and categorize healthy food (e.g., "salad") as insubstantial and tasteless [12]. Whereas women emphasize the notion of dieting and its role in weight loss and body image, men tend to regard food as a means to enhance fitness and strength [25]. Popular mens' magazines such as Men's Health reinforce this image, focusing on meat-based diets for the development of muscular physiques and decrying feminized practices such as vegetarianism and domestic cooking [24]. Indeed, when men have partaken in domestic cooking they are widely perceived as incompetent within this feminized space [27]—although in special circumstances "masculine" cooking is constructed as efficient, sophisticated, and distinctive rather than the messy, mundane, and uninspiring attributions tied to women's cooking [28]. In health promotion contexts though, media features directed at men emphasize the constricted and unhealthy male diet while at the same time ridiculing mens' engagement with healthier diets [29]. Recent work in the United States also suggests that meat eating for men has become more important as a way of affirming masculinity in the midst of "softer" contemporary masculinities which depart from traditional ideals of strength [30]. Taken together, such findings suggest that men's diets are nutrition-poor and place them at risk from serious diet-related diseases [31].

Only relatively recently researchers have begun to investigate men's eating habits, and the picture is more complex than gender stereotypes would suggest. For example, Roos et al. [32] interviewed men from different professional and social class backgrounds and found that while carpenters largely regarded food as fuel and favored meat-centered diets, engineers were interested in aesthetic, taste, and pleasurable aspects of eating and enjoyed a more varied diet. This example underlines the intersection of gender (masculinities) with other social dimensions such as class, and other social categories can be important here, including race, ethnicity, and age. For example, in a survey study by Courtenay et al. [33], it was found that most groups of men had poorer diets than women—it was only Hispanic men who compared well with their female counterparts. Other work suggests that older men are more reluctant to engage in healthy eating compared to younger men [34], while younger men may see cooking as a means of displaying masculinized values such as autonomy and control [35]. And work by Galdas and Cheater [36] points to the role of cultural traditions and rituals in inhibiting healthier eating practices in older men of South Asian origin. Another important influence on (heterosexual) men's health and dietary practices is relationship status, since female partners often play a significant role in supporting men toward healthier living and better nutrition [37]. There is also evidence that when men are ill or frail, they may be less responsive to healthy eating interventions, preferring to leave responsibility for food to women [38]. On the other hand, gendered expectations may well mean that wives and partners consolidate their male partner's unhealthy food preferences [39], while for some urbanized middle-class professional men who live alone healthy eating is embraced [35].

Where men do take an interest in nutrition is in sport and fitness contexts. Body building is a classic example where men pay very close attention to food intake, calorie consumption and expenditure, and bodily consequences, perhaps influenced by muscular torsos adorning the covers of popular men's magazines more than health concerns [40]. Given the increased visibility of the male body in popular magazines, billboards, and society generally, it is likely that some (younger) men at least will be influenced or inspired by such images to work on attaining similar bodily definitions through taking up strict dietary regimes as well as exercise programs. It is likely too that in competitive sporting contexts, ranging from cycling to athletics and team sports, nutrition plays a key part in preparation for events [41]. Related to this is the upsurge in interest from men in fashion, grooming, and appearance concerns generally [42] since a desire to project and maintain a particular image is likely to involve dietary and other (e.g., exercise) programs. In studies of "metrosexual" men, for example (men interested in fashion, grooming, and self-care [43]) we see reference to food and alcohol in relation to the effects on skin appearance and a general concern with looking healthy [44]. As men become more interested in their physical appearance in Western youth-centered, image-conscious consumer-driven societies, then it is likely that disordered eating patterns may result, with more men presenting with traditionally "female" conditions such as anorexia and bulimia, with estimates ranging from 10% to 25% of eating disorder cases [45]. In the context of weight training and muscle-centered exercise, the use of steroids is significant with male gym users in pursuit of the modern lean-but-muscular ideal [42]. Compared to women, who are said to have a unidimensional relationship with body weight as they desire slimness, men have been found to have a bidirectional relationship with their weight in that some complain of being too large and some too small [46,47]. A Scottish study [48] on adiposity in men in low socioeconomic groups found that men of normal weight wanted to be larger, overweight men were happy as they were and only obese men wished to lose weight.

Conversely, bigger men who are medically defined as obese may well reject healthy eating advice in order to maintain a body size and shape deemed to be desirable. For example, in an interview study with gay male "bears"—typically large, hairy, "masculine" gay men—Gough and Flanders [49] encountered much resistance to mainstream health promotion, as one participant states:

> I think, the bear community does encourage you to remain the weight you are, provided you fit within these ranges, of overweight and obese, not skinny but not too big that you look ridiculous, The society BMI would like me at 12 stone [76.2 kg, or 168 pounds], the bear community wants me to be meaty, the bear community wins hand down because being this size changed my whole outlook on life, because I have, whether its [name of a northern city], the fact that I've matured, I've got more friends here, than I ever had in my whole life.

Within the bear community, it is larger bodies which are celebrated and eroticized, so any targeted health or nutrition advice would need to take account of the "alternative" group identity and norms which pertain here. Gay communities are particularly lacking in research on health-related lifestyle choices beyond safe sex, HIV, and AIDS.

Another societal phenomena has been the rise of cooking programs [50], and with it the heralding of the (male) chef hero. Again, it is likely that such programs and associated books will encourage some men into the kitchen to experiment with new ingredients and foodstuffs, and since a varied diet is often linked to a healthy diet, this development is perhaps to be welcomed. An area ripe for more research is the changing nature of men's relationship with food and its implications for health, with reference to the diversity of men's circumstances, relationships, and community influences. What are the eating habits of young working class men, and how do these compare with their more affluent counterparts? How relevant is health for men situated differently with respect to age, sexual orientation, and ethnicity? What role do marriage and similar commitments play in male nutritional behaviors? These and other questions are important to address in future research so that we can design effective interventions tailored to specific groups of men.

PROMOTING NUTRITION IN MEN'S HEALTH

The question of what works for men in terms of health promotion is vexed. We do not really have much evidence—there are few evaluations of existing initiatives. One thing is important though, and that is overcoming men's traditional antipathy toward "interference" in their lives. For example, Gough and Conner's [12] interview study with men revealed skepticism toward government and media-sponsored healthy eating campaigns, perhaps reflecting a "masculine" orientation to self-reliance and personal control. Other research has also encountered a strong theme around men making their own health-related decisions:

> I just think blokes will do it when they want to do it. They won't be told. It's like anyone could tell me I need to stop smoking but I'll do it when I'm ready to stop smoking and not when someone tells me to […] I watch all the adverts and I do think I should stop smoking. But I'm not ready to stop smoking, I might never be ready to stop. If a doctor tells me "you need to stop smoking" then it's my decision whether I do or don't (Robertson [17], pp. 122).

But this male emphasis on independence can be deployed in health promotion campaigns. For example, in the United Kingdom the Men's Health Forum has published a series of "man" manuals focusing on different aspects of men's health, and a prominent feature in these texts is the insistence on the individual's capacity to set and achieve personal goals. One of the manuals focuses on obesity reduction, and some extracts from different sections of the text pertaining to diet illustrate the centrality of male autonomy (see Ref. [51]):

> Make your decisions based on logical discussion with yourself rather than allowing them to be a fait accompli (Section 2.5)

> Knowing how powerful your thoughts are will give you another tool for your kitbag (Section 2.6)

> Weight management is just a matter of choosing the right foods (Section 4.11)

This emphasis on solitary decision making is peculiar in that other people and situational constraints are absent, as if men inhabit a private universe untouched by others or social pressures. However, the underlining of self-reliance makes sense from a masculine point of view. In fact, this text (and other manuals) invokes a range of masculinized attributes and activities in order to encourage men to lose weight and get fit. The theme of "goal setting" is of course familiar in other "masculine" domains such as sport, management, and the military [52]. Indeed, these three domains are variously invoked to help promote individual performance. For example, men are invited to "plan your attack" (Section 3.23) in order to increase physical exercise, to "fight the insulin resistance" (Section 4.12), and advised that "the key to winning the war of terror on fat is to boost your metabolic rate through diet and regular exercise" (Section 4.14). As well, the Football Association is cited in the context of advice on water intake (Section 4.10) and nutrition (Section 4.18). Indeed, the first page proper (Section 4.11) features a half-page photograph of five England footballers advertising the manual and an acknowledgment below the Football Association's "encouragement and assistance." The world of work is also presented at various points to highlight the problems and possibilities of healthy activities. For example, the case of policemen (Sections 4.10 through 4.16) is used to illustrate the health risks posed by a desk job with little opportunity for exercise of healthy eating combined with a male-centered drinking culture. Whatever the "masculine" context or discourse, men are consistently advised to use their logical minds and inner strength to achieve a healthy weight.

However, there is a debate here about the extent to which masculinity is promoted over health. It has been argued elsewhere [51] that although recourse to stereotypical notions of masculinity may help to gain mens' attention and may even encourage men to make beneficial changes to their lifestyle, there is a risk that masculinized discourse privileges, say, self-reliance, mental toughness, and mastery may end up maintaining or even regressing men's health promotion efforts as interpersonal, social, and cultural considerations are erased from the picture. For example, there is no point stressing the importance of personal goal setting without taking into account a man's work patterns, family responsibilities, social obligations, and so on. The situation is complex. For some men who live alone, we know that healthy living can be more difficult without the support of a partner [38], so merely being alone does not equate with a proactive achievement orientation. There are other suggestions that homosocial environments can be used to promote healthy eating in men. In one Canadian study, for example, men who learned to cook with other men improved not only their skills in the kitchen but also their healthy eating practices [53]. The role of men in supporting each other toward healthier lifestyles is complicated, however. One recent study has examined how men, signed up to an all-male online weight management group sponsored by the magazine Men's Health, support each other in their weight control efforts [54]. In total seven "threads" were analyzed, with those declaring their age ranging from 19 to 40 years; all participants self-defined or could be defined as overweight or obese from the information provided. It was found that support was couched in understated and indirect way, for example, "I understand what your saying mate" or "sod the heartbreak man you should be proud of what you are doing." As well, any display of emotion linked to struggling with diet and weight loss was dismissed as "girly":

> Harpsie 11 (thread 1: 09/01/2009 11:28AM 1–10) The reason that people believe you could be inspirational as there are a lot of guys out there that have punished their bodies so much to extent where you were: And are at rock bottom in weight and confidence, a lad who sees this post and reads it through to the end will be sat there thinking God

> if this guy can do it then so can I!!!! You are inspiring people like others on here that by saying and showing (in the words of Dys). Losing weight is not hard stop moaning and get to it. I think you need to read back this post my friend and see how far you have come. Any way enough of this girly stuff ….

Here, a pragmatic, action-oriented discourse is privileged over emotional expression, thereby reinforcing the masculine character of the homosocial support group environment. Such considerations would need to be borne in mind when designing "male-friendly" diet-based interventions.

Staying with weight loss, there have been similar moves to construe diet-based weight management programs as "male-friendly." Although primary care trusts in the United Kingdom have been keen to increase recruitment of men on to commercial diet organizations such as "Weight Watchers" or "Slimming World" [55], even when specifically targeted, the impact has been very modest. For example, "Slimming World" attempted to raise awareness in men about the problems with being overweight and set up a national network of men-only groups. However, the percentage of men compared to women attending the groups went from 3% to only 5% [56]. NHS weight loss interventions such as "counterweight" have been found to have only 26% of participants as male [55]. The literature is mixed on how to better recruit men onto weight loss interventions. Some success has been found with interventions designed specifically for men which highlight exercise and lifestyle changes rather than diet-based schemes, especially those which invite talk of emotional eating [57]. Occupational weight management programs have also been shown to be more successful in recruiting men [58]. Other research suggests that individualized programs are better, particularly with regards to diet [59].

There is some suggestion that men are unlikely to seek health advice or change their habits until or unless they experience a health scare [11]. Such medical events typically prompt men to reflect on and reevaluate their lifestyle choices, engendering behavior change in key areas such as diet. But even here the situation is complex. For example, in a recent study by Mróz et al. [60] men diagnosed with prostate cancer showed varying commitments to dietary change, ranging from little or no change to major overhaul. Most men opted for relatively minor changes:

> I'm just doing things a little more intensely, and maybe varying or supplementing what I used to eat with things such as blueberries and sardines and fish. That's really I think the only, the best way to say it is that I'm intensifying, always trying on a healthy diet, but now I'm just doing it a little bit more intensely and consciously

Moreover, men who self-define as healthy and/or can be categorized as leading a healthy lifestyle may be reluctant to cite health as a factor in their lifestyle practices. An interview study by Sloan et al. [61] with "healthy" men found that factors other than health were cited when describing health-relevant practices, such as following a particular diet regime, avoiding or minimizing alcohol intake, and exercise programs, including sporting performance. In the following extract, the interviewee ("Paul") is responding to a question about when he began to take account of his health:

> Paul: … when I started to take the basketball seriously. That's when I started to look at my health and kind of how my body reacts and stuff. And trying to learn and understand more about food and what it does to my body.
>
> Int.: Did you not think about it before then?
>
> Paul: No I never gave it a thought; I just lived and ate whatever.
>
> Int.: There is nothing that you can think of that made you change it?
>
> Paul: Well yeah I kind a used to smoke, not much, but playing basketball made me not want to smoke. Cos I knew that it was kinda abusing my body. I need my lungs to be at the full capacity rather than clogged and stuff. So I stopped smoking.

Here, Paul accounts for his transition to a healthier lifestyle in terms of enhancing his sporting performance—health is subordinated to a more valued sporting context, where the talk is functional and technical, treating his body as an instrument to be worked upon and refined. Other studies also indicate that when men take up traditionally feminized practice such as cooking and healthy eating, they tend to reframe the activity in question in conventionally masculine terms. For example, those men who advocate reduced meat diets may emphasize the rationality of their choice toward healthier living [62], while those who cook for other men at work or at home may imbue their cooking with hypermasculine discourse centered on competence [63]. For example, in Bennett and Gough's [54] analysis of postings to an online male-only weight loss forum, cooking healthy food was still centered around meat, alcohol, and homosocial bonding:

> in my opinion my kebab tastes better than the ones you get in the kebab house after a night out! Worked for me and two of me mates Friday night. Whu_1989 (thread 1: 12/01/2009 11:57AM 20–21)

In the same study, men also glossed the kitchen as a masculine space central to the manufacturing of manly (muscular) bodies:

> I think the saying "a sixpack is made in the kitchen and not in the gym" is 100% true. Matt14 (thread 5: 23/12/2008 2:24PM 2–3)
>
> Be a beast in the gym and a beast in the kitchen, that's where good bodies are made. Danroye (thread 1: 12/01/2009 2:55 6)

Similarly, media portrayals gloss kitchen-based activities as masculine, even in the seemingly innocuous context of breadmaking:

> But what's really remarkable is that in each case it's the man of the house who's up to his elbows in flour. Suddenly men who've never shown the slightest interest in matters culinary are talking Italian flour and sourdough starters. "I've become

> a baking widow," laments one friend, as another batch of breadsticks are proudly produced from the oven. "Why can't he take up golf like any normal husband?" Chef Richard Bertinet puts the appeal down to the hunter-gatherer thing. "It's like natural foraging. You transform a few base elements into something that will provide for your family. Seeing your child eat your own bread is very Satisfying. I think it's also that most men are natural show-offs in the kitchen. We may not like the day-to-day stuff, but we love to cook to impress." (The Times, Loafing about—Foodie at large, 15/10/05)

So, breadmaking, referenced as unusual for men ("remarkable"; not "normal"), is somehow transmuted into breadwinning and attributed to an evolutionary hunter-gathering instinct [29].

It is clear then that health promotion efforts around diet targeting men need to be designed with care and sensitivity to valued aspects of gendered identities. A blunt focus on outmoded and simplistic stereotypes of masculinity may well work to some extent in gaining mens' attention but risk reinforcing gendered norms linked to poor health in the first place. On the other hand to ignore salient masculinities may well miss valuable opportunities to engage men in changing their eating and related practices. What we must not do is assume that all men are the same when it comes to food intake [29]. Mens' ideas and practices around food will vary with respect to myriad factors including parental influence, social class, age, work patterns, and relationship status, to name a few. For example, for those men in long-term relationships the role of partners in supporting (or undermining) health promotion efforts needs to be factored in, along with any childcare responsibilities, work patterns, and financial pressures, while for single men it may be more important to establish supporting networks and resources to facilitate healthier eating. In general, we can develop more tailored and effective healthy eating initiatives for specific groups of men as research expands the understanding of mens' diverse preferences, practices, and priorities.

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31 Management and Prevention of Urological Diseases in Men

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CONTENTS

Prostate 391
Benign Prostatic Hyperplasia 391
Prostate Cancer 393
Penis 394
Erectile Dysfunction 394
Circumcision 395
Testes 396
Testis Cancer 396
Androgen Deficiency in the Aging Male 396
Bladder 397
Overactive Bladder 397
Bladder Cancer 398
Kidney 398
Urolithiasis 398
Kidney Cancer 399
Appendix A: The AUA Symptom Index 400
References 400

Urological diseases in men encompass a broad range of illnesses ranging from acute to chronic, benign to malignant, and medical to surgical. The economic burden of treatment reflects their broad scope: in 2000, over $1 billion, $1.2 billion, and $320 million were spent treating benign prostatic hyperplasia, prostate cancer, and erectile dysfunction (ED), respectively [1]. The primary care provider will most likely be the first to encounter men with urological complaints and can play a significant role in the prevention, diagnosis, and treatment of men with urological diseases. This chapter will highlight major urological health issues in men, with a focus on diagnostic and preventive measures useful for the primary care provider.

PROSTATE

Benign Prostatic Hyperplasia

Benign enlargement of the prostate is an age-dependent phenomenon and is directly related to exposure to androgens. As men age, androgens induce a variety of changes at the cellular level leading to hyperplasia of the stromal (smooth muscle) and glandular (epithelial) cell types of the prostate. This process may result in increased bladder outlet resistance, which has a variety of clinical consequences, the most important of which are bothersome lower urinary tract symptoms (LUTS)—symptoms related to the storage and elimination of urine from the bladder through the urethra—that can significantly impact upon a man's quality of life. LUTS may include complaints such as nocturia, frequency, urgency, hesitancy, intermittency, weak stream, and sensation of incomplete voiding, however do not typically include incontinence. The mainstay of evaluation and treatment of men with benign prostatic hyperplasia (BPH)-related LUTS is aimed at preventing the progression and bother of voiding symptoms.

Historically, men diagnosed with BPH had only one treatment option—surgical resection. Now transurethral resection of the prostate is reserved for men with cases refractory to medical management. If left untreated, BPH can result in persistent hematuria, recurrent urinary tract infection, urinary retention, and rarely chronic kidney disease. However, the most common clinical consequence of BPH is progressive LUTS related to dysfunctional urination.

While the relationship of LUTS and histologically confirmed BPH is not direct, the prevalence of BPH and LUTS increases as men age. In a large cross-sectional study in the United States, 13% of men aged 40–49 years complained of LUTS that were either moderately or severely bothersome and this number steadily increased up to 28% of men in their

seventh decade of life [2]. This increasing prevalence with age has been estimated to be about the same as autopsy-proven BPH; however, LUTS can be a result of other entities such as overactive bladder (OAB) [3,4].

Although most men complaining of LUTS have BPH, LUTS are not specific for BPH. Thus, the American Urological Association (AUA) recommends that the initial evaluation of LUTS involves a focused history, urinalysis, digital rectal examination (DRE), serum prostate-specific antigen (PSA) in selected patients (patients who have >10 years life expectancy), and the AUA symptom index (AUA SI or International Prostate Symptom Score [IPSS]) [5]. The AUA SI is a questionnaire that measures the severity of LUTS and is a useful instrument to help stratify patients with BPH-related LUTS who may benefit from treatment. The eight domains of the symptom index—frequency, urgency, nocturia, weak stream, hesitancy, intermittency, incomplete emptying, and impact of symptoms on quality of life are scored from one (least severe) to five (most severe). The AUA SI has been validated and shown to be effective in identifying men who would benefit from treatment and is a useful tool to follow their progress during or after treatment (Appendix A).

BPH-related LUTS have a significant impact on various measures of health. Men who develop progressive BPH-related LUTS that go untreated tend to report a worsening in their condition that has an increasingly negative impact on quality of life [6]. Additionally, men in nontreatment (placebo) arms of large randomized controlled trials involving medical treatment were shown to be at increased risk for acute urinary retention, urinary tract infection, urosepsis, need for invasive procedures to treat BPH, and most commonly worsening LUTS. Untreated BPH-related LUTS has also been shown to be associated with decreased quality and frequency of sexual activity and an individual's overall perception of general health [7,8]. Fortunately, less than 25% of men with BPH-related LUTS will demonstrate progressive disease [8].

The 2010 AUA guidelines enumerate multiple treatment options for men with LUTS related to BPH. Watchful waiting refers to the most conservative approach: patients who have mild symptoms (or patients with moderate to severe symptoms who are not significantly bothered by them) may be followed without intervention [5]. Dietary modifications such as reductions in alcohol and caffeine intake as well as decreasing overall fluid intake may also improve LUTS [9,10].

Medical therapy for BPH has been shown to be effective at reducing symptoms and halting disease progression. There are two different classes of medications—α-receptor blockers and 5α-reductase inhibitors (5-ARIs). α-Blockers primarily target the α1A receptors located in prostatic stroma and help to reduce overall prostatic smooth muscle tone, thus decreasing bladder outlet resistance [11]. These medications are most useful to improve the bothersome voiding symptoms in men with BPH-related LUTS. The other medication for the treatment of BPH-related LUTS, 5-ARIs, prevents the conversion of testosterone to dihydrotestosterone in the prostate. The lack of dihydrotestosterone reduces the proliferation of prostatic tissue and reduces prostate size by as much as 20%–40% after 6 months of treatment [12,13]. Similar to α-blockers, 5-ARIs improve BPH-related LUTS; however, they also reduce the risk of urinary retention and the need for surgical intervention by as much as 50% [8,13]. If medical treatment is chosen, those patients without obvious prostatic enlargement on DRE may be started on α-blocker therapy for symptom relief primarily. If there is evidence of prostatic enlargement on DRE (>30 mL or grams of prostate tissue), patients may be started on 5-ARIs either as monotherapy or in combination with α-blockers [5]. Treatment with a 5-ARIs in combination with an α-blocker has been shown to be more effective at reducing LUTS and preventing the progression of LUTS as compared to using either agent alone in men with significant BPH-related LUTS [8]. As with any treatment choice, a balanced discussion regarding the risks of medication including decreased volume of ejaculate, breast tenderness, and rarely ED should be held with the patient.

Although widely used, phytotherapeutics and dietary supplements such as saw palmetto, phytoestrogens, and African plum have not been proven to be effective at preventing or treating BPH-related LUTS. In addition to the lack of clear evidence demonstrating treatment efficacy, there is broad variation in the potency and concentration of such substances which makes it very difficult to track comparisons. The AUA therefore recommends that providers evaluating patients with BPH should not endorse dietary supplements or phytotherapy [5].

Patients who demonstrate evidence of kidney or bladder damage due to BPH, recurrent urinary tract infections, bladder calculi, hematuria, or LUTS refractory to medical management should be considered for treatment with more invasive measures [5]. While transurethral resection of the prostate (TURP) remains the "gold standard" for surgical intervention, a variety of other measures including laser vaporization, endoscopic enucleation, transurethral microwave thermotherapy (TUMT), and transurethral needle ablation (TUNA) have been shown to be effective at treating symptomatic BPH [5,14]. Open prostatectomy is also an effective surgical option; however, it is reserved for extraordinarily large glands [15].

The main thrust of treating BPH is symptom relief and prevention of disease progression; however, emerging evidence demonstrates that there may be ways to prevent BPH and BPH-related LUTS. Although to date there are no recommended preventive measures, modifiable lifestyle factors are linked to BPH and LUTS. Obese men have been shown to be 40% more likely to undergo prostate-related surgery and have a twofold increased risk of reporting LUTS than their nonobese peers [16,17]. Likewise, elevated fasting blood glucose and diabetes are both associated with BPH and BPH-related LUTS [18,19]. In contrast, exercise has been associated with up to 25% risk reduction from developing BPH and LUTS [20]. Therefore, in addition to the numerous other

health benefits of weight loss and physical activity, men may also reduce their risk for BPH and BPH-related LUTS with an active lifestyle.

Prostate Cancer

Accounting for over 25% of new cancer cases in the United States, prostate cancer remains the most commonly diagnosed, non-skin-related, malignancy in American men. The American Cancer Society estimates that in 2010, over 200,000 men will be diagnosed with prostate cancer and over 30,000 will die of their disease [21]. In North American and European countries, the absolute lifetime risk of prostate cancer is ~8% [22]. Clearly, prostate cancer poses a significant threat to male health; however, significant uncertainty remains in how to prevent, diagnose, and treat prostate cancer effectively. This is because there is broad heterogeneity with prostate cancer: low-grade disease behaves in a relatively indolent fashion, while high-grade disease can be expediently lethal. Although there is controversy over its usefulness, serum PSA testing has dramatically changed the diagnosis and treatment of prostate cancer over the past 30 years. In the era of PSA-related prostate cancer screening, most prostate cancers are now diagnosed in the early stage with metastatic disease at initial presentation relatively rare [23].

Age confers the greatest risk for prostate cancer. In the United States, autopsy studies demonstrated that 50% of men aged 50–59 years had microscopic foci of cancer in the prostate and this increased to 75% of men older than 85 years [24]. While the incidence of clinically detected prostate cancer is much lower, very few (<0.1%) patients diagnosed with prostate cancer are younger than 50 years old and about 85% of men diagnosed with prostate cancer are age 65 years or older [25]. In the United States, the risk of a white male being diagnosed with prostate cancer increases from about 2% in the fifth decade, and increases to 6% in the sixth decade and as high as 8% in the seventh decade [21].

Men with a family history of prostate cancer are two to five times more likely to be diagnosed with this disease when compared to the general population. First-degree relatives, namely a father or brother with prostate cancer, double a man's lifetime risk and increasing the likelihood of a younger age at diagnosis. There are also rare forms of hereditary prostate cancer, which can place a man as high as five times the normal risk for prostate cancer [22].

Race also impacts a man's risk for developing prostate cancer. In the United States, the lifetime risk of developing prostate cancer is 18%, or one in five for African American men as compared to white men with a one in six or 15% risk. Furthermore, African American men are almost twice as likely to die from prostate cancer as compared to whites [21]. This is likely due to multiple influences including genetics, socioeconomic status, and environmental factors such as diet and lifestyle, as immigrants of African descent have a different incidence of prostate cancer in other countries [26]. This has also been observed in other races, where Japanese American and Chinese American men have a higher incidence of prostate cancer as compared to their native Japanese and Chinese male counterparts [26]. This observation suggests that the American lifestyle plays a role in the pathogenesis of prostate cancer. Indeed, high-fat diet and obesity have been linked, although indirectly, to an increased incidence or clinical progression of prostate cancer [26,27]. Access to care may also play a role, as those cancers found in African American men are significantly more advanced than those found in a similar population of white men, suggesting that white men are more likely to get screened for prostate cancer [28]. In contrast, men with a Hispanic or Latino, American Indian, Alaskan Native, and Asian or Pacific Islander background living in the United States have a decreased risk of prostate cancer with respect to whites in the United States for reasons which are unclear [21].

Hormonal factors also play a role in the development of prostate cancer. Androgens directly influence the development and growth of the prostate, and although a direct relationship has not been established, there is some evidence suggesting that prostate cancer is related to circulating testosterone levels. In a large longitudinal study, men with testosterone levels in the upper quartile had a 2.6-fold increased risk of developing prostate cancer [29].

As the cost of medical services continues to increase, disease prevention has become a major focus in both health care delivery and industry. Prostate cancer prevention has been the focus of several recent randomized controlled trials with over-the-counter supplements and prescription drugs. Vitamin E, vitamin D, and selenium, all proven antioxidants, have been purported to decrease carcinogenesis by reducing DNA mutation as a result of oxidative stressors [30–32]. However, in a large prospective randomized trial, neither vitamin E nor selenium was shown to be effective at preventing prostate cancer in men at normal risk and there actually may be an increased risk of prostate cancer for patients who take vitamin E [33].

Two different 5-ARIs have been evaluated for their use in prostate cancer prevention. Many investigators rationalized that since these drugs reduced intraprostatic androgen concentration, they may reduce carcinogenesis. Finasteride, a type 2 5-ARI, was shown to decrease the risk of being diagnosed with prostate cancer by almost 25% in a low-risk population of men (aged >55 years with PSA <3.0 ng/dL and a normal DRE). Another more recent trial demonstrated that dutasteride, a nonselective 5-ARI, conferred a 23% relative risk reduction for the diagnosis of prostate cancer [34]. Considerable controversy exists surrounding the overall benefit of chemoprevention of prostate cancer with either dutasteride or finasteride [35]. Although chemoprevention with 5-ARIs may provide a reduction in prostate cancer risk, side effects of these agents include sexual dysfunction, gynecomastia, and possibly an increased risk of cardiovascular events. Furthermore, there was also an increase in the incidence of high-grade prostate cancer in those patients taking finasteride or dutasteride, indicating

that chemoprevention may upgrade indolent cancers into more aggressive disease [33,36].

Despite these two large randomized controlled trials demonstrating that 5-ARIs reduce the risk of prostate cancer, their use in clinical practice is sparse. Over 60% of urologists and 80% of primary care providers do not use them for chemoprevention of prostate cancer [37]. In a joint statement written in 2008, the AUA and American Society of Clinical Oncology (ASCO) concluded that while selective men may benefit from a discussion of the risks and benefits of 5-ARIs for chemoprevention of prostate cancer, no chemoprevention agent could be recommended for widespread use [38]. Until there are further studies demonstrating a reduction in cancer-specific mortality as well as cost-effectiveness, chemoprevention will likely not be a recommended strategy toward the prevention of prostate cancer.

Prostate cancer screening is widely performed by primary practitioners as well as urologists. Screening with serum PSA and DRE, a practice that became pervasive in the early 1990s, has reshaped the landscape of prostate cancer diagnosis. Previously, prostate cancer screening was based on DRE alone, a notoriously poor method of detection, and cancers would often be found at an incurable stage. With the more sensitive PSA testing, there has been an attendant stage migration characterized by an increase in disease confined to the prostate and a decrease in the age at diagnosis [39]. Since the implementation of PSA screening, the lifetime risk of prostate cancer has increased from 9% in 1985 to 17% 2009 [35]. The ramifications of this stage migration have led to the much of the controversy surrounding prostate cancer diagnosis and treatment.

Given the heterogeneity and the widespread prevalence of the disease, many prostate cancers are not clinically significant—in other words, men will die from other causes rather than from their prostate cancer. Also, PSA is not a specific marker for prostate cancer and may be elevated in other conditions such as enlarged prostate, urinary tract infection, and prostatitis. Thus there is a risk for overdiagnosis and overtreatment as well as difficulty interpreting the test results. Two recent randomized controlled trials attempted to address the overall validity of PSA screening by testing its correlation with prostate cancer–specific mortality. The ERSPC, a European-based study, demonstrated that prostate cancer screening with PSA conferred a 20% reduction in the rate of death from prostate cancer; however, the authors concluded that there was significant overdiagnosis and overtreatment to achieve this goal [40]. The U.S.-based study, the prostate cancer portion of the PLCO trial, demonstrated that after 7–10 years of follow-up there was no difference in prostate cancer–specific mortality in men screened with PSA as compared to those who were not screened [41]. The major limitation with each of these trials is the relatively short follow time of <10 years. Since the mortality benefits of PSA screening may not be realized for 15–20 years, these studies may have been too short in their follow-up to specifically evaluate the utility of PSA screening.

The current AUA best practice guidelines for PSA testing recommend that the risks and benefits of prostate cancer screening with PSA testing be discussed with men aged 40 years and over. Those men agreeable to pursue screening should have a baseline PSA checked at 40 years of age as the risk of developing prostate cancer has been linked to baseline PSA level. Patients at higher risk, namely African Americans and those with a family history, should undergo annual screening starting at the age of 45 years. All men should undergo annual prostate cancer screening with PSA, at the age of 50 years [42]. DRE should always accompany serum PSA, as this increases the sensitivity for detecting prostate cancer [42].

PENIS

Erectile Dysfunction

Once thought to be predominantly due to psychological factors, the understanding of erectile has dramatically changed in the past two decades. Now we understand ED to be a complex interplay between vascular, neurological, hormonal, and psychological pathways. Erectile function appears to be an overall barometer for a man's health as data have demonstrated a correlation between self-reported ED and a poor overall perception of one's own health [43]. Whether ED contributes to self-perceived health status or is an end manifestation of systemic disease, it is one of the most common and important issues that can be addressed by the primary care provider.

Normal erectile function relies on a complex interaction between the vascular and neurological network within the penis. The paired penile arteries are the main blood supply to the corpora cavernosa, the erectile bodies of the penis. In the flaccid state, smooth muscle tone within these vessels is high, allowing a low blood flow state. During arousal, parasympathetic nerve input induces release of neurotransmitters such as nitric oxide (NO) that causes smooth muscle dilation within the penile arteries, allowing the corpora cavernosa to fill with blood, and eventual tumescence. In the erect state, the venous outflow is occluded due to the increased blood within the corporal bodies, allowing for the penis to remain erect until ejaculation occurs [44]. Any disease process that affects these pathways has the potential to cause ED.

In the United States, as many as one in four men between the ages of 20 and 75 years have ED and the estimated number of new cases diagnosed annually is over 600,000 per year [43,45]. The prevalence of ED increases with increasing age as only 7% of men up to 29 years have ED in comparison to 18% of men aged 50–59 years [46]. Importantly, the majority of men reporting ED also report other comorbid conditions such as diabetes, hypertension, hyperlipidemia, smoking, or depression [43,47].

Regardless of etiology, the frontline therapy for the treatment of ED has become phosphodiesterase type 5 inhibitors (PDE5i). Under normal conditions, NO is released by parasympathetic nerve endings located within the penile corpora in response to sexual stimulation, which generates the production of cyclic guanosine monophosphate (cGMP), a potent vasodilator. This process initiates and maintains an erection. Phosphodiesterase type 5 degrades cGMP, inducing vascular endothelial contraction, which leads to penile detumescence. PDE5i's inhibit the degradation of cGMP, thus increasing cGMP concentration within the cavernosal arterial endothelium resulting in vasodilation [48]. The AUA best practice guidelines on ED currently recommend that any PDE5i—sildinafil, tadalafil, or vardenafil—be offered as first-line therapy for ED unless patients are unfit for sexual activity or are taking nitrates for chest pain [49].

The link between depression and ED is well established and the two conditions can reinforce each other, making each one more severe [50]. Unfortunately, the mechanism of this interaction has not been well characterized [51]. Men with depression have less desire for and derive less satisfaction with sexual interaction. The lack of libido in these men may also be linked to hypogonadism, suggesting that low testosterone may relate to concomitant depression and ED [51]. Since these two conditions share many of the same symptoms such as fatigue, loss of libido, poor appetite, and dysphoria, a primary care provider may find it useful to check early morning serum testosterone and prolactin levels in men with such complaints.

The use of antidepressant medications has been associated with sexual dysfunction rates as high as 60%–70%, with pure selective serotonin reuptake inhibitors (SSRIs) faring the worst. Although not all sexual dysfunction related to SSRI use is specifically ED, paroxetine has the highest reported ED rate of 40% [52]. SSRI-related sexual dysfunction appears to be dose related, and manipulating the dosage and class of antidepressant medication has been shown to be effective at improving sexual function; however, this should be done with caution as doing so risks antidepressant withdrawal and the relapse of depression [53].

Sildenafil has been shown in several studies to improve SSRI-related ED. Men taking SSRI and sildenafil reported improvement of erectile function similar to men with ED not taking an SSRI [51]. Sildenafil and vardenifil may also be effective in treating men presenting with ED and untreated depressive symptoms. In two trials, men with mild depressive symptoms and ED reported significant improvement in both erectile function as well as depressive symptoms when given a PDE5i [51].

Perhaps the most well-understood cause of ED is cardiovascular disease. The onset of ED has been shown to be an early harbinger of cardiovascular disease, and some clinicians advocate that the discovery of ED during routine evaluation should prompt further cardiovascular evaluation [54]. Obesity, hypertension, heart disease, and diabetes have all been linked to ED [55,56]. Although less clear, other studies have found a correlation between smoking and ED, where smoking may potentiate the effects of other cardiovascular diseases on erectile function [47]. ED has also been linked to other modifiable risk factors such as alcohol consumption and sedentary lifestyle [55].

In addition to hypertension, antihypertensive medication may also lead to ED. β-Blockers appear to be associated with the highest risk, with a relative risk similar to men with untreated hypertension. A potential link between ED and thiazide diuretics for hypertension has been reported; however, this relationship is less established as compared to β-blockers [55,57]. Other medications for hypertension including angiotensin-converting enzyme inhibitors, calcium channel blocker, and α-blockers have not been shown conclusively to be associated with ED [55,57].

Lifestyle modification may also improve erectile function, or at least delay the progression of ED. In obese men with ED, without other cardiovascular risk factors, exercise and dietary modification aimed at weight loss was shown to improve erectile function [58]. Smoking cessation has been shown to improve ED, and appropriate glycemic control in younger patient with type 2 diabetics may also reduce the risk of developing ED [59,60].

The AUA Guidelines in 2005 recommend that men first presenting with ED be tested with morning serum testosterone, complete blood count, blood glucose, lipid levels, and renal function testing [49]. Initial medical therapy, if the patient is fit enough for sexual activity, should consist of any of the PDE5i. There have been no studies to date demonstrating the superiority of one PDE5i over another [44]. Absolute contraindications to PDE5i therapy include use of nitrates, high- or intermediate-risk cardiovascular disease, retinitis pigmentosa, and non-arteritic anterior ischemic optic neuropathy [44]. It may take up to eight uses before a PDEi is effective, and patients who do not respond to treatment may also benefit from discussion on patient and partner expectations as well as reminders on how to properly take the drug [61]. If these measures ultimately fail, referral to a urologist is indicated.

Circumcision

The only absolute indication for circumcision in the adult male is phimosis, a process referring to the inability to retract the foreskin. Relative indications include treatment of balanoposthitis, improved hygiene, prevention of penile cancer, and prevention of HIV transmission and other sexually transmitted diseases [62]. Unfortunately, there are no current evidence-based guidelines advocating circumcision for these conditions. Given that penile cancer is exceedingly rare (especially in industrialized countries), studies designed to show any reduction in its incidence related to circumcision would be very difficult.

Perhaps the strongest support for preventive circumcision is its relationship to the transmission of HIV. Three

randomized studies in Africa have demonstrated that circumcision is effective at reducing the transmission of HIV, where transmission is largely based on heterosexual intercourse. In all trials, risk reduction was over 50% at 2 years of follow-up. Clearly, circumcision does not replace other prevention measure such as abstinence or the use of barrier methods, as there were still many seroconversions in the control arms of each study [63]. In contrast, circumcision in homosexual men has not been clearly shown to decrease HIV transmission [64]. Currently, the U.S. Centers for Disease Control state that evidence is strong enough to inform heterosexual men on the potential benefits of circumcision for HIV prevention; however, it cannot be recommended as a potential benefit for homosexual men until further studies are done [65]. Regardless, conversations about circumcision should be approached with caution, as there is evidence that men may engage in higher risk behavior once circumcised due to an overestimation of the preventive efficacy of this procedure [63,64].

TESTES

Testis Cancer

Testis cancer is the most common solid malignancy in young males, and the incidence has been increasing over the past century. A white male in the United States faces a 1 in 500 lifetime risk of developing testis cancer, almost twice that as it was in the first half of the twentieth century. This trend appears to be increasing as we move into the twenty-first century [66,67]. In contrast, African American males carry a threefold less risk of developing testis cancer as compared to white males; however, African American men are approximately two times more likely to be diagnosed with testis cancer than African men [67].

In addition to racial and environmental influences, cryptorchidism (undescended testis) is thought to contribute to carcinogenesis in the testis [68]. By 6 months of age, both testes should be easily palpable within the scrotum. If the testis is not palpable, or is palpable but retracts into the inguinal canal, it is considered undescended. Orchiopexy is a safe procedure in which the testis is brought down into an anatomical location within the scrotum and should be performed at 6–12 months of age [69]. Until recently, evidence demonstrated that orchiopexy did not reduce the risk of testis cancer for an individual with cryptorchidism; it merely made the affected testes easy to examine [70]. However, a recent study showed that males with cryptorchidism who underwent orchiopexy after puberty were about twice as likely to develop testicular cancer than those who had surgery prior to the age of 13 years [71]. Additionally, patients with a history of undescended testis have a 5%–10% chance of developing testis cancer in the contralateral testis, warranting close follow-up [72].

Testicular microlithiasis, an asymptomatic and largely incidental condition diagnosed by ultrasound and characterized by multiple small echogenic foci within the testicular parenchyma, has also been suggested to be a risk factor for testis cancer [73]. Currently, there is controversy over the exact nature of this association and most experts advocate follow-up including regular physician visits and self-examination. Further testing in men with this condition should be reserved for high-risk patients such as those with infertility, cryptorchidism, or a history of testis cancer [74].

As late as 1970, the mortality rate from testicular cancer was as high as 17%; however, with the advent of multimodal therapy including chemotherapy, surgery, and radiation, testis cancer has one of the highest and most durable cure rates of all malignancies, with an overall survival rate of 96% in 2005 [21]. One of the most important factors in cure, and one in which primary care providers can exert a major influence, is preventing a delay in diagnosis. The most common presenting symptom of testis cancer is a painless lump or swelling of the testicle. Less commonly, patients may show other signs and symptoms including testicular pain, gynecomastia, or systemic manifestations related to distant metastases (e.g., cough due to pulmonary metastases) [75]. Unfortunately, young men may not seek evaluation at the initial onset of symptoms or signs. A delay in diagnosis is associated with more advanced disease as well as an increased risk of cancer-specific mortality. Men who waited more than 6 months after the first onset of their symptoms had a cancer-specific survival of ~85% as compared with those who sought treatment within 3 months of symptom onset who showed a 97% cancer-specific survival at 5 years [76].

Currently, experts do not advocate large-scale screening for testis cancer [77]. However, there is some evidence that patient education and testicular self-examination may lead to early diagnosis [78,79]. It seems prudent, therefore, for the primary care provider to educate young men about testis cancer and the possible benefits of testicular self-examination.

Androgen Deficiency in the Aging Male

Testosterone is a hormone predominantly produced in the testes and is under the regulation of gonadotropin luteinizing hormone (LH), which is secreted from the pituitary gland. Testosterone is responsible for development of secondary sex characteristics in males, and has numerous other effects in the musculoskeletal, nervous, and cardiovascular systems.

As men age, testosterone production decreases. It is now widely recognized that low testosterone, also known as androgen deficiency in the aging male (ADAM), can lead to a variety of symptoms and conditions that may improve with the administration of exogenous testosterone. Unfortunately, there are very few well-conducted studies to direct clinicians in the diagnosis and treatment of ADAM.

The true prevalence of androgen deficiency is not known, but a study borne out of the Massachusetts Male Aging Study predicts that in the United States, 2.4 million men age of 40–69 years likely have ADAM, and rates increase

with age [80]. Furthermore, the rate seems to be increasing with longer life expectancy. Thus, given the widespread prevalence, primary care providers should be familiar with presenting signs and symptoms of this condition. Recognized clinical characteristics of ADAM include ED, low or loss of libido, impaired cognition, depressed mood, fatigue, low hematocrit, increased fat mass, decreased muscle mass, decreased bone mass, and overall diminished quality of life [81].

Unfortunately, many of the signs and symptoms of androgen deficiency overlap with characteristics of other disease processes. There are two questionnaires that have been tested including the Androgen Deficiency in Aging Men questionnaire and the Aging Males' Symptoms Scale that have been shown to have sensitivities of 88% and 96%, and specificities of 60% and 30%, respectively [82,83]. Thus, while these questionnaires are useful screening measures, they fall short of being comprehensive diagnostic tools [84].

Along with a thorough medical history and physical examination, measurement of serum testosterone is a key component in the diagnosis of ADAM. Normal values are based on distributions of age-matched males; however, there may be variability depending on assay. When total testosterone is below 200 ng/dL, patients are most likely hypogonadal, whereas testosterone levels above 400 ng/dL are most consistent with the normal state [85]. Due to circadian rhythmic variations in its production, serum testosterone should be measured between 8:00 a.m. and 11:00 a.m. No other laboratory values are needed in initial testing; however, if testosterone levels are low or below normal, it is useful to recheck testosterone along with serum LH and prolactin [81]. Testicular examination may also be useful, as testis volume below 15 mL may be associated with androgen deficiency [86].

Exogenous testosterone replacement is the mainstay of treatment in men with ADAM. In the United States, several preparations are available. Intramuscular injections and transdermal preparations are the most widely studied and have been shown to be effective, while oral preparations are associated with unreliable hormone levels, aberrant lipid profile, and liver toxicity [81,87,88].

Proven benefits of testosterone replacement include lowered serum low-density lipoprotein, increased muscle mass/decreased fat mass, decreased bone turnover and increased bone density, and improvement of sexual desire and erectile function [89–92]. Furthermore, there is evidence that treatment of the metabolic syndrome with exogenous testosterone improves all associated parameters, namely a decrease in blood pressure, decrease in fasting blood glucose, decrease in abdominal girth, and improvement of serum lipid profiles [93].

The Sexual Medicine Society of North America currently recommends testosterone replacement therapy in men who have signs and symptoms of hypogonadism accompanied by low testosterone levels [94]. Furthermore, some experts suggest a 3-month trial in men demonstrating symptoms but have borderline normal testosterone levels [84]. Currently, there is no established target treatment testosterone level, but experts have recognized that patients with testosterone levels above 400 ng/dL are likely not to be hypogonadal [85]. Patients should be monitored for adverse effects throughout treatment. A baseline assessment of serum lipid profile, liver profile, and complete blood count should be obtained and monitored every 3–6 months after beginning treatment [94]. Furthermore, because testosterone can possibly exacerbate BPH-related LUTS and prostate cancer, DRE and serum PSA should be performed prior to treatment and then every 3–6 months thereafter for 1 year followed by yearly prostate evaluation on patients older than 40 years [94].

BLADDER

Overactive Bladder

The International Continence Society defines the OAB syndrome as "urinary urgency, with or without urge incontinence, usually with frequency and nocturia" [95]. Once thought of as a condition that primarily affected women, a growing body of recent research has identified that a significant proportion of men may suffer from OAB. The prevalence of LUTS suggestive of OAB in men over the age of 18 years old is about 10%, no different from that of women, and the likelihood of diagnosis increases as men age [96,97]. In contrast to women where LUTS are understood to be primarily due to bladder dysfunction, LUTS in men may be due to BPH, OAB, or both [98].

Due to this multifactorial etiology, diagnosis and treatment of men with OAB may be difficult. Currently, data are not robust enough to provide evidence-based guidelines to help clinicians with this condition. In addition to a history and physical examination, a urinalysis should be performed to rule out urinary tract infection, and a post-void residual urine should be checked prior to any treatment, as men who do not empty their bladder should not be started on therapy for OAB, given the risk of urinary retention with anticholinergic agents [98]. The AUA SI may also be a useful tool to assess OAB-related LUTS in men [99]. Within the AUA SI, storage symptoms (daytime frequency, nocturia, and urgency) may be more suggestive of OAB than voiding symptoms (weak stream, hesitancy, straining, and intermittency). However, no objective evidence currently exists to support this [95,99].

As with women, the mainstay of treatment for OAB in men is anticholinergic pharmacotherapy. In an attempt to maximize efficacy and minimize side effects, the use of nonselective anticholinergics such as oxybutinin have been largely supplanted by those agents selective for bladder receptors including tolterodine, solifenacin, fesoterodine, and darifenacin [100]. It appears that anticholinergics are most effective at treating LUTS suggestive of OAB when men have either failed α-blocker therapy or when anticholinergics are used in combination with α-blockers [101,102].

Anticholinergics in men appear to be well tolerated, and adverse effects, including urinary retention, are low in properly selected patients [102]. Further long-term studies are needed to confirm these findings.

Bladder Cancer

Urothelial carcinoma (UC), also known as transitional cell carcinoma, is a neoplastic process arising from the pseudostratified columnar (urothelial cell) epithelium lining the urinary tract. Although UC can occur anywhere in the lining of the urinary tract other than the distal urethra, the bladder is the most common location. The American Cancer Society states that bladder cancer is four times more common in men than in women and accounts for ~7% of all cancers, just behind prostate, lung, and colorectal malignancies [21]. White men are two times more likely to get bladder cancer as compared to African American men; however, African Americans have a significantly higher mortality rate than white men. This does not appear to be due to treatment disparities and the reason for this increased risk of mortality is unclear [103]. In the United States, the most common histotype of bladder cancer is UC, followed by squamous cell carcinoma, which is the most prevalent histotype in the Nile River Valley due to the presence of schistosomiasis.

Tobacco use plays a major role in the development of bladder cancer. Men who smoke are fourfold more likely to develop bladder cancer as compared to men who never smoked. Tobacco use may be responsible for anywhere from 30% to 50% of incident bladder cancer cases. The degree of inhalation and duration of smoking correlate directly with increased risk, while smoking cessation can decrease the risk of bladder cancer by up to 40% at 4 years [104]. The risk of secondhand smoke is less clear. It does not appear to be as important of a risk factor when the exposure happens during adulthood, however could be when exposure occurs during childhood [104–106]. Other less common risk factors include occupational exposure to chemicals including aromatic amines, pelvic irradiation, and exposure to cyclophophamide [107]. Occupations that have been associated with bladder cancer are individuals who work with organic chemicals as well as autoworkers, metalworkers, and machine workers [108,109].

The most common sign of bladder cancer is painless gross hematuria; however, hematuria associated with bladder cancer can be intermittent or microscopic. The AUA Best Practice Statement, written in conjunction with the American Academy of Family Physicians, does not advocate for routine urine screening for blood given that microscopic hematuria can be the result of a variety of different processes, including benign conditions. To date, no data indicate that widespread urinalysis screening for blood is useful, even in the smoking population [110]. Although screening urinalysis is not advocated for bladder cancer, the primary care provider should carefully evaluate microscopic hematuria found on routine examination. If risk factors such as age greater than 40 years, smoking history, irritative voiding symptoms, exposure to industrial chemicals, history of gross hematuria, or history of a urological disorder are present, patients should have a complete evaluation including upper tract imaging of the kidneys and ureters as well as cystoscopy to evaluate the lower urinary tract. Upper tract imaging can include renal ultrasonography, intravenous urography (IVU), computed tomography (CT) urogram, or retrograde pyelography. Although no imaging modality has been shown to be superior, CT urography is emerging as the treatment of choice [111]. Cystoscopy includes complete evaluation of the bladder and urethra, and can be performed by a urologist as an office procedure with minimal risk. Urine cytology should also be collected through a voided specimen or during cystoscopy [110].

The majority of bladder cancers are noninvasive at presentation and most will not progress to locally invasive or metastatic disease in the United States [112]. Although most bladder cancer can be treated with minimally invasive techniques, there is a high propensity for this cancer to recur. Therefore, patients with a history of bladder cancer should have routine long-term follow-up including cystoscopy and upper tract imaging with their urologist [113].

KIDNEY

Urolithiasis

The term urolithiasis refers to stones formed anywhere in the upper or lower urinary tract. Lower urinary tract calculi, namely bladder stones, are predominantly a result of urinary stasis due to incomplete bladder emptying, largely due to bladder outlet obstruction from prostatic growth. As we now have effective ways of managing BPH, the incidence of bladder stones has dramatically decreased. Upper urinary tract calculi are formed in the kidney and can become lodged in the narrow diameter of the ureter. In contrast to lower urinary tract calculi, urinary stasis plays only a minor role in upper tract calculi formation. Other metabolic factors are much more important and will be the focus of this section.

Recent studies estimate that up to 10% of men in the United States will at some point form a kidney stone, a rate at least twice that of females. Stone formation risk increases with age and peaks at the sixth decade of life. Most recently, there appears to be an overall rise in the incidence of stone formation within all age groups in the United States [114]. Morbidity from stone disease can range from minor flank pain requiring oral analgesics to renal failure or life-threatening urosepsis. Annual health care expenditures in the United States for the diagnosis and management of urolithiasis exceed $2 billion [114].

There is little known about primary prevention of kidney stones, since routine imaging on asymptomatic

patients is not usually performed. We can, however, glean information on stone prevention from studies addressing secondary prevention—measures to deter stone formation in patients with a previous episode of urolithiasis. Between 35% and 50% of first-time stone formers will have a repeat episode, making prevention in this population of paramount importance [115]. While all patients with more than one stone episode should be followed by an urologist, primary care providers can help identify risk factors for stone disease and assist patients in preventive lifestyle changes.

Fluid intake is one of the most important modifiable risk factors in kidney stone formation. Randomized studies have shown that fluid intake of 3 L/day or taking in enough fluid to produce >2.5 L of urine per day can reduce the risk of stone recurrence by over 50% when patients are followed for up to 5 years after their initial stone episode [116].

The type of fluid may influence stone formation as well. Stone-forming patients who decrease the amount of soft drinks they consume, particularly those that are acidified by phosphoric acid such as colas, likely decrease their risk of stone recurrence by about 30% [117]. In contrast, increasing liquids high in citrate content, particularly lemonade, may prevent stone recurrence. Lemonade intake has been demonstrated to increase urinary citrate, which is known to prevent stone formation; however, better studies are needed to confirm a direct link between lemonade consumption and decreased stone formation [118,119].

The concomitant increase of stone disease and obesity has led many researchers to investigate a link between the two conditions. Although there have not been any large longitudinal studies performed to date, retrospective analysis strongly suggests that obesity is a risk factor for stone formation. One study demonstrated that patients with a body mass index (BMI) over 30 kg/m^2 had a twofold increased risk in developing symptomatic nephrolithiasis [120]. Although the pathophysiological mechanism is not clear, some studies suggest that an increase in BMI leads to a decrease in urine pH which is a major risk factor for multiple different types of kidney stones [121]. It stands to reason that weight loss would reduce the risk of stone formation; however, to date there has been no published evidence to support such a preventive measure.

While weight gain likely induces metabolic changes leading to increased risk for stone formation, surgically induced weight loss measures can also place patients at a higher risk for developing urolithiasis. Patients who undergo Roux-en-Y gastric bypass have a 1.7-fold increased risk of stone formation due to increased absorption of oxalate through the gut [122]. This leads to hyperoxaluria (increased urinary oxalate) and hypocitraturia (decreased urine citrate), both risk factors for the development of kidney stones [123]. Gastric banding for weight loss may not be associated with the same risk of increased urinary oxalate and decreased urinary citrate after Roux-en-Y gastric bypass; however, further studies are needed to confirm this [124].

Kidney Cancer

Renal cell carcinoma (RCC) is the most common malignant neoplasm of the kidney, and one of the more lethal urological cancers. Historically, RCC commonly presented with the classic triad of flank pain, hematuria, and a palpable abdominal mass, and this uniformly represented advanced disease. Fortunately, this is rarely observed today. The proliferation of abdominal imaging with CT and magnetic resonance imaging (MRI) has led to a stage migration, with the majority of RCC diagnosed in the United States at a clinically localized stage [125,126]. Concomitant with this stage migration is an increase in the incidence of RCC and a decrease in its mortality rate [127].

Risk factors for RCC include familial cancer syndromes, hypertension, obesity, and smoking. Familial cancer syndromes including Birt–Hogg–Dube syndrome, hereditary papillary renal carcinoma, hereditary leiomyomatosis, and most commonly von Hippel–Lindau syndrome are associated with RCC [128]. There appears to be a dose–response relationship with developing RCC and the comorbid conditions of hypertension and obesity. Fortunately, controlling hypertension appears to reverse this risk, while it is unclear whether weight loss can do the same [129]. Likewise, there is likely a dose-dependent relationship with exposure to tobacco. Very little evidence exists to attest to a decrease in risk with smoking cessation; however, if smoking cessation does modify risk, it likely does not do so until 10 years from cessation. No definitive studies have shown a link between RCC and passive smoke inhalation [130].

There are currently no recommended screening modalities for RCC; however, some incidental renal masses may be followed conservatively. Most small renal malignancies have a slow growth rate (about 3 mm/year) as well as a low risk of metastasis (1%–2%). Clinical stage T1 renal masses, in particular those under 4 cm, may be cautiously watched with serial CT scans in patients who are not surgical candidates or do not desire surgery [131]. The primary treatment modality for RCC, especially clinically localized disease, is surgical resection of the kidney, as RCC is refractory to radiotherapy and currently available chemotherapeutic agents [131]. Surgical cure rates for clinical stage 1 disease (<7 cm with no nodal involvement) exceed 90% with either radical or partial nephrectomy. Laparoscopic radical nephrectomy has been shown to be effective at managing clinically localized disease and is less morbid than open radical nephrectomy [132]. However, recent studies have suggested that radical nephrectomy may place patients at higher risk for developing chronic kidney disease; thus nephron surgery (i.e., partial nephrectomy) should be performed whenever possible [131,133]. While open partial nephrectomy remains the treatment of choice, laparoscopic approach, including robotic-assisted partial nephrectomy, appears to have similar success rates in the hands of experienced surgeons [131,134].

APPENDIX A: THE AUA SYMPTOM INDEX

Patient Name:_____ DOB:_____ ID:_____ Date of assessment:_____

Initial Assessment() Monitor during:_____ Therapy () after:_____ Therapy/surgery ()_____

AUA BPH Symptom Score

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 or more times	
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
						Total Symptom Score	

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32 Health Promotion and Risk Reduction in Men

Lisa Terre, PhD

CONTENTS

Gender Socialization 405
Symptom Reporting and Health care Utilization 406
Stress and Coping 407
Substance Use Behaviors 407
Smoking 407
Alcohol 408
Dietary Habits and Weight Regulation 409
Eating Attitudes and Practices 409
Obesity 410
Physical Activity, Sports-Related Injury, and Body Dissatisfaction 410
Men's Exercise Prevalence 410
Sports-Related Injuries 411
Body Dissatisfaction 411
Maintaining Active Lifestyles 411
Conclusion 412
References 412

The past several decades have witnessed escalating public health concern about the status of men's health. Reflecting this growing alarm, discussions about the hazards of masculinity have grown increasingly high pitched.[1–11] This state of alert is not without merit. Indeed, most health metrics reveal a decided masculine disadvantage, marked by high risk, morbidity, and premature death.[12–15] Unfortunately, this "live fast, die young" pattern shows no sign of ameliorating any time soon.[8,13–26]

Although research has only just begun to unravel the complex web of contributing dynamics, crosscutting biological, psychological, and social forces all have been implicated. Nevertheless, evidence increasingly highlights the primacy of lifestyle behaviors.[1–4,9,10,14,17,26] Accordingly, this chapter considers evidence-based perspectives on the health-promoting and risk-reducing behaviors that affect men's health.

GENDER SOCIALIZATION

Among the many influences on men's health-related lifestyles, probably none has been more widely discussed than masculine socialization. Most cultures provide a basic blueprint for the differential socialization of boys and girls, the precise contours and boundaries of which vary across communities and cohorts. These cultural imperatives set acceptability limits for certain socially constructed gender roles.[1–4,27–32] Through a confluence of interacting forces, these stereotypes are inculcated through social modeling and direct reinforcement of sex-typed behaviors that are progressively shaped across development.[3,27,28,30,33] Because these societal ideals are telegraphed in various ways, through myriad communication channels, and interpreted through each man's idiosyncratic biopsychosocial filter, the incorporation and enactment of these collective values differ considerably.[28,33–38] Through the intricacies of this socialization process, each man's "masculine identity" evolves based on a multidimensional set of gendered schema encompassing, for instance, subjective satisfaction with his masculine gender, perceived pressure for masculine gender conformity, self-appraised congruence with masculine stereotypes, and salience of masculinity to his broader self-concept, just to name a few[28,38–40] (see Tobin et al.[38] for a recent review). Interestingly, each potentially orthogonal facet of this masculinity multiplex may have different health implications.[32,33,35,38–40]

As noted earlier, background characteristics (e.g., ethnicity, social class, age, biological attributes, etc.), other life roles, and concurrent identities add further heterogeneity to men's conceptualizations of masculinity, the behavioral idioms through which they are expressed, and their repercussions on health.[10,19,31,41–55] As an illustrative case in point, masculine health risk disparities are especially acute among socially disenfranchised men (e.g., low SES, ethnic and sexual minorities).[12,56–66] Likewise, across the life span, masculinity may pose in different guises based on cohort

effects, shifting developmental influences, contemporaneous life experiences, and perceived norms.[19,32,36,53,54,67–75] Consequently, averaged data purporting to describe men's health, masculinity, or socialization will not accurately capture the experience of every man.[41,44,52,53,68–70]

Notwithstanding widespread acknowledgment of men's heterogeneity, considerable study has been devoted to elucidating normative trends in gender development.[33–36,38,76,77] Although a comprehensive review of the extensive gender development literature is beyond the scope of this chapter, it generally is accepted that gender role contingencies are ubiquitous very early in life. For instance, male baby shower announcements, nursery decorations, and birth congratulation cards commonly are illustrated with sports designs and other action patterns whereas those for girls often are decorated in muted tones with passive silhouettes and delicate accessories.[27,30,78,79] Throughout early childhood, these gender scripts become more fully articulated in the context of daily life, as sex-typed conduct and attitudes are progressively incentivized and rewarded.[27,30,76]

For example, despite some incongruous findings,[76,77,80] differences have been reported in parenting behavior as a function of child gender. Illustratively, during infancy, boys may be handled more robustly than girls.[3,79,81] In the preschool years, independence, aggression, and risk behaviors may be tolerated more in boys than girls (for whom safety and hygiene often are prioritized).[27,29,30,79,82] Moreover, some parents may be more likely to encourage active problem solving and the inhibition of expressed vulnerability (such as feelings of dependency, fear, and anxiety) in male versus female children.[29,82–84] Through repeated exposure to these and other gendered contingencies, socially constructed masculine norms gradually become internalized, at least to some extent.[27,29,79,82]

Beyond the family, peers play an especially pivotal role. Consistent with the concrete cognitive processes and rule-governed behavior characteristic of early childhood, elementary school students' gender stereotypes often appear somewhat exaggerated and rigidly held.[81,35–38,85] During these early years, sex aggregation in peer relationships typically becomes evident as boys' and girls' interests and play patterns diverge.[35,36,76,86] In contrast to girls' more interpersonal priorities, boys are more likely to prefer competitive group activities (e.g., sports, games) that provide an opportunity for demonstrating competence and status in the male group hierarchy.[27,33,76,77,86] In this regard, boys may be especially prone to prefer more strongly sex-typed peers and to penalize gender nonconformity in their social groups.[27,29,30,33,82,87] This developmental phase of same-sex propinquity provides important opportunities to rehearse basic masculinity scripts as a scaffold for subsequent elaborations.[27,76,77,86]

During adolescence, converging biopsychosocial processes (e.g., changing physiology and appearance, reorganization of social roles and family relationships) set in motion cascading demands for readjustment. Chief among these developmental tasks is identity formation. At this time, social networks typically expand to include more opposite-sex relationships, providing chances to try on different masculine roles for goodness-of-fit with broader self-conceptualizations still under construction. Often, the aspects of masculinity adopted during adolescence reflect both continuities and discontinuities with earlier development,[33,34,76,77,88] yielding an individualized, but still evolving, pattern of masculine ideals with the potential to color health appraisals and decisions for better or worse.[1–4,32–34,38,64,89]

Contrary to the popular emphasis on masculinity's downside risks, research has started to accentuate the potential benefits of traditional masculine socialization. Illustratively, stereotypical orientations toward achievement, self-reliance, and persistence may be used adaptively in the service of promoting men's illness coping, recovery, and empowerment for important self-care regimens.[44,48,63–65,67,90] These recent findings have suggested it is not masculinity per se that may be detrimental to health but rather the specific configuration of masculine attributes that may differentially predict health vs. harm.[19,32,63–65,67,90] It is to this topic that the discussion now turns.

SYMPTOM REPORTING AND HEALTH CARE UTILIZATION

Men's general tendencies to minimize somatic and emotional symptoms have been widely discussed and reported. Indeed, caricatures of traditional masculinity often center on notions of "toughing out," "manning up," or otherwise projecting an image of strength and invulnerability.[82,91–94] For instance, although men generally demonstrate high tolerance to a range of noxious stimuli (perhaps based on complex interactions of biopsychosocial mechanisms),[91,92,95–98] men adopting traditional masculine identities may be most likely to minimize symptoms, especially in the presence of women.[99,100]

A corollary of this idealized toughness is a parallel tendency to eschew wellness and preventive self-care as excessively feminine.[2,4,10,21,22,24,101] An illustrative case in point is men's suboptimal adherence to preventive cancer recommendations ranging from screening to early intervention for incipient symptoms, all of which exact a high toll on cancer survival.[16,18,20,25] To the extent that perceived vulnerability is a critical prerequisite to self-care, the need to defend an invincible self- and public image may interfere with the adoption of preventive health practices, perception of emerging symptoms, and likelihood of professional consultation.[16,17,25,102]

This tendency to avoid help seeking is epitomized by recent data indicating that many men have no regular health care provider and do not access health services regularly.[14] For example, results of the 2009 National Health Interview Survey[14] revealed that 22% of men (vs. 12% of women) reported having no usual place of health care and 26% (vs. 13% of women) had no office visits in the last year. Among those identifying a regular health care venue, men were more inclined to use hospital emergency rooms or outpatient departments than women.[14]

Men not only have less frequent contact with health practitioners, but also may be less active participants in

patient–provider exchanges (e.g., requesting less information, clarification, and advice) than their female peers. Perhaps as a consequence, men may receive less professional guidance on health-relevant matters, including lifestyle.[103–108] In addition, at least some men may face special barriers acknowledging emotional problems and accessing psychological services, even for common concerns such as substance abuse, depressed mood, and interpersonal difficulties.[21,70,109–112]

Beyond the social stigma still associated with psychological issues generally, some men may perceive psychological interventions as especially off-putting given their learned penchant (based on parental admonitions, peer censorship, and media images) to privilege action over feeling.[21,70,109–116] Accordingly, targeted outreach efforts increasingly seek to breach the traditional wall between help seeking and masculinity.[16,19,20,25,49,94,116–119]

As an interesting marquee case, the National Institute of Mental Health (NIMH)-sponsored "Real Men, Real Depression Campaign" provides education about aspects of depression relevant to some men (e.g., substance abuse, risky sexual practices, aggression/violence) and peer models of diverse men sharing their experiences and treatment for mood disorders.[110,120] By helping to reshape perceived masculine norms, these kinds of social marketing approaches help promote a masculine ethos of acceptance for addressing health concerns. However, unless these types of broad-based initiatives are coordinated with more customized approaches, the benefits of reaching "every man" could be offset by a proper fit for none.[11,49,93,94,97,110,116,120]

STRESS AND COPING

Although the health-detrimental consequences of chronic life stress are well documented, the influence of individual appraisal and management strategies often is underappreciated.[121–125] Given the typical discrepancies between men's and women's lived experiences, it is not surprising that gender may mediate stress appraisal and reactivity.[126–129]

Early in development, masculine child-rearing patterns tend to incentivize the acquisition of active problem-solving skills over those related to emotional processing and communication.[77,83,130] Other socialization experiences (e.g., peers, media) reinforce this traditional masculine propensity in which agency figures prominently and emotionality is constrained.[29,84,116,130] These motivational priorities differentially heighten the salience of certain cues such that perceived threats to mastery or social dominance may be appraised as especially stressful, provoking a cascade of psychoneuroimmunological dysregulations. Paradoxically, masculine tendencies to inhibit stress-related emotionality actually may heighten physiological arousal and risk of externalizing behavior problems (discussed later).[29,77,84,89,130] By comparison, traditionally socialized women may be somewhat more likely to appraise perceived challenges to interpersonal relationships and intimacy as particularly stressful.[27,131]

In addition to biasing attention and responsiveness to certain cues, socialization experiences contribute to the management of stress-related demands. Although the coping repertoires of most well-adjusted individuals contain assorted strategies applied flexibly depending on the situational vagaries, certain gendered coping propensities have been reported in the literature.[77,128,132–136]

One of the most robust findings centers on the use of social support. Specifically, during stressful transactions, men seem especially prone to react with "fight or flight" (i.e., active interpersonal aggression or distancing to defer hostilities), perhaps in part based on men's learning histories in which emotional displays of vulnerability were ridiculed as excessively feminine.[29,77,84,137] By comparison, women may favor a "tend and befriend"[136] strategy, in which nurturing relationships are sought out and emotions are shared.

Both approaches offer potential advantages and disadvantages.[77,134,136,137] For example, active problem solving that provides relief from negative emotional processing may be associated with a more rapid stress response and recovery compared to passive rumination about upsetting circumstances and emotions, which may prolong distress.[77,126,127,132,134,137–144] However, the benefits of emotional distancing may come at the expense of social support's potentially health-enhancing effects.[132,145–147]

Specifically, because men typically have more superficial social networks than their female counterparts, men tend to have fewer intimate support resources. Indeed, for many men, a spouse or romantic partner may be the only or primary source of sustained encouragement and inspiration for healthier lifestyle choices.[77,148–152] Consequently, partner support has been a somewhat better predictor of men's physical and emotional well-being than that of women. However, it is worth noting that some mixed findings and cohort differences recently have been observed, perhaps reflecting a narrowing of gender-differentiated social roles and expectations among younger groups.[77,136,148,150–152]

Interestingly, these gendered coping tendencies have been associated with disparate risk and resilience trajectories. To the extent that active coping boosts self-efficacy and perceived control, prototypically masculine agentic orientations may bode well for certain types of psychological and somatic well-being (e.g., reduced probability of depression and anxiety, better odds of chronic disease adjustment).[71,134,139,141,144] At the same time, however, the tendency to act out during stressful encounters may contribute to men's heightened risk for externalizing problems such as disruptive, aggressive, and other antisocial behaviors, especially among those adhering to traditional masculine roles.[2,10,29,53,77,89,130,134,137,153–156]

SUBSTANCE USE BEHAVIORS

Smoking

Abundant evidence documents the significant morbidity and mortality associated with smoking.[157,158] Despite the incessant public dissemination of these risks, 23% of men still smoke.[14,26] In addition, men are prone to engage in especially hazardous patterns of use with high levels of

dependence.[14,159–161] According to recent data from the Centers for Disease Control (CDC), men not only smoke more cigarettes per day (7% of men vs. 3% of women usually smoke ≥35 cigarettes per smoking day) but also typically initiate the habit earlier, with more than one-third starting before the age of 16 years (35.1% of men vs. 28.5% of women).[14,26]

Accordingly, considerable scientific effort has been dedicated to pinpointing sex-typed mechanisms of tobacco initiation, dependence, and cessation. Although multiple age-related smoking trajectories have been identified based on complicated biopsychosocial interactions, research has highlighted social influence processes as especially critical components of smoking onset, particularly during adolescence when emerging masculinity scripts may combine synergistically with normative developmental tendencies toward impulsivity and sensation seeking to heighten men's smoking susceptibilities.[158,162,163] These propensities may be further incentivized and reinforced by the smoking habits of personally relevant models (e.g., family members, peers, and media celebrities).[74,162] For instance, popular media that subtly glamorize smoking shape not only the masculine cultural zeitgeist but also individual opinions, expectancies, and perceived norms toward smoking acceptance.[74]

Indeed such collective pressures have been identified as among the most potent risk factors for smoking initiation and progression, probably exerting their influences through a variety of mechanisms.[66,162,164] For example, to the extent that smoking is perceived as more or less culturally acceptable, an individual smoker's social status may shift either toward or away from the mainstream.[164,165] In addition, the smoking behaviors of intimate others (e.g., partners, roommates) also provide proximal cues that may prompt experimentation among the uninitiated or trigger smoking urges among current or former smokers, thereby foiling individual quit intentions and self-regulation efforts.[149,164,165]

Galvanized by substantial evidence that creating a norm of nonacceptance actually facilitates risk reduction, masculine smoking portrayals increasingly have been appropriated in the service of abstention and cessation.[74,166] Some especially interesting recent initiatives have capitalized on the masculine archetype of "father as family protector" to motivate men's smoking cessation prior to the impending birth of a child.[167,168] Although much of this work remains preliminary, life transitions often present teachable moments that enhance receptivity to lifestyle modification advice, as seen in smoking cessation interventions with pregnant women either alone or with their partners.[73,167–171]

However, much more remains to be learned about the potential interpersonal transmission of smoking processes.[149,164,165] To the extent that male audiences may be somewhat harder to reach professionally[158,172] (as discussed earlier), combined with empirical hints that men's smoking attitudes and behaviors may be especially influenced by the smoking status of significant women in their lives (e.g., romantic partners or supportive female peers),[173,174] women who either do not smoke or have quit with professional assistance may be well positioned to support men's abstinence or cessation efforts.[158,173,174]

Yet, emerging findings have sounded a cautionary note. Specifically, the beneficial effects of partner support may depend on men's perceptions of their significant others' intentions. Partner behaviors that are perceived as collaborative and encouraging of men's self-control skills and self-efficacy have been shown to enhance healthy behavior change, whereas partner behaviors appraised as coercive or overprotective actually may yield counterproductive outcomes, perhaps by triggering resistance and/or by spiking perceived self-efficacy.[102,175] In short, although dyadic approaches hold considerable promise, the nuances inherent in couples support demand more rigorous study.[164,172,173]

Beyond collective dynamics, considerable interest has focused on potential intrapersonal sources of smoking disparities given the myriad biopsychosocial differences that potentially could impact sex-typed tobacco dependence and cessation processes. Unfortunately, despite the proliferation of studies, few actionable mediators consistently have emerged to date.

For instance, although gender differences in smoking motivations, relative strength of different relapse cues, and cessation barriers all have been reported, these gender differences have not consistently predicted treatment outcome or relapse.[157–160,176–179] Moreover, despite some suggestions that men may have higher rates of successful cessation and may benefit more from nicotine replacement than their female counterparts,[157,160,176–179] the preponderance of available evidence has highlighted roughly comparable treatment outcomes between men and women.[157,159,161]

Consequently, even though sensitivity to gender-specific concerns and barriers is an important clinical consideration for enhancing perceived treatment relevance,[157] gender per se may not be the most robust predictor of outcome. For this reason, growing research interest has coalesced around the advantages of redirecting interventions away from umbrella variables such as gender in favor of more proximal predictors such as specific tobacco-dependent behaviors (e.g., time to first cigarette, previous quit attempts, number of cigarettes smoked each day) and cognitive-behavioral change processes (e.g., stage of change, self-efficacy, and smoking expectancies).[157,158,161,163]

Alcohol

According to the CDC, alcohol-induced morbidity and mortality are on the rise in the United States. In 2007, 23,199 U.S. deaths were alcohol-induced, representing a 4.3% increase over 2006. Compared to their female counterparts, men's 2007 age-adjusted rates of alcohol-induced mortality were 3.2 times higher.[15]

Men's hazardous drinking (including excessive use and binge drinking) raises their odds for alcohol dependence (17% men vs. 8% women) and scores of associated problems as reflected in more alcohol-related hospitalizations, injuries (resulting from traffic crashes, physical assaults, etc.), and disproportionate rates of certain alcohol-linked sequelae (e.g., reproductive and sexual dysfunction, cancer of the

mouth, throat, esophagus, liver, and colon).[26,180–185] Because the topic of this chapter centers on lifestyle, the scope is intentionally focused on modifiable risk and protective factors, notwithstanding widespread recognition that a full appreciation of men's risks requires consideration of complicated biopsychosocial synergies including sex differences in alcohol pharmacokinetics and genetics.[186–188]

Suffice it to say, no single set of risk factors uniquely predicts specific alcohol use disorders (AUDs) in all men. Confirming suspicions based on the clinical heterogeneity long-observed among AUDs, evidence increasingly highlights multiple alcohol trajectories across development based on individualized risk–resilience patterning. Although a variety of nonspecific liabilities have been identified (including genetic and neurobiological markers, positive alcohol expectancies, and personality traits such as impulsivity and antisociality), others may be especially relevant to AUD pathways in men.[184,185,189]

Interestingly, in contrast to the gender disparities reflected in adult AUD prevalence data (discussed earlier), alcohol experimentation rates and patterns typically appear roughly comparable between early adolescent males and females. However, as youth negotiate the developmental transition from adolescence into early adulthood, gender-specific trajectories become more pronounced, paralleling socialization influences that may heighten men's risks for excessive alcohol use.[184,185,190,191] As an example, alcohol use is seen as a culturally normative part of traditional masculinity that is modeled pervasively (e.g., media, family, peers) and rewarded by social contingencies that typically tolerate more alcohol use in men versus women.[74,162,192] Because parents tend to allow boys more autonomy with looser monitoring than that of their sisters, boys may have earlier opportunities for unsupervised alcohol access. In addition, given the masculine cultural norms discussed previously, boys may experience more peer encouragement for risky alcohol use and suffer less general social censure for excessive drinking. Hence, compared to the potentially restraining influence of cultural admonitions that stigmatize women's overconsumption (especially in public), social contingencies may exacerbate risk for men with other biopsychosocial vulnerabilities.[49,184,185,193–195] Although some of these cultural risks may attenuate as masculinity scripts become progressively diverse and social changes continue to soften gender role boundaries,[88,182] tackling the problem of alcohol misuse will require a coordinated multidisciplinary "effort of societal change … [that addresses] alcohol use early, continuously, and in the context of human development using a systematic approach that spans childhood through adolescence into adulthood." (Ref. [191, pp. iii–vii]).

DIETARY HABITS AND WEIGHT REGULATION

Eating Attitudes and Practices

Imprudent dietary habits confer significant health risks across the life span, adversely impacting most leading causes of morbidity and mortality, including cardiometabolic diseases (e.g., hypertension, heart disease, stroke, diabetes) and certain cancers.[75,196,197] In yet another bid to foster more mindful eating habits, the CDC has renewed its continuing outreach efforts with a recent publicity surge imploring Americans to more carefully consider their food selections and portion sizes.[198] Unfortunately, imprudent food-related habits and their associated repercussions are not showing much improvement, especially among men.[75,196,199–201]

Evidence has long suggested that men's eating attitudes and practices tend to be less health promoting than those of their female counterparts.[5,75,196,202] By and large, men acknowledge the benefits of healthy eating, but often claim less interest in food matters generally and nutrition in particular compared with other food selection criteria (such as taste and convenience). Accordingly, men's eating patterns may tilt more toward palatable but unhealthy choices translating into disproportionate intakes of unhealthy fats and sodium relative to fruits, vegetables, and fiber.[5,75,196,202,203]

Consistent with the observations that men may be somewhat less focused than women on curbing their intakes of palatable but unhealthy food, preliminary brain research has indicated that exposure to high-calorie images (e.g., waffles with whipped cream and syrup, chocolate cake) provokes more heightened cortical responding in the cognitive processing/behavioral control regions of women than men.[204,205] Moreover, some reports also have raised the possibility that men may be somewhat less inclined to alter eating habits in response to medical issues (e.g., gastrointestinal problems, overweight, and obesity), even when such modifications offer symptom relief.[75,206,207]

To be sure, myriad factors jointly contribute to men's food-relevant attitudes and practices. However, the most frequently discussed centers on cultural influences. For instance, given that meal planning and preparation traditionally have been considered part of women's domestic work, traditionally socialized men may not see these activities as within their domain of interest or responsibility. In a similar vein, the notion of carefully measured portion sizes ("eating light") has a decidedly delicate flair that runs counter to the stereotype of hardy meals suitable for hardworking men ("man-sized").[5,75,203,208] This masculine idiom is animated by ubiquitous media depictions of men displaying immoderate eating behaviors without the real-world, health-detrimental repercussions.[74,75]

Although not specifically male-focused at the present time, extant evidence has highlighted psychological mediators of eating habits and change processes that may inform research on gender differences. For instance, accumulating findings have suggested that emotional and cognitive styles may predict differential attentiveness and responsiveness to health communications. Specifically, fear (and its associated risk-centered perceptions) may heighten the salience of potential threats and receptiveness to appeals framed in terms of loss. In contrast, anger (and related perceptions involving personal control) may bias attention more toward potential rewards, thereby increasing responsiveness to messages emphasizing potential gain.[209] To the extent that traditionally

socialized men (vs. women) may be more inclined toward anger (vs. anxiety, as discussed earlier), there may be some merit to further investigating the potential impact of gender role on reactions to different food-related messages.

Other separate but relevant research has indicated that food perceptions and expectations about calorie content may be associated with altered metabolic responses. As an illustrative case in point, Crum and colleagues recently reported distinctive ghrelin hormone profiles mediated by expectancies about the nutritional content of two identical milk shakes (labeled high-fat, high-calorie "indulgent" or low-fat, low-calorie "sensible"). These findings raise the possibility that food labels touting an item's healthful qualities actually may have the downside potential of reducing perceived satiation and increasing intake.[210,211] These findings are especially provocative when taken together with evidence (discussed earlier) suggesting that at least some men may be prepared to favor food's flavor qualities over its health attributes.

Obesity

The ominous public health implications of imprudent dietary attitudes and practices are conspicuously embodied in the skyrocketing trajectory of men's obesity and related cardiometabolic comorbidities, the risks of which climb with body mass index (BMI).[199,200] Unfortunately, because men may be especially prone to accumulate fat intra-abdominally, their BMI-associated health risks may be further exacerbated.[206,212] Yet, only about 30% of men's BMIs fall within the "healthy" range (BMI ≥18.5 to <25).[14]

Notwithstanding men's high prevalence of overweight and obesity (averaging roughly 42% and 28%, respectively, with substantial variation by race/ethnicity),[14] some men may be reluctant to participate in weight control interventions. This hesitancy may be partially rooted in men's general disinclination to seek help.[94,110,114–116] However, the traditionally feminine clientele and thrust of many programs also may contribute.[206,212] In response to these potential barriers, some preliminary reports tentatively have suggested that tailoring interventions to men's specific weight concerns may increase participation rates. For instance, program features such as men-only groups held in alternative settings (e.g., workplace, gyms, male-oriented practices) promoting "masculine" goals (such as muscularity, strength, and performance) may be especially well received.[75,196,203,206,208,212] To the degree that these kinds of masculine trappings enhance perceived relevance and appeal, they may serve an important foot-in-the-door function for men who would otherwise not access professional services. However, the real measure of their potential benefit ultimately will depend on the extent to which these "male-friendly" programs actually help men achieve and sustain healthy weight regulation.

Regrettably, converging evidence has indicated that individual approaches alone may not be the most cost-effective strategies for slowing obesity's progression given the omnipresent cues for overindulgence and underactivity that saturate modern life.[200,201,213–216] Considering that an accumulation of small lifestyle corrections can translate into clinically meaningful cardiometabolic improvements, coordinated multilevel approaches (from the individual to the ecological) are being advocated to consistently incentivize more healthy eating habits across multiple life domains.[199,212,215,217–221]

PHYSICAL ACTIVITY, SPORTS-RELATED INJURY, AND BODY DISSATISFACTION

The benefits of regular physical activity have been well established across the intervention spectrum from primary prevention efforts promoting population-wide health to secondary and tertiary care aimed at reducing risks and optimizing the management of chronic conditions (including cardiovascular disease, cancer, multiple sclerosis, psychological distress, age-related cognitive and mobility decline).[222–236]

Men's Exercise Prevalence

Generally speaking, men tend to be somewhat more active than women overall.[14,237] However, too few American men consistently maintain optimal exercise amounts and levels.[232,238–240] Although precise prevalence estimates vary depending on the specific criteria, recent CDC data indicate that only about one-third of adult men *regularly* engage in leisure-time exercise (operationalized as light–moderate activity ≥5 times/week on average for ≥30 min or vigorous activity ≥3 times/week for ≥20 min)[26] and half *never* engage in bouts of vigorous activity ≥10 min/week.[14]

Exercise prevalence is highest among young adult (18- to 24-year-old) Caucasian men compared to those who are older, ethnic/cultural minorities, and/or members of other socially disenfranchised groups.[14,26] For instance, probability of leisure-time physical activity consistently covaries with education and income such that men ranked in the highest SES categories are the most likely exercisers.[14,26]

Of course, physical activity patterns are complexly influenced by myriad biopsychosocial factors that may shift across the life span. However, athletic prowess (especially in competitive body contact sports) figures prominently in men's socialization as a critical part of traditional masculine identity.[3,241]

Boys' socialization toward vigorous activity begins early in the family, where activity preferences and habits are incentivized and shaped through direct experiences and observations of significant others' behaviors and attitudes.[27,33,76,77,242–245] Indeed, boys typically receive more parental encouragement for sports involvement than their sisters.[242,243] Depending on each boy's adoption of traditional masculine ideals (discussed earlier), these early familial experiences bolstered by broader social contingencies throughout childhood and adolescence (e.g., peers, media, etc.) may contribute to boys' generally higher exercise self-efficacy, which predicts actual activity levels.[24,241,242,244,246,247] Interestingly, social support for exercise may be a stable feature of men's lives well into adulthood, which could at least partially contribute to men's relative activity advantage.[248]

Sports-Related Injuries

Despite the benefits of physical activity, dominant competitive norms may increase men's susceptibilities to certain sports-related hazards. One of the most actively researched and discussed has been the relationship between masculinity and sports injury risk. Consistent with men's generally higher rates of unintentional injury across the life span,[30] masculine competitive propensities in body contact sports may heighten the probability of sustaining serious high-impact injuries (including head, neck, spine, joint, ligament damage) and their sequelae (such as post-concussive syndromes).[249–258]

Body Dissatisfaction

Adding to competitive masculine pressures, shifting cultural conceptualizations of the ideal physique may be pushing the desire for muscularity to unhealthy levels.[259,260] As the gap broadens between the typical and idealized appearance of a healthy male body, the odds of body dissatisfaction escalate along with related problems such as psychological distress (e.g., manifested as low self-esteem, mood problems, dysfunctional eating) and unintended consequences of harmful body-sculpting strategies (e.g., excessive exercise, use of anabolic–androgenic steroids, imprudent dietary practices, and unapproved supplement use).[208,261–265] In this regard, numerous studies have observed a recent trend toward body dissatisfaction and body image concerns among boys and men, with some suggestion that boys' efforts to attain a lean, muscular body may be evident as soon as the early elementary school years.[261–266]

Although just beginning to emerge, research tracking predictors of youngsters' body dissatisfaction have explored a variety of potential influences including social (e.g., demographic, familial, peer, and other contextual characteristics), psychological (personality attributes, cognitive biases, internalization of cultural appearance ideals, propensity toward social comparison), and biological (e.g., body mass) factors.[263,265,267] Unfortunately, because studies have differed in participants' ages, predictors examined, and the length of follow-up, it is difficult to trace a conclusive path at the present time. However, consistent with broader life span literature, longer studies tentatively have suggested a shifting pattern of risk and resilience as youth navigate through different developmental periods.[263] Taken together, converging evidence underscores the importance of introducing young men to the advantages of health-promoting exercise goals over more misguided priorities, including evidence-based, customized strategies to actualize each man's potential.

Maintaining Active Lifestyles

As noted, adult men's exercise levels tend to decline with age. Illustratively, 2005–2007 CDC data indicate that the percentage of men who regularly engage in leisure-time physical activity plummets from roughly 42% in young adults (ages 18–24 years) to approximately 23% in seniors (≥75 years of age).[26] Accordingly, considerable attention has focused on the potential proximal influences that may sustain active lifestyles.

Although evidence-based conceptualizations of exercise adoption and maintenance tend not to be gender-specific, interventions targeting social cognitive factors have shown promise both generally and specifically for men.[236,268] For instance, research with male participants has supported the benefit of personally meaningful goals to improve exercise participation, with some studies suggesting that men may be oriented toward competence-building activities, particularly when these pursuits coincide with existing recreational preferences and resources.[268–270] Other research on exercise barriers has highlighted life transitions and stressful life events (e.g., marriage/divorce, SES changes, neighborhood relocation, parenthood, retirement) as potential obstacles to initiating and maintaining exercise habits.[268,269,271,272]

Intrapersonal attributes also have been studied with considerable recent attention to the relationships among activity, mood, and well-being. Although reciprocal and dynamic influences have been acknowledged across the life span,[273] some research has prospectively linked emotional status to subsequent activity changes, with negative mood states predicting activity declines and positive emotions forecasting increases.[246,273,274] Of course, given that negative emotional states (e.g., depression) are partially defined by feelings of fatigue and reduced self-efficacy, particularly when symptoms reach clinical significance, the exercise-derailing effects of dysphoric moods are not surprising. Likewise, it makes sense that positive emotions fueled by their associated optimism, energy, and positive outcome expectancies could be harnessed in the service of motivating and sustaining active living.[246,274–277]

More interesting, however, are emerging suggestions that emotional status may have special relevance for exercise promotion in sedentary men. For instance, Baruth et al.[246] recently reported that positive emotional outlook on life was especially predictive of subsequent physical activity increases among initially inactive men compared to women, for whom other influences may have predominated. Findings such as these call attention to the importance of comprehensively assessing the full range of influences that may impact men's readiness to change.[201,246]

As an illustration of one such comprehensive framework, Bryan et al.'s transdisciplinary model of voluntary exercise[278] considers multiple domains of possible mediators. Although not specifically male-oriented but consistent with the broader literature,[201,223,246] this model has incorporated the potential contributions of physiological exercise responses (e.g., body temperature, cortisol, lactate concentration), subjective experiences (e.g., mood changes, perceived exertion), and social cognitive motivations (e.g., attitudes, intentions, self-efficacy). Research driven by this kind of forward-leaning perspective has merit for further exploring the complex dynamics that may promote, sustain, or derail active lifestyles for different men across the life span.[201,228,278]

CONCLUSION

The evidence base on men's health has progressed by leaps and bounds over the last decade. Although foundational research sought to simply document between-gender differences, contemporary perspectives now explore the mediators and moderators that may explain men's lifestyle disparities. In the process, the conceptual understanding of masculinity has moved away from being seen as one-dimensional hazard to a complex dynamic of personalized processes and outcomes that may confer both risks and resiliencies.[10,28,72,73,279]

This more sophisticated take on "men's health" shifts the focus away from male sex per se to the more proximal person–environment contingencies that shape the acquisition, disruption, or solidification of different lifestyle options across the life span.[73] Indeed, as discussed throughout this chapter, culturally constructed gender roles may heighten the prepotency of some risks, but their actualization depends on the complicated ways idiosyncratic masculinity schema interact with other health-relevant factors.

Despite the whirlwind of enthusiasm touched off by early interventions aimed at the generic man, real-world implementation has yielded predictably suboptimal results, as witnessed by the largely disappointing outcomes associated with decades of public health appeals for multiple risk factor reduction.[280–283] Although broad-based initiatives may raise men's awareness, remodel perceptions of health-detrimental group norms, and nudge some men closer to readiness for lifestyle improvement, one size will not come close to fitting all. In the end, the promise of promoting men's health rests less on targeting men's average or typical risks and more on increasing the personal relevance of strategies that recognize men's heterogeneity and comprehensively address different risk and resilience profiles.[72,157]

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Part VII

Endocrinology and Metabolism

Samuel Crockett, MD

33 Lifestyle and Insulin Resistance

Samuel Crockett, MD

CONTENTS

Introduction 421
Obesity: A Predictor Insulin Resistance 421
Elevated Free Fatty Acids, Muscle, and Insulin Resistance 422
Elevated Free Fatty Acids, the Liver, and Insulin Resistance 422
Obesity, Free Fatty Acids, and Insulin Secretion 423
Insulin Resistance in Obesity 423
Lifestyle and Insulin Resistance 424
Physical Activity and Insulin Resistance 424
Nutrition and Insulin Resistance 424
Smoking and Insulin Resistance 425
Stress and Insulin Resistance 425
Summary 426
References 426

INTRODUCTION

It is estimated that in Westernized countries, 25%–35% of the population has insulin resistance or health problems associated with this metabolic disorder.[1] Insulin resistance is a condition that represents the presence of an impaired biological response to insulin. In muscle and adipocytes, it is manifested by a decreased insulin-stimulated glucose transport and metabolism. In the liver, there is an impaired suppression of hepatic glucose output.[2] Insulin resistance has both genetic and acquired components. A number of factors influence the sensitivity to insulin. They include age, weight, ethnicity, abdominal fat (especially visceral fat), physical activity, and medications.[3] Insulin resistance is seen in a number of clinical conditions including diabetes mellitus, obesity, hypertension, dyslipidemia, cardiovascular disease, and polycystic ovary disease.[4–10] Type 2 diabetes is rarely seen in insulin-resistant people without some degree of β-cell dysfunction. However, first-degree relatives of people with type 2 diabetes have insulin resistance at a time when they are nonobese, implying a strong genetic component in the development of insulin resistance.[11–13] Cross-sectional studies suggest that genetic factors, intrauterine environment, early childhood, and adult environmental factors are relevant in determining insulin resistance.[14] Long-term predictors of insulin resistance looking at the influence of lifestyle and metabolic factors have been reported. In a large (n = 770) population-based study, the Uppsala Longitudinal Study of Adult Men, multiple factors were found to be operative. Metabolic, lifestyle, and socioeconomic factors independently contributed to predict insulin sensitivity, supporting a complex background of insulin resistance. Saturated fat intake and socioeconomic status were independent predictors that appeared to be as important as physical activity. However, after 20 years of follow-up, body mass index (BMI) was still the strongest predictor of insulin sensitivity following adjustment for lifestyle factors and homeostasis model assessment for insulin resistance (HOMA-IR), even in men with a normal BMI.[15]

OBESITY: A PREDICTOR INSULIN RESISTANCE

Obesity is a significant predictor of risk for insulin resistance, particularly visceral as opposed to subcutaneous adiposity.[16] As global obesity has become more evident, concern has increased. At least 1 billion people worldwide are thought to be overweight or obese (BMI $\geq$ 25 kg/m^2) and at least 300 million people are thought to be obese (BMI $\geq$ 30 kg/m^2).[17] Data from the U.S.-based 2007–2008 National Health and Nutritional Examination Survey (NHANES) shows that 32.2% of men and 35.5% of women are obese. The presence of obesity increases with age and is highest for non-Hispanic black men (37.3%) and non-Hispanic black women (49.6%). A significant linear increase in obesity has occurred in the last 10 years. Of considerable concern, 5% of Americans have a BMI of >40 kg/m^2 or are morbidly obese.[18] Previously, the increase in obesity defined by BMI has been matched by increases in abdominal obesity.[19–22] This has been true for both adults and children.

The epidemic of obesity that is occurring in the United States and in other Westernized countries can be explained in large part by the increasing availability of energy (abundant food) and falling requirements for physical activity. In this environment, insulin resistance occurs at two primary levels: The first is energy balance which is the balance between how much energy an individual takes in and how much

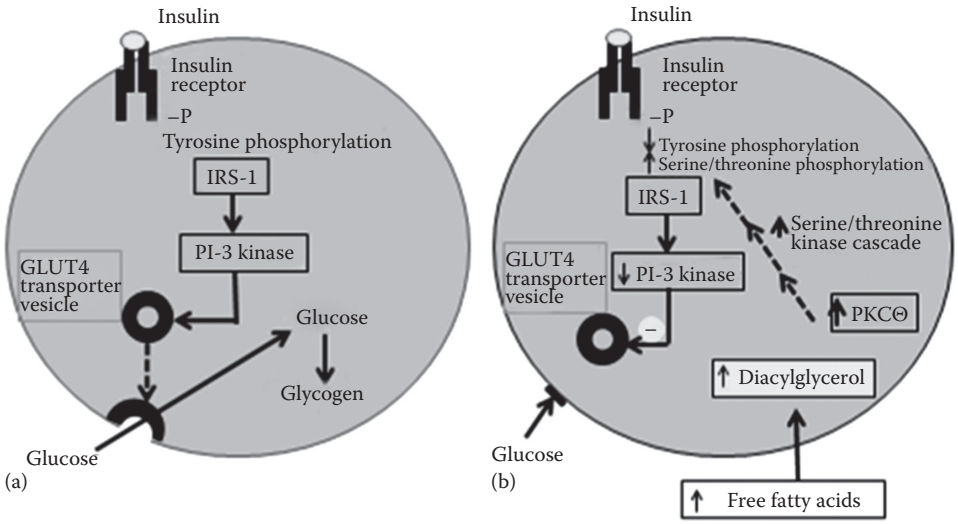


FIGURE 33.1 Mechanisms of insulin sensitivity (a) and resistance (b) in muscle. IRS, Insulin receptor substrate; PI3, phosphatidylinositol 3-kinase; PKCΘ, protein kinase CΘ; GSK3, glycogen synthase kinase 3; GS, glycogen synthase; circle with minus indicates inactivation; dotted line indicates inhibition. (Adapted from Shulman, G., *J. Clin. Invest*., 106, 171, 2000; Samuel, V. et al., *Lancet*, 375, 2267, 2010.)

one expends. When individuals have ceased linear growth, but remain in positive energy balance, they accumulate fat. There are both genetic and environmental influences on energy balance. For example, identical twins tend to achieve similar degrees of overweight, whether raised together or apart. On the other hand, populations that have changed from traditional diets low in calories and fat to more Westernized diets higher in both have an increasing prevalence rate of obesity, demonstrating the importance of environmental influences on energy balance. The second level at which insulin resistance occurs is fat accumulation. Fat accumulation is important in the development of insulin resistance with at least two general factors determining the degree to which individuals accumulate fat and develop insulin resistance. The first factor is where the fat is deposited. Deposition in adipose tissue is associated with less insulin resistance than localization in liver or muscle. The second factor is a number of cytokines and hormonal factors that are secreted by adipose tissue, particularly visceral adipose tissue (VAT). Tumor necrosis factor-α (TNF-α), resistin, and adiponectin are three factors made by adipose tissue that appear to act as hormones to regulate insulin sensitivity in muscle and/or liver.

Elevated Free Fatty Acids, Muscle, and Insulin Resistance

Chronically elevated blood levels of free fatty acids (FFA) have been linked to the onset of insulin resistance in skeletal muscle and liver.[23–26] A direct and causative relationship between intracellular fat metabolites and insulin resistance appears to be mediated via alterations in the insulin signaling pathway. In normal skeletal muscle, insulin binds to its receptor, activating the receptor tyrosine kinase activity, with the subsequent phosphorylation and activation of insulin receptor substrate 1 (IRS-1). When phosphorylated, IRS-1 activates phosphatidylinositol 3-kinase (PI3K); this enzyme through signaling promotes the docking and fusion of GLUT4-containing vesicles to the plasma membrane and the transport of glucose into the cell (Figure 33.1a).[27] In skeletal muscle, the proposed mechanism for alteration in insulin signaling is as follows: increased delivery of FFA to the muscle leads to an increase in intracellular fatty acid metabolites to include fatty acyl CoA, ceramides, and particularly diacylglycerol. These activate a serine/threonine kinase cascade initiated by protein kinase CΘ (PKCΘ) which leads to the phosphorylation of serine/threonine sites on IRS-1. The serine/threonine phosphorylations reduce the ability of IRS-1 to activate PI3K. As a result, glucose transport activity and other events downstream of insulin receptor signaling (e.g., glycogen synthesis and glycolysis) are decreased[28,29] (Figure 33.1b).

Elevated Free Fatty Acids, the Liver, and Insulin Resistance

Ectopic lipid accumulation in the liver is termed hepatic steatosis. It is associated with elevation of liver enzymes, obesity, insulin resistance, and type 2 diabetes. Elevated FFA from visceral fat and chylomicron remnants from dietary lipids enter the liver through the portal circulation. Accumulation of triglycerides in hepatocytes results from this increase in FFA and chylomicron remnant inflow and also de novo from lipogenesis of absorbed carbohydrates. Normal insulin action in the liver has many similarities to insulin action in muscle. In the liver, insulin activates the insulin receptor kinase, which phosphorylates IRS-1 and IRS-2, leading to the activation of PI3K and ultimately Akt2. Akt2 activation promotes glycogen synthesis and inhibits gluconeogenesis (Figure 33.2a).[23] In the liver, the precise effect of FFA levels remains an area of ongoing discussion and investigation with the sequence of events and the mediators linking FFA to insulin resistance and liver disease progression being better defined.[25,26] A proposed model for hepatic insulin resistance

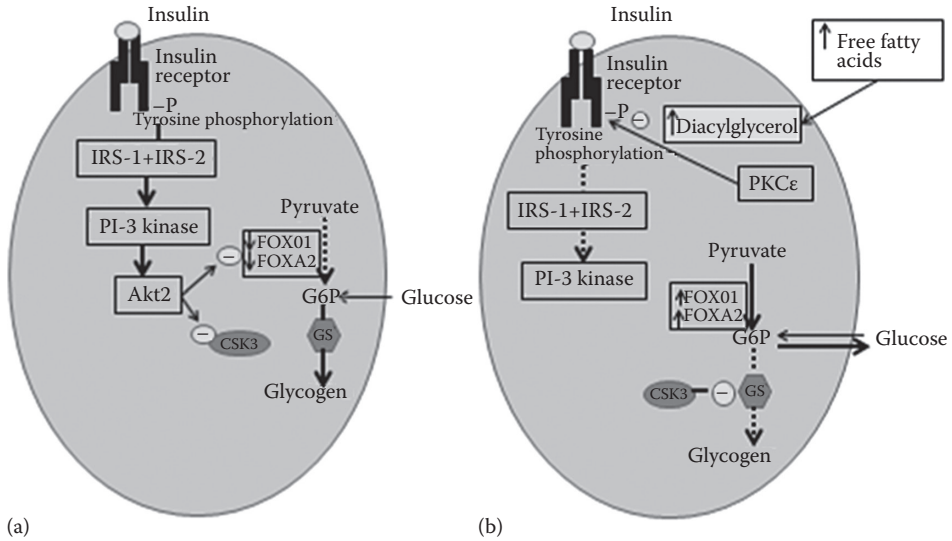


FIGURE 33.2 Mechanisms of insulin sensitivity (a) and resistance (b) in liver. IRS, Insulin receptor substrate; PI3, phosphatidylinositol 3-kinase; PKCε, protein kinase Cε; FOX01, forkhead box 01; FOXA2, forkhead box A2; GSK3, glycogen synthase kinase 3; GS, glycogen synthase; circle with minus indicates inactivation; dotted line indicates inhibition. (Adapted from Shulman, G., *J. Clin. Invest*., 106, 171, 2000; Samuel, V. et al., *Lancet*, 375, 2267, 2010.)

involves interference of insulin signaling, with decreased IRS-1 and IRS-2 phosphorylation by the insulin receptor impairing the ability of insulin to activate hepatic glycogen synthesis and suppress hepatic glucose production (HGP). As in muscle, PKC and in particular PKCε appears to play an essential role in the pathogenesis of hepatic insulin resistance (Figure 33.2b).[26] HGP is increased in insulin resistance. The brain needs glucose in order to function, with ~50% of glucose utilization in the fasting state accounted for by brain utilization. Glucose production by the liver, and to a lesser extent by the kidneys, supplies the brain with this glucose. In people with type 2 diabetes, basal HGP is increased. As the rate of basal HGP increases, so also does the fasting plasma glucose. In type 2 diabetes, glucose overproduction by the liver is accompanied by a 2.5- to 3-fold increase in fasting plasma insulin levels indicative of severe insulin resistance relating to the insulin suppressive effect on HGP. This increase in basal HGP is explained by an increase in gluconeogenesis.[29]

Adipose tissue in obesity is stressed resulting in enlarged adipocytes, the activation of inflammatory responses, and the recruitment of macrophages. Enlarged adipocytes are resistant to the antilipolytic effect of insulin and have a diminished fat-storing capacity.[30,31] This leads to the prolonged elevation of plasma FFA. When the adipocyte-storing capacity is exceeded, the chronic, prolonged elevation of plasma FFA levels which, as previously reviewed, induces hepatic and muscle insulin resistance, stimulates gluconeogenesis, and impairs insulin secretion.[32–40] These dysfunctional adipocytes produce excessive amounts of insulin resistance–inducing inflammatory and atherosclerosis-provoking adipocytokines (TNF-α, interleukin-6 [IL-6], plasminogen inhibitor-1 [PAI-1], monocyte chemoattractant protein-1 [MCP-1]) and fail to secrete normal amounts of insulin-sensitizing adipocytokines such as adiponectin. The secretion of the adipocytokines and the increased lipid overflow into the arterial circulation not only induce insulin resistance but also effect vascular smooth muscle cells leading to acceleration of the atherosclerotic process.[41,42]

Obesity, Free Fatty Acids, and Insulin Secretion

Obesity and the chronic elevation of FFA levels impair insulin secretion.[43,44] Studies have demonstrated that elevation of FFA for 48 h in offspring of two type 2 diabetic parents markedly impairs both first and second phase insulin secretion. Conversely, a sustained reduction in the FFA concentration by the use of acipimox in nondiabetic subjects with a strong family history of type 2 diabetes improves insulin secretion.[45] Exposure to FFA has been shown to cause a marked inhibition of insulin mRNA expression, decreased glucose-stimulated insulin release, and reduction of islet insulin content.[46] Obesity and chronic FFA elevation not only bring about insulin resistance, but also can decrease insulin secretion.

Insulin Resistance in Obesity

The prevalence of insulin resistance in obesity is not precisely known. In studies of insulin resistance and obesity, the study populations have been too small to evaluate prevalence.[47–49] In Pima Indians, insulin sensitivity measured by insulin clamp technique has been shown to decline with increasing BMI.[50] This finding was, however, nonlinear with most of the decrement in insulin sensitivity occurring for small increments in BMI. In a study of 1146 obese individuals in the database of the European Group for the Study of Insulin Resistance using the euglycemic clamp technique, the nondiabetic, normotensive obese subjects had a relatively low prevalence of insulin resistance. When insulin-mediated glucose utilization

was normalized by the metabolically active (lean) mass, the obese group was only 15%–25%, on average, less sensitive to insulin than the lean group, with no difference between men and women. Also the prevalence of insulin resistance among the obese subjects was low with only one in four individuals insulin resistant at the bottom decile of the lean group. In the presence of definite obesity (BMI 28–50 kg/m^2), only one in two individuals was insulin resistant. Although obesity is the quintessential insulin-resistant state, in simple obesity, insulin resistance may not be as prevalent as once thought. This may affect the response to weight loss as it relates to the risk of diabetes and cardiovascular disease.[5]

LIFESTYLE AND INSULIN RESISTANCE

Lifestyle may be defined differently by patients, health care professionals, educators, or research investigators. Lifestyle in the context of this chapter will be defined generally as the modifiable environmental factors of physical activity, nutrition, smoking, and stress. All of these factors have been demonstrated to affect insulin resistance.[51–54] Four factors, food choices and portion size, inactivity, tobacco use, and stress have been reported to account for 75% of chronic disease.[55]

Physical Activity and Insulin Resistance

Physical activity and health have been positively associated for well over 50 years. The beneficial effects of moderate to vigorous physical activity have been more clearly defined in recent years.[56–60] Humans are designed for movement. Obtaining dietary energy and nutrients from the environment has traditionally required expenditure of energy through human body movement. In the Western world, modern humans have relatively low levels of energy expenditure compared with contemporary hunter-gatherers.[61] Morris et al. in the early 1950s conducted studies among London Transport Executive and Post Office employees. The results demonstrated that the physically active men (bus conductors and postmen) had lower mortality rates from heart disease than less active workers (bus drivers and telephone switchboard operators).[62] These early studies provided epidemiological evidence for a role of physical activity in averting premature mortality. More recently, the Harvard Alumni Study and the Aerobics Center Longitudinal Study have demonstrated the benefits of physical activity and fitness in decreasing the relative risk of mortality.[63,64] In intervention trials, physical exercise has variably decreased body weight, visceral fat, and insulin resistance.[65–68] Molecular mechanisms of insulin-stimulated glucose uptake involve the main insulin-responsive glucose transporter GLUT-4. GLUT-4 is primarily located in muscle and adipose cells. Muscle is the principal site of insulin-stimulated glucose disposal with less glucose being transported into adipose tissue. GLUT-4 is recycled between the plasma membrane and intracellular storage pools. GLUT-4 differs from other glucose transporters in that about 90% of it is sequestered intracellularly in the absence of insulin or other stimuli. Insulin-stimulated intracellular movement of GLUT-4 is initiated by the binding of insulin to the extracellular portion of the transmembrane insulin receptor. Its binding activates tyrosine kinase phosphorylation at the intracellular portion of the receptor. The chief substrate for tyrosine kinase is insulin receptor substrate 1 (IRS-1). In both adipocytes and skeletal muscle, subsequent activation of phosphatidylinosital-3 kinase is necessary for the stimulation of glucose transport by insulin.[27,69,70] This is sufficient to induce at least partial translocation of GLUT-4 to the plasma membrane[71–73] (Figure 33.1a). The mechanism by which bouts of exercise effect glucose transport involves the stimulation of GLUT-4 transporters. The signals that mediate exercise-induced GLUT-4 recruitment differ from those that mediate insulin-induced recruitment, in that phosphatidylinosital-3-kinase activity is not required for the exercise effect.[74,75] Exercise-induced stimulation of GLUT-4 translocation is normal in insulin-resistant subjects. Thus in subjects who are insulin resistant, or at high risk for type 2 diabetes, regular physical activity can be of significant benefit.

Both aerobic and resistance exercise have been demonstrated to decrease insulin resistance and improve glucose tolerance.[76,77] Davidson et al. in a randomized controlled trial of overweight and obese older, white adults demonstrated the benefit of aerobic and combined resistance and aerobic exercise for simultaneous reduction of insulin resistance and functional limitation.[78] Although this study found combined resistance and aerobic exercise is an optimal exercise strategy to decrease insulin resistance, considerable improvement was observed in response to aerobic activity alone.

Nutrition and Insulin Resistance

Type 2 diabetes is a classical example of an insulin-resistant state. Numerous lifestyle intervention studies have demonstrated the benefit of physical activity and nutrition in the prevention[79–81] and treatment of type 2 diabetes.[82] These studies demonstrate both a primary and secondary (weight loss) effect of lifestyle on insulin resistance.

Over the last 20–25 years Dietary Guidelines for Americans (DGA), dietary recommendations intended to decrease chronic disease among American adults have been published.[83,84] Insulin resistance is an important risk factor in the pathogenesis of cardiovascular disease and type 2 diabetes. Fogli-Cawley et al. examined the relationship between a diet consistent with the 2005 DAG and insulin resistance in the Framingham Offspring Cohort. A dietary adherence index which excluded weight and physical activity was used to measure nutritional adherence. The study was controlled for adiposity, overweight, and physical activity. Their findings suggested that women who consumed a diet more consistent with the 2005 DGA had better insulin sensitivity than those who did not. The reason for this observed difference was not apparent. This finding may have been secondary to the adjustment for waist circumference, a strong predictor of insulin resistance, or to a difference in dietary patterns or adherence between men and women. This relationship was not demonstrated in men.[84] It appeared that those individuals

who fully met the intakes for fiber, whole grains, dark green vegetables, *trans*-fat, and alcohol had significantly less insulin resistance as measured by HOMA-IR than those who did not meet the intakes. However, an overall healthy diet pattern was more strongly associated with less insulin resistance than any individual component.[84]

Nutrition has an important influence on insulin resistance in addition to weight gain secondary to caloric excess.[84–86] Several nutrients appear to influence insulin sensitivity although not to the extent of that observed with weight loss. Those foodstuffs include total amount of fat, nature of dietary fatty acids, nature of carbohydrate, and amount of protein. The habitual intake of fat, regardless of the nature of the fatty acids, correlates positively and significantly with plasma insulin concentrations.[87] This finding has been reported in several large studies.[88–90] In these studies, when body mass was taken into account, the significant relationship between fat intake and insulin levels diminished. In the Insulin Resistance Atherosclerosis Study, the insulin-sensitivity index remained significantly and inversely related to the fat intake in obese but not nonobese individuals.[90] The mechanisms are uncertain because the quantity of fat eaten does not necessarily cause obesity. Triglyceride accumulation in skeletal myocytes is a feature of insulin resistance and obesity.[91] The amount of physical activity also attenuates the adverse effect of fat on insulin sensitivity.[89,90] Insulin sensitivity appears to be influenced more by saturated fatty acid intake than polyunsaturated fatty acid intake.[90,92] Vessby from analysis of fatty acids concluded that increases in saturated fatty acids, such as palmitate, are linked to insulin resistance versus high levels of polyunsaturated fatty acids which are neutral or oppose insulin resistance.[93] The relationship of saturated and polyunsaturated fatty acids to insulin sensitivity has been reported in a number of studies.[94–96] In well-controlled dietary intervention trials, decreasing saturated fatty acids, and increasing monosaturated fatty acids improved insulin sensitivity, though only when total fat intake was not excessive.[97,98] Although all studies have not come to the same conclusion, experimental human and animal studies have demonstrated that dietary fat, especially saturated fat, can affect insulin sensitivity.

In a nested substudy of Prevencion con dieta Mediterranea (PREDMED), a multicenter, randomized, parallel-group primary prevention trial in Spain, 418 nondiabetic subjects aged 55–80 years were randomized to a low-fat diet (control group) or one of two Mediterranean diets supplemented with either extra virgin olive oil (1 L/week) or mixed nuts (30 g/day). Diets were without limits, with no advice on physical activity given. The main outcome was diabetes incidence as diagnosed by 2009 criteria. Following a median follow-up of 4 years, the diabetes incidence was 10.1%, 11%, and 17.9% in the Mediterranean diet with olive oil, with mixed nuts, and the control group, respectively. This is a 52% reduction in the incidence of diabetes. The initial explanation for the results of decreased incidence of diabetes without weight loss was that monounsaturated fats in olive oil and nuts are less oxidized and contribute to reduced insulin resistance and that the components of the Mediterranean diet are rich in antioxidant compounds with anti-inflammatory effects.[99]

The role of dietary fiber has been difficult to assess due to other carbohydrate moieties and the large number of bioactive nutrients and nonnutrients in plant foods. However, evidence does exist that there are links between the amount of ingested fiber and plasma insulin concentration. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, dietary fiber was linearly but inversely correlated with post-glucose load plasma fasting and 2 h insulin concentrations, BMI, and waist–hip ratio.[100] Intake of whole grain foods is reported to be associated with a lower level of VAT whereas eating more refined grains is linked to a visceral adipose increase.[101] A significant inverse association was found between the intake of whole grain foods and waist measurement after adjusting for age, sex, smoking status, total energy, and alcohol consumption. Whole grain consumption had an inverse association with subcutaneous adipose tissue (SAT) and VAT. In multivariable models, refined grain intake demonstrated a positive relationship with SAT and VAT. In joint evaluations, the SAT *p* value was attenuated and nonsignificant whereas the VAT had a relationship with whole grains and refined grains. Causality for these findings will require further study.

Diets low in carbohydrates and enriched with protein have been popularized due to their short-term weight loss effects. In a controlled trial of a low-carbohydrate versus a low-fat diet, obese subjects who were insulin resistant or overtly diabetic showed greater weight loss when carbohydrates were reduced and insulin sensitivity in the diabetic individuals improved.[102] Increasing the proportion of protein relative to carbohydrates within an energy-restricted diet resulted in weight loss with less reduction in lean muscle mass and greater reductions in blood glucose and triglycerides.[103]

Smoking and Insulin Resistance

Smoking and the use of nicotine-containing products have an effect on insulin resistance and insulin sensitivity. Chronic cigarette smokers were found to be insulin-resistant, hyperinsulinemic, and dyslipidemic when compared with matched groups of nonsmokers.[104] In people with type 2 diabetes, smoking markedly aggravated insulin resistance.[105] Nicotine abstinence appears to improve insulin resistance, and smoking cessation methods relying on nicotine replacement appear to decrease insulin sensitivity.[106,107] Smoking remains a significant modifiable lifestyle risk factor.

Stress and Insulin Resistance

Stress and the physiological response to stress play an important role in insulin resistance and insulin sensitivity. Acute stress is associated with a severe, yet reversible form of insulin resistance.[108,109] Psychological stress also can be associated with insulin resistance.[110]

Stress has been defined as a state of threatened homeostasis or disharmony caused by intrinsic or extrinsic forces or stressors.[111] Chronic stress is defined as a pathological state

of prolonged threat to homeostasis by persistent or frequently repeated stressors and is felt to significantly contribute to the pathophysiology of disease.[112] The body's response to stress relies on the integrity of the neuroendocrine, cellular, and molecular infrastructure located in the central nervous system (CNS) and periphery. Centrally, the hypothalamic–pituitary–adrenal (HPA) axis and the efferent sympathetic/adrenomedullary system represent the effector links through which the brain influences various organs and tissues during stress. Activation of the HPA is accomplished by arginine vasopressin (AVP) and corticotrophin-releasing hormone (CRH) release from the hypothalamus, activation of adrenal corticotropic hormone (ACTH) in the pituitary with subsequent increased secretion of the glucocorticoid, cortisol from the adrenal gland. The glucocorticoids exert pleiotropic effects through their many intracellular receptors throughout the body. The autonomic nervous system provides a rapid response system that controls a wide variety of functions since most body systems are affected by either the sympathetic nervous system, parasympathetic nervous system, or both. Recently, it has been demonstrated that cytokines and other humoral mediators of inflammation are potent activators of the central stress–response neurotransmitter circuits providing the afferent limb of a feedback loop by which the CNS and immune system communicate in order to defend homeostasis under conditions of systemic inflammation. In inflammatory sites, TNF-α, IL-1, and IL-6 are secreted in a cascade fashion into the general circulation. All of these proinflammatory cytokines have the ability to directly or indirectly enhance the activation of the HPA. Indirect activation by the HPA is also induced by cytokine-mediated stimulation of the central noradrenergic stress system.[113] Mobilization of the stress response by activation of the HPA and the sympathetic nervous system is normally programmed to be of limited duration. Chronic stimulation of the stress–response leads to the syndromal state that Selye described in 1936.[114,115] Continued action of glucocorticoids on metabolic pathways leads to increased visceral adiposity, decreased lean body mass, and insulin resistance. With a continuous supply of proinflammatory cytokines to the systemic circulation, there can be a chronic stimulus for activation of the HPA axis, creating a cycle of hypercortisolism inducing adipocyte accumulation and vice versa. With the inflammatory nature of obesity and the interplay among HPA, proinflammatory cytokines, and adipose tissue, a reciprocal link appears to underlie the impact of chronic stress to the development of obesity and conversely the contribution of obesity to the chronic activation of the stress system.[116–118]

In postsurgical stress, insulin resistance is characterized by normal sensitivity but decreased responsiveness of glucose oxidation, lipolysis, and plasma FFA oxidation. Glycogen synthesis and direct FFA oxidation are virtually unresponsive.[108]

SUMMARY

Insulin resistance is associated with numerous clinical conditions that contribute to decreased quality of life and chronic illness. Insulin resistance can be brought about, increased, ameliorated, or eliminated by changes in lifestyle. Providing effective lifestyle intervention including stress management programs, clear and appropriate prescriptions for physical activity, nutrition, and weight loss that result in decreased visceral adiposity and proinflammatory cytokines offer an effective approach to decrease insulin resistance and its deleterious effects on the body, health, and quality of life.

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34 Lifestyle Approaches to the Prevention and Treatment of Diabetes

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CONTENTS

Overweight and Obesity: Halting the Epidemic 432
Prediabetes: Preventing Diabetes 432
Diabetes Prevention Trials 432
Nutrition Therapy for Prediabetes 433
Weight Loss Interventions 433
Carbohydrates and Insulin Resistance 434
Mediterranean Diets 434
Whole Grains and Dietary Fiber 434
Dietary Fats 434
Glycemic Index/Glycemic Load 435
Alcohol 435
Micronutrients 435
Physical Activity 436
Bariatric Surgery 436
Diabetes: Improving Metabolic Outcomes 436
Nutrition Interventions for Type 1 Diabetes 437
Nutrition Interventions for Type 2 Diabetes 437
Summary 437
References 437

In the United States and worldwide, the prevalence of diabetes and prediabetes has increased dramatically. In 2011, the total prevalence of diabetes in the United States in all ages was 25.8 million people or 8.3% of the population. Of these, 18.8 million are diagnosed and 7.0 million are undiagnosed. This is an increase from 4.9% of the population in 1990 and 7.3% in 2000. In U.S. adults aged 65 years and older, 10.9 million, or 26.9% had diabetes in 2010. Of great concern are the estimated 79 million U.S. adults with prediabetes who are at high risk for type 2 diabetes and cardiovascular disease (CVD) [1].

In no other disease does the role of lifestyle—healthy and appropriate food choices and physical activity—play a more important role in both prevention and treatment than in diabetes. Multiple studies have shown that lifestyle strategies implemented in individuals at risk for diabetes (prediabetes) can effectively prevent or delay type 2 diabetes [1]. Type 2 diabetes is known to be a progressive disease and although lifestyle interventions are effective at any time in the disease process, they have their greatest impact earlier in the course of the disease [2]; thus the importance of intervening early with lifestyle approaches in both the prevention and treatment of diabetes.

The progression of type 2 diabetes and the changes in lifestyle interventions and medications that must occur over the continuum of prevention and management are illustrated in Figure 34.1 [3]. Preventing obesity and increasing physical activity is a high priority for the prevention of diabetes and other chronic diseases. Identifying individuals with prediabetes and implementing prevention interventions is essential. However, as the disease progresses the goal of nutrition therapy is to prevent and manage the long-term complications of diabetes.

First-line therapy for disease reduction for diabetes and CVD includes stopping cigarette smoking and reducing glucose, LDL cholesterol, and blood pressure to recommended goals. Nutrition therapy includes a reduction of body weight by 5%–10% in overweight and obese individuals, an increase in physical activity to 30–60 min/day of moderate-intensity activity, and implementation of a cardioprotective diet, which includes an increase in whole grains and fiber and a decrease in saturated and *trans*-fatty acids and dietary cholesterol.

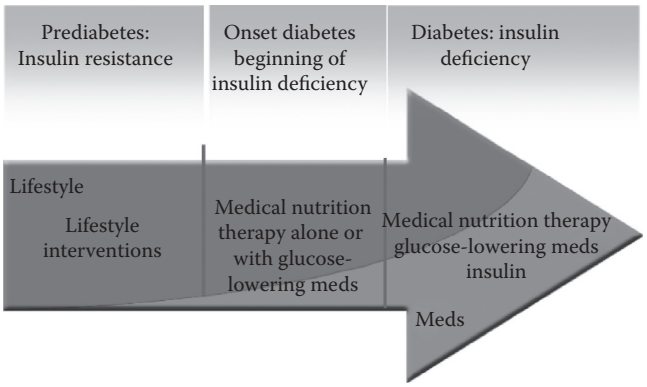


FIGURE 34.1 Type 2 diabetes: A progressive disease. (From Franz, M.J., *Am. J. Lifestyle Med*., 1, 327, 2007.)

OVERWEIGHT AND OBESITY: HALTING THE EPIDEMIC

Overweight and obesity are strongly associated with insulin resistance and the hope is that slowing the rising prevalence of obesity will have a positive impact on slowing the epidemic of diabetes and other chronic diseases. Body mass index (BMI = kg/m^2) and waist circumference (WC) are used to classify overweight and obesity and associated disease risk (Table 34.1) [4,5]. Although some obesity researchers suggest that it may not be possible to decrease the current numbers of overweight and obese persons in the United States, preventing the increase that has been occurring at an increasing rate is an important goal [6]. In programs designed to increase physical activity and decrease energy intake, the physical activity goal is to increase the number of steps an individual takes throughout the day by about 2000 steps above baseline and the decreased energy intake goal is to eat 100 fewer calories per day [7].

PREDIABETES: PREVENTING DIABETES

The increase in diabetes worldwide has made prevention of type 2 diabetes a top priority. Prediabetes is defined as hyperglycemia not sufficient to meet the diagnostic criteria for diabetes (Table 34.2) [8]. Categories of increased risk for diabetes (prediabetes) are listed in Table 34.3 [8]. Impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and hemoglobin A1c (A1C) values in the 5.7%–6.4% identify persons at increased risk for diabetes as well as CVD. They should be counseled about effective strategies to lower their risks [8]. As A1C rises, the risk of diabetes rises disproportionately. Individuals with A1Cs between 6.0% and 6.49% are considered to be at very high risk for diabetes.

Diabetes Prevention Trials

Five clinical trials—Finnish Diabetes Prevention Study (DPS) [9], Diabetes Prevention Program (DPP) [10], Da Qing [11], Toranomon Study [12], and Indian DPP [13]—have compared lifestyle interventions to a control group with risk reduction for type 2 diabetes ranging from 29% to 67% from lifestyle interventions. The two most frequently cited are the Finnish Prevention Study and the DPP, both reporting a risk reduction of 58% from lifestyle interventions compared to a control group. In both, structured education programs emphasizing a reduced energy and reduced fat (~30% of total energy) intake, regular physical activity, and regular participant contact resulted in a weight loss of 5%–7% of baseline weight and a 58% reduction in risk of developing diabetes. This amount of weight loss was also associated with improvements in hypertension and lipid profiles.

Intensive lifestyle interventions are the safest, most efficacious, and usually the least expensive way to prevent diabetes; however, several clinical trials have shown that medications

TABLE 34.1
Classification of Overweight and Obesity by BMI and WC and Associated Disease Risk

		WC-Associated Disease Risk[a]	
Classification	**BMI (kg/m^2)**	**≤WC Cut Point (≤40 in. [102 cm] for Men and ≤35 in. [88 cm] for Women)[b]**	**>WC Cut Point (>40 in. [102 cm] for Men and >35 in. [88 cm] for Women)**
Underweight	<18.5		
Normal	18.5–24.9		Increased[c]
Overweight	25.0–29.9	Increased	High
Obesity (Class I)	30.0–34.9	High	Very high
Obesity (Class II)	35.0–39.9	Very high	Very high
Extreme obesity (Class III)	≥40	Extremely high	Extremely high

Sources: Data are from National Heart, Lung, and Blood Institute, *Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults*, National Institutes of Health, Bethesda, MD, 1998; Alberti, K.G.M.M. et al., *Circulation*, 120, 1540, 2009.

[a] Disease risk is for type 2 diabetes, hypertension, and CVD and compares with risk for an individual with normal BMI.

[b] Lower WC cut points (≤35 in. [90 cm] in men and ≤31 in. [80 cm] in women) seem to be more appropriate for assessing increased disease risk in Asian Americans.

[c] Even in persons of normal weight, WC can be associated with disease risk.

TABLE 34.2
Criteria for the Diagnosis of Diabetes

A1C ≥6.5%. The test should be performed in a laboratory using a method that is certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.[a]

or

Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.[a]

or

2 h plasma glucose (PG) ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). This test uses the equivalent of 75 g anhydrous glucose dissolved in water.[a]

or

Classic symptoms of diabetes and casual PG ≥200 mg/dL (11.1 mmol/L)

Source: Adapted from American Diabetes Association, *Diabetes Care*, 34(Suppl 1), S11, 2011.

[a] In the absence of unequivocal hyperglycemia, results should be confirmed with repeat testing.

TABLE 34.3
Categories of Increased Risk for Diabetes (Prediabetes)[a]

A1C 5.7%–6.4%

or

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG

or

2 h PG in the 75 g OGTT 140–199 mg/dL (7.8–11.0 mmol/L): IGT

Source: From American Diabetes Association, *Diabetes Care*, 34(Suppl 1), S11, 2011.

[a] For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

(i.e., metformin, acarbose, orlistat, rosiglitazone, voglibose, pioglitazone) can also prevent or delay progression from prediabetes to diabetes. The American Diabetes Association recommends that only metformin be considered as drug therapy for individuals with prediabetes [8]. Metformin is most effective in individuals with a BMI of at least 35 kg/m^2 and who are under the age of 60 years. Cost, side effects, weight gain, and lack of persistence of effect in some studies are concerns with other medications.

Although medical professionals are often skeptical about the ability of individuals to make permanent lifestyle changes, support for the role of lifestyle interventions comes from follow-up of participants in three large prevention studies. A sustained reduction in the rate of conversion to type 2 diabetes of 43% was reported at 20 years in the Da Qing study [14], a 43% reduction at 7 years in the Finnish DPS [15], and 34% reduction at 10 years in the DPP [16]. Lifestyle intervention resulted in sustained lifestyle changes and a reduction in diabetes incidence, which remained after the individual lifestyle counseling was stopped [15]. A cost-effectiveness analysis suggested that lifestyle interventions as delivered in the DPP are cost-effective [17]. Group delivery of the DPP intervention in community settings has the potential to be less expensive while still achieving similar weight loss [18].

Nutrition Therapy for Prediabetes

The goal of nutrition therapy for prediabetes is to prevent or delay the progression to type 2 diabetes. Interventions proven to be effective include a reduced energy intake leading to moderate weight loss and increased physical activity. Weight loss (5%–10% of body weight) and regular physical activity (30 min daily) are the recommended goals. To be effective requires individual or group counseling and continued support until lifestyle changes become permanent.

Weight Loss Interventions

To determine expected weight loss from weight loss interventions, a systematic review and meta-analysis of randomized clinical trials for weight loss with a minimum duration of 1 year was undertaken [19]. Eighty studies with a total of 26,455 subjects, primarily completers, were identified and the data pooled to determine mean weight loss from eight different interventions used in the trials—diet alone, diet and exercise, exercise alone, meal replacements, very low-calorie diets, orlistat, sibutramine, and advice alone. A mean weight loss of 5–8.5 kg (5%–9% of baseline weight) was observed in the first 6 months from interventions involving a reduced energy diet and/or weight loss medications. A plateau in weight loss was observed between ~6 and 12 months and in studies extending to 48 months, a mean 3–6 kg (3%–6%) of weight loss was maintained with none of the groups experiencing weight regain to baseline. In contrast, advice-only and exercise-alone groups experienced minimal weight loss at any time point.

Adaptive mechanisms that occur with a reduced energy intake—such as hormonal regulation of appetite [20], adaptive thermogenesis requirements leading to a decrease in energy expenditure [21], and a decline in weight maintenance energy requirements [22]—appear to prevent the majority of "dieters" from achieving an ideal body weight. However, the weight loss that can be achieved is important in reducing risk of diabetes. Therefore, individuals should be counseled on weight loss strategies to improve health (decreased risk of diabetes and CVD) and not for cosmetic reasons.

There is no "miracle diet" for weight loss. A large, long-term trial tested the efficacy of weight loss diets that were high or low in carbohydrate, protein, or fat [23]. The 2 year trial involved 811 individuals with 80% completing the study. Weight loss from each diet averaged 6 kg (7% of baseline weight) at 6 months with an average weight loss of 4 kg at 2 years. All diets reduced risk factors for diabetes and CVD. Satiety, hunger, satisfaction with the diet, and attendance at group sessions were also similar for all groups.

Of importance for weight management is a reduced energy diet that an individual can follow long term. Attendance at group sessions; support from family, peers, or health care

professionals; setting realistic weight loss goals; monitoring food intake by food records; and regular physical activity have been shown to assist in accomplishing weight management goals.

Carbohydrates and Insulin Resistance

It is often assumed that a high carbohydrate intake contributes to insulin resistance and to increases in triglyceride concentrations. Observational and intervention studies provide support for the concept that high-carbohydrate diets, at the very least, do not adversely affect insulin sensitivity and may be beneficial for insulin sensitivity [24,25]. Furthermore, carbohydrate appears to only increase triglyceride levels when energy intake and weight are constant and carbohydrate intake is ~55% of total energy intake [26]. In low-carbohydrate diets, energy from carbohydrate is generally replaced with energy from fats, usually saturated fatty acids (SFA). As discussed later, high intakes of dietary fats, especially SFA and *trans*-fatty acids, are associated with a decline in insulin sensitivity. Excess energy intake, regardless of the energy source, and positive energy balance contribute to insulin resistance through the production of obesity.

Of concern is the increased consumption of sugar-sweetened beverages (SSB), which includes soft drinks, fruit drinks, iced teas, and energy and vitamin–water drinks. A meta-analysis of 11 studies that included 310,819 participants and 15,043 cases of type 2 diabetes found that individuals in the highest quartile of SSB (most often one to two servings per day) had a 26% greater risk of developing type 2 diabetes than those in the lowest quartile (none or less than one serving per month) and a greater risk for metabolic syndrome [27]. SSBs can contribute to weight gain and obesity and therefore healthy alternative beverages are recommended.

Mediterranean Diets

A traditional Mediterranean Diet (MedDiet), characterized by high consumption of vegetables, legumes, grains, fruits, nuts, and olive oil; moderate consumption of fish and alcohol; and low consumption of red and processed meat and whole fat dairy products, has been reported to have a protective effect against diabetes [28]. In prospective cohort study, 13,380 Spanish university graduates without diabetes at baseline were followed for a median of 4.4 years. Participants with the highest adherence to a traditional MedDiet food pattern had the lowest risk of developing diabetes [29]. Recently, implementation of a non-energy-restricted traditional MedDiet supplemented with either extra virgin olive oil or mixed nuts was compared to a low-fat diet among individuals without diabetes but at high cardiovascular risk. After a follow-up of 4 years, the MedDiet reduced the incidence of diabetes by 52% [30]. It is encouraging to note that changing foods eaten can substantially reduce diabetes risk without weight loss.

Prediabetes and metabolic syndrome have multiple similar components—enlarged WC, lipid abnormalities, hypertension, insulin resistance, and an elevation in fasting glucose levels. A meta-analysis of 50 studies (epidemiological and clinical trials) with 534,906 participants showed that adherence to the MedDiet was associated with decreased risk of metabolic syndrome and improvements in WC, lipids, blood pressure, and glucose [31]. Therefore, adherence to a MedDiet can effectively prevent both the metabolic syndrome and diabetes.

Whole Grains and Dietary Fiber

In a number of studies, primarily observational, increased intake of whole grains and dietary fiber is inversely associated with insulin resistance and risk of type 2 diabetes [32]. In a meta-analysis of data from 14 cohorts comprising ~48,000 participants, greater whole grain intake was associated with lower fasting glucose and insulin concentrations independent of demographics, other dietary and lifestyle factors, and BMI [33]. The Dietary Guidelines Advisory Committee (DGAC) reviewed whole grain/fiber evidence and concluded that limited evidence shows that consumption of whole grains is associated with a reduced incidence of type 2 diabetes in large prospective cohort studies [34]. Whole grain–containing foods have been associated with improved insulin sensitivity, independent of body weight; increased intake of dietary fiber has also been associated with improved insulin sensitivity. Persons at risk for diabetes are encouraged to meet the Dietary Guidelines for Americans 2010 recommendations which are to consume at least half of all grains as whole grains and to limit the consumption of foods that contain refined grains, especially grain foods that contain solid fats, added sugars, and sodium [34].

Dietary Fats

Prevention studies have focused on reduced dietary fat as a key component of the intervention. However, since their implementation, it has become clear that the type of fats consumed is of importance as well as their contributions to total energy intake. The DGAC reviewed fatty acid and cholesterol evidence and concluded that strong evidence indicates that intake of SFA is positively associated with (1) increased serum total and LDL cholesterol and increased risk of CVD and (2) increased markers of insulin resistance. Conversely, decreased SFA intake improves measures of both CVD and type 2 diabetes risk. A 5% energy decrease in SFA, replaced by monounsaturated fatty acids (MUFA) or polyunsaturated fatty acids (PUFA), decreases risk of CVD and type 2 diabetes in healthy adults and improves insulin responsiveness in insulin-resistant and type 2 diabetes individuals [34]. The effect assumes no change in energy intake when MUFA and/or PUFA are substituted for SFA and may result from changes in membrane lipid profiles related to type of fatty acids ingested. The DGAC concluded that growing data support a risk of type 2 diabetes from SFA consumption and these support the need for fat-modified diets in persons with prediabetes and those with established type 2 diabetes. The recommendation is to reduce intake of SFA and replace them with MUFA and PUFA [34].

Of interest is the DGAC conclusion on the effect of dietary cholesterol intake on risk of CVD. Overall the evidence shows that consumption of dietary cholesterol in the

amount of one egg per day is not harmful and is not associated with risk of CVD or stroke in healthy adults, although consumption of more than seven eggs per week is associated with increased risk [34]. However, they note an important distinction among individuals with type 2 diabetes in which increased dietary cholesterol is associated with CVD risk. Therefore, the recommendation is to limit dietary cholesterol to less than 200 mg/day for persons with or at high risk for CVD and type 2 diabetes.

Glycemic Index/Glycemic Load

The role of the glycemic index (GI) and glycemic load (GL) and risk of diabetes has been controversial. The evidence for benefit of low GI/GL diets was reviewed by the American Diabetes Association [26], and it was concluded that there is not sufficient, consistent evidence to conclude that low GI/GL diets reduce the risk of diabetes. The DGAC reviewed 10 longitudinal prospective observational studies published since 2000. In five studies, high GI was positively associated with type 2 diabetes, four reported no association of GI with type 2 diabetes, and one reported an inverse association. Only one study found a positive association between GL and risk of type 2 diabetes; six studies found no relationship; and two studies found an inverse association. The DGAC concluded that when selecting carbohydrate foods, there is no need for concern with their GI or GL. What is important to heed is their calories, caloric density, and fiber content [34].

Alcohol

Observational studies suggest a U- or J-shaped association between moderate consumption of alcohol and increased risk of diabetes [35–37]. A meta-analysis based on 32 studies found that compared to no alcohol use, moderate consumption (one to three drinks per day [15–45 g alcohol]) was associated with a 33%–56% lower incidence of type 2 diabetes and a 34%–55% lower incidence of diabetes-related coronary heart disease. However, compared with moderate consumption, heavy consumption (more than three drinks per day [45 g alcohol]) was associated with up to a 43% increased incidence of type 2 diabetes [35]. Another meta-analysis of 15 studies reported that compared to lifestyle abstainers, the risk for type 2 diabetes among men was most protective when consuming 22 g/day alcohol and became deleterious at just over 60 g/day alcohol. Among women, consumption of 24 g/day alcohol was most protective and became deleterious at 50 g/day alcohol [36].

Despite the benefit of alcohol when consumed in moderation, when consumed in excess, alcohol can cause serious health problems and increased diabetes risk. Therefore, if alcohol is consumed, it should be consumed in moderation—up to one drink per day for women and two drinks per day for men—and only by adults of legal drinking age [34]. The biological response for the benefits of alcohol may be that in small clinical trials and observational studies light to moderate amounts of alcohol have been shown to improve insulin sensitivity and raise HDL cholesterol levels. The type of alcoholic beverage does not make a difference.

Micronutrients

Two micronutrients of interest in the prevention of diabetes are chromium and vitamin D. Generally, supplements are most likely to be beneficial in persons with known deficiencies. Chromium deficiency is difficult to determine and ideal vitamin D blood levels have been controversial. The 2010 Institute of Medicine (IOM) challenged the assumption that many Americans are vitamin D deficient. Many laboratories consider a vitamin D blood level of 30–40 ng/mL to be ideal, but the IOM report stated a vitamin D level of 20 ng/mL was sufficient [38].

Two systematic reviews of randomized controlled trials examined the effect of chromium supplementation on glucose metabolism [39,40]. Data from the trials showed no effect of chromium on glucose or insulin concentrations in persons without diabetes. A randomized, placebo-controlled trial using 800 μg/day chromium picolinate in subjects with IGT also found no significant beneficial effect of the supplement on glucose, insulin resistance, or lipids [41].

Several but not all epidemiological studies have shown an association between low serum 25-hydroxy (OH) vitamin D and impaired glycemia; vitamin D interventions trials have had conflicting results [42,43]. The Women's Health Study found a significant inverse association between total (food plus supplements) vitamin D intake and risk of type 2 diabetes when adjusted for age [44]. A study using data from disease-free adults in the National Health and Nutrition Examination Study also reported increased risk for prediabetes and prehypertension in individuals with lower vitamin D levels (≤28.6 vs. >26.6 ng/mL) [45]. In contrast, the Nurses' Health Study found no relationship between vitamin D intake from supplements and incident type 2 diabetes after further adjustment for confounders [46]. The Women's Health Initiative (WHI) Clinical Trials and Observational Study also examined whether low levels of serum 25-OH vitamin D are associated with increased risk of developing type 2 diabetes. In this racially and ethnically diverse population of postmenopausal women, regardless of the cut points used or as a continuous variable, lower 25-OH vitamin D levels were not associated with increased risk of developing diabetes [47].

Several trials have not found benefit from vitamin D supplementation. The WHI calcium plus vitamin D intervention trial found that supplementation with 400 IU vitamin D_3 and 1000 mg calcium was not associated with a reduced risk of developing diabetes over an average follow-up period of 7 years [48]. In the RECORD trial, a substudy examined whether oral vitamin D_3 (with or without calcium) was associated with a reduction in the development of diabetes and did not find evidence that vitamin D_3 in a daily dose of 800 IU, or in combination with 1000 mg calcium, was able to prevent the development of diabetes [49]. The results of ongoing trials of higher doses of vitamin D supplementation are needed before recommendations for vitamin D supplementation for the prevention of type 2 diabetes can be made.

Physical Activity

Increases in physical activity significantly reduce the risk of type 2 diabetes and, independent of weight loss, improve insulin sensitivity [50,51]. In a meta-analysis of 20 prospective cohort studies, individuals who regularly engaged in physical activity of moderate intensity had an ~30% lower risk of type 2 diabetes as compared with sedentary individuals even in those who did not lose weight [51]. A post hoc analysis of the Finnish DPS examined the association between walking and incidence of type 2 diabetes. After adjustment for other activities, dietary factors, and BMI, at least 2.5 h/week of walking was associated with a 63% lower risk of type 2 diabetes as compared with <1 h/week [52]. Protection from diabetes occurs from moderate-intensity activities, such as brisk walking, as well as from vigorous physical activity. Benefits of exercise are particularly apparent in overweight individuals and in those at greatest risk for diabetes.

Biological mechanisms have been identified for beneficial effects of physical activity on glucose metabolism independent of body fatness. Exercise increases insulin-stimulated glycogen synthesis through an increased rate of insulin-stimulated glucose transport by GLUT4 glucose transporters and increased glycogen synthase activity [53]. In addition, increased muscle mass may contribute to the beneficial effects.

Physical activity recommendations for cardiovascular fitness and reduced risk of chronic health problems including type 2 diabetes include

- Moderate-intensity aerobic physical activity a minimum of 30 min 5 days/week (150 min/week) (i.e., walking 3–4 miles/h) above usual activity
- Vigorous-intensity aerobic physical activity a minimum of 20 min 3 days/week (90 min/week)

The physical activity should be distributed over at least 3 days/week, with no more than 2 days without activity. Muscle-strengthening activities involving all major muscle groups two or more days/week are also recommended [54].

To prevent weight gain, 60 min of moderate- to vigorous-intensity activity most days of the week (increase energy expenditure by ~150–200 kcal) is recommended. To prevent regain of weight loss, at least 60–90 min of daily moderate-intensity physical activity while not exceeding food caloric requirements may be required.

Bariatric Surgery

Studies suggest that for morbidly obese subjects, bariatric surgery can reduce the incidence of diabetes. Sjoström et al. published 2 and 10 year data from the Swedish Obese Subjects (SOS) study that included 407 morbidly obese subjects who underwent bariatric surgery and matched controls. The majority had vertical banded gastroplasty (~70%), some had simple banding (~24%), and a few gastric bypass (~6%). At 10 years, the incidence of diabetes was 7% in the surgery group compared to 24% in the control group. Weight loss was maximal after 1 year in the surgical groups (~26% in the vertical banded gastroplasty) whereas the maintained weight change after 10 years in the vertical banded gastroplasty group stabilized at 16%. The 2 and 10 year incidence rates of hypertriglyceridemia and hyperuricemia (along with diabetes) were lower in the surgery groups than in the control group; however, the incidence of hypertension and hypercholesterolemia did not differ between the groups [55]. Bariatric surgery was also associated with a reduction in overall mortality as compared to the control group [56]. However, the majority of the research involves the role of bariatric surgery in patients already diagnosed with type 2 diabetes and not in persons with prediabetes [57].

Because improvement in glucose and insulin sensitivity occur rapidly and before significant weight loss, it has been suggested that the decreased risk is related to the diversion of nutrients away from the gastrointestinal tract and by delivery of incompletely digested nutrients to the ileum rather than to weight loss per se [58]. Of increasing interest is the study of enterohormonal changes that occur after bariatric surgeries and their influence on appetite, continued reduced food intake, and prevention of weight regain [57].

DIABETES: IMPROVING METABOLIC OUTCOMES

There are important nutrition therapy intervention differences between preventing and treating diabetes. For example, although weight loss is an important strategy for prevention, nutrition therapy for diabetes focuses on interventions shown to improve and maintain metabolic outcomes related to glucose, lipids, and blood pressure. As the disease progresses, weight loss may or may not be of benefit for achieving glycemic goals [59]. However, there are other nutrition therapies, independent of weight loss, that contribute to improved metabolic control.

Improving health through food choices and physical activity is the basis for nutrition recommendations for diabetes [26]. Randomized controlled trials and observational studies of diabetes nutrition therapy provided by registered dietitians have demonstrated decreases in A1C of ~1% to 2% (range = −0.5% to −2.6%), depending on the type or duration of diabetes [60]. These outcomes are similar to those from glucose-lowering medications. Nutrition therapy is reported to lower LDL cholesterol by 15–25 mg/dL, or by 9%–12%, compared to baseline values or to a Western diet [61]. Nutrition therapy for hypertension is reported to decrease both systolic and diastolic blood pressure ~5 mm Hg [62].

Outcomes of nutrition therapy interventions are evident by 6 weeks to 3 months. Central to these interventions are multiple encounters to provide education and counseling on a continued basis. Just as there is no one medication or insulin regimen that is effective for all individuals with diabetes, there is not one type of effective nutrition intervention. Shown to be effective interventions are reduced energy/fat intake, carbohydrate counting, simplified meal plans, guidelines for healthy food choices, individualized meal planning

strategies, exchange lists, insulin-to-carbohydrate ratios, physical activity, and behavioral strategies [59]. Choosing nutrition interventions that individuals with diabetes can implement is essential.

Nutrition Interventions for Type 1 Diabetes

The first priority for persons requiring insulin therapy is to integrate an insulin regimen into their lifestyle. The food/meal plan is developed first and is based on the individual's appetite, preferred foods, and usual schedule of meals and physical activity. An insulin regimen can then be integrated into the food and physical activity schedules. Persons are encouraged to learn carbohydrate counting. An insulin-to-carbohydrate ratio can then be used to adjust bolus (mealtime) insulin doses based on planned carbohydrate intake [26,59].

Nutrition Interventions for Type 2 Diabetes

As individuals move from prediabetes and being insulin resistant to type 2 diabetes and insulin deficiency, one of the goals of therapy is to achieve near-euglycemia in hope of slowing β-cell exhaustion. Moderate weight loss may be beneficial for some individuals, primarily those who are still primarily insulin resistant, but for many it is too late for weight loss to improve hyperglycemia. At later stages of the disease when medications—including insulin—need to be combined with nutrition therapy, weight gain often occurs and preventing this becomes important.

Persons receiving either nutrition therapy alone, glucose-lowering medications, or fixed insulin doses generally do better if carbohydrate intake is consistently distributed throughout the day on a day-to-day basis. Diets too low in carbohydrate may eliminate too many foods that are important sources of vitamins, minerals, fiber, and energy [59]. Teaching individuals how to make appropriate food choices (often by means of carbohydrate counting) and using data from blood glucose monitoring to evaluate outcomes are interventions that can be implemented for successful nutrition therapy.

Regular physical activity is encouraged, primarily from the benefits associated with enhanced cardiorespiratory fitness that are independent of weight, but exercise must be undertaken regularly to have continued benefits [63]. It is important to monitor metabolic outcomes to determine if medications need to be added (or adjusted). Many individuals with type 2 diabetes also have dyslipidemia and hypertension, so decreasing intakes of saturated and *trans*-fats, cholesterol, and sodium should also be a priority.

SUMMARY

Nutrition therapy for both prediabetes and diabetes begins by developing rapport with the individual. Whether provided individually or in groups, nutrition therapy involves a common process: (1) assessment (evaluation at follow-up visits)—what lifestyle changes is the individual willing and able to make; (2) diagnosis of nutrition-related problems—used to develop nutrition interventions; (3) nutrition interventions—implemented using self-management education and counseling; and (4) monitoring and evaluation of nutrition-related outcomes. Planned follow-up and ongoing education and support is essential for continued success.

It is important that all health care providers understand nutrition therapy issues and guide and support the individual's efforts to make and maintain lifestyle changes. Evidence supports the importance of referring patients with prediabetes or diabetes for medical nutrition therapy as soon as the diagnosis is made, promoting and reinforcing the importance of lifestyle modifications to patients, and providing support for the nutrition therapy process.

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35 Lifestyle Medicine and the Treatment of Glucose Intolerance

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CONTENTS

Scope of Glucose Intolerance 441
Susceptibility to Diabetes: How Lifestyle Factors Cause the Development of Prediabetes and Diabetes 442
Lifestyle Interventions for Diabetes Prevention 445
Lifestyle Interventions and Management of Diabetes 447
Common Components of Lifestyle Interventions Programs 448
Conclusion 450
References 450

Glucose intolerance from prediabetes to frank type 2 diabetes mellitus (T2DM) is a major public health problem. T2DM is an economically costly disease[1] and a major contributor to morbidity and mortality. Uncontrolled T2DM can lead to renal dysfunction, peripheral and autonomic neuropathy, vision problems, and cardiovascular disease.[2] Fortunately, there is strong evidence that lifestyle interventions, programs promoting behavior change to improve diet, increase physical activity, and reduce weight, can prevent or delay the development of T2DM in high-risk populations and result in better disease management and improved outcomes in patients with T2DM. This chapter discusses the scope of glucose intolerance worldwide, describes how lifestyle choices affect insulin action, and examines the effects of lifestyle interventions on T2DM prevention and control.

SCOPE OF GLUCOSE INTOLERANCE

Glucose intolerance ranges from prediabetes to diabetes. Prediabetes, a precursor to and a risk factor for T2DM, includes (1) impaired fasting glucose (IFG), a fasting plasma glucose (FPG) of 100–125 mg/dL following the American Diabetes Association definition used in the United States or 110–125 mg/dL following the World Health Organization definition used elsewhere, or (2) impaired glucose tolerance (IGT), a 2 h post-load glucose of 140–199 mg/dL in a 75 g oral glucose tolerance test (OGTT). Diabetes is defined as FPG >125 mg/dL, 2 h post-load glucose >199 mg/dL, or both.[3]

Glucose intolerance is a global problem, affecting an increasingly large percentage of the population. Worldwide, the number of adults aged 20–79 years with diabetes (~95% of all cases of diabetes are T2DM) is estimated to be 285 million (prevalence: 6.6%); by 2030, it is expected that 438 million will have diabetes (prevalence: 7.8%).[4] The United States, India, and China share the bulk of the diabetes burden, with more than 70 million people with diabetes in 2000, an estimate projected to increase to nearly 152 million by 2030.[5] These estimates likely underestimate the actual number of cases of T2DM worldwide, due to underreporting and because they do not include the most recent data from China that report a prevalence of diabetes in adults of 9.7% (92.4 million people).[6] Furthermore, projections estimating the future burden of diabetes are likely to rise given the overall population trends of increasing weight, aging, and urbanization.[5]

Traditionally, T2DM has been thought of as a disease of affluence; this is no longer the case. T2DM prevalence is increasing at an alarming rate in rural and aboriginal communities[7–9] and ~70% of people with diabetes live in low- and middle-income countries.[4] For example, in India, a country where 70% of the population lives in rural communities, there are over 40 million cases of T2DM.[10] In 2005–2006, a study in Sri Lanka reported that the prevalence of diabetes for adults aged 20 years or older was 11.0% in rural communities and 13.6% in urban settings.[11]

In the United States, it is estimated that 12.9% of the population aged 20 years or older has diabetes (including both diagnosed and undiagnosed diabetes).[12] Prevalence of diagnosed diabetes, which is now 7.7%, is expected to rise to 12% by 2050.[13] Diabetes affects some racial groups disproportionately; the prevalence of diabetes is 17% for non-Hispanic blacks, 14.7% for Mexican Americans, and 12.2% for non-Hispanic whites.[12] Native Americans have even higher rates of diabetes,[12,14] and in one study of Asian Indians living in a major U.S. city, the prevalence of diabetes was 18%.[15]

Furthermore, T2DM is often asymptomatic, which results in a delay in disease diagnosis with many people with T2DM only identified when secondary complications have developed. Global estimates of the prevalence of undiagnosed

diabetes are high. In the United States, the proportion of diabetes cases that are undiagnosed for all age adults is 40% and ranges from 32.5% for 20- to 39-year-olds to 46.0% for individuals 75 years of age or older.[12] Another study comparing 13 European cohorts reported the opposite trend. In men, undiagnosed diabetes rates were highest in the youngest age ranges (70% in men aged 30–39 years and 60% in men aged 40–49 years) and decreased with increasing age. In women, the highest proportion of undiagnosed diabetes (58%) was in middle-aged individuals (aged 40–49 years), although there was no clear trend of increasing or decreasing prevalence over age.[16] In Australian adults, approximately half of all people with diabetes were previously undiagnosed.[17] The DECODA study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia), an analysis of 11 Asian cohorts, found that undiagnosed diabetes prevalence ranged from 1.0% to 6.5% among Chinese and Japanese people and from 1.9% to 7.2% among Asian Indians.[18] The prevalence of undiagnosed diabetes in Thailand is estimated to be even higher: 9.6%.[19]

Data for the prevalence of prediabetes, especially the prevalence of IFG, are scarce. Worldwide, it is estimated that the prevalence of IGT is 7.9% (344 million people).[4] In the United States, the prevalence of prediabetes is 29.5% among people over 20 years and varies by race/ethnic group, ranging from 25.1% for non-Hispanic blacks to 31.7% for Mexican Americans. IFG is more common than IGT; the prevalence of IFG is 25.7%, compared to 13.8% for IGT.[12] In Europe, the prevalence of prediabetes rises with age (<15% for ages 30–59 years and between 15% and 30% after 60 years of age) and differs by gender.[16,20] For Asian populations, prediabetes prevalence is less than 18% for ages 30–59 years and 18%–26% after 60 years of age in Chinese and Japanese populations and less than 24% for Asian Indians aged 30–59 years and 20%–27% for Asian Indians 60 years of age or older.[18] The Korean prevalence of prediabetes by IFG criteria is 23.9%, or roughly 8.1 million people.[21]

SUSCEPTIBILITY TO DIABETES: HOW LIFESTYLE FACTORS CAUSE THE DEVELOPMENT OF PREDIABETES AND DIABETES

The increasing global prevalence of diabetes reflects both genetics (an expansion of nonwhite populations who have a predisposition to develop diabetes) and the environment (increases in both age and lifestyle-related factors—overweight and sedentary activity). Changes in lifestyle behaviors, namely excessive caloric intake and physical inactivity, lead to increases in insulin resistance which increase the risk of developing prediabetes and T2DM.[22] Higher body mass index (BMI) and lack of physical activity are both independently and strongly associated with increased risk of diabetes.[23] Aging also plays a role in increased insulin resistance; however, this appears to be attributable mainly to age-related obesity and inactivity, since older individuals who are nonobese and physically fit are not insulin resistant compared to nonobese, fit, younger individuals.[24]

Understanding the factors that make an individual susceptible to T2DM is an important area of study. Susceptibility to T2DM can be related to genetic predisposition and temporal susceptibility to epigenetic modulation.[25,26] The underlying genetic makeup of individuals and their experiences during pregnancy and childhood impact their susceptibility to diabetes development. Temporal modulation of genetic factors, often described as "metabolic programming," results from specific metabolic and nutritional influences that foster metabolic adaptations persisting throughout life.[27–29] The heritable changes that lead to chronic disease might occur during gametogenesis, preimplantation of embryogenesis, fetal and neonatal periods of development, puberty, or aging.[25]

In individuals with a genetic susceptibility to glucose intolerance, obesity and inactivity increase the risk of T2DM. This is illustrated clearly in the Pima Indians of the Southwest United States.[30] Adult Pima Indians living on a reservation in Arizona have a high prevalence of obesity (69%), little physical activity, and the highest prevalence of T2DM of any race/ethnic group in the United States (37.5%, see Figure 35.1). In contrast, Pima Indians living in Mexico, with the same genetic background but less obesity and more physical activity, have an 8.0% prevalence of diabetes, and non-Pima Mexicans, with levels of obesity and physical activity comparable to Pima Indians living in Mexico, have only a 2.5% prevalence of diabetes. When obesity and physical activity are comparable (Mexican Pimas compared to other Mexicans), genetics results in an approximately threefold increase in diabetes prevalence. Within the same genetic group (Pima Indians living in the United States or in Mexico), lifestyle factors ("environment") increase the diabetes prevalence almost fivefold.

Furthermore, changes in lifestyle factors can increase T2DM risk even in populations with low baseline genetic risk. The prevalence of diabetes is approximately four times higher among second-generation Japanese Americans than among native Japanese.[31] Japanese Americans display changes in lifestyle factors related to diabetes; Japanese Americans weigh more than their Japanese counterparts, though this is not statistically significant, and Japanese Americans consume a statistically significantly greater percentage of daily calories from animal protein compared to similarly aged men from Japan.[32]

Lifestyle factors can modify the balance needed between insulin secretion and insulin action, the two factors needed for normal glucose tolerance (NGT). Across a range of insulin action, glucose homeostasis can be maintained if insulin secretion is adequate. Figure 35.2 shows that if insulin action decreases (e.g., insulin resistance increases due to weight gain and/or inactivity) but β-cells can compensate for insulin resistance by an increase in insulin secretion, NGT is sustained and progression to diabetes does not occur. In contrast, individuals with impaired β-cells have inadequate compensatory secretion of insulin. If individuals with impaired β-cells become insulin-resistant, hyperglycemia ensues, potentially resulting in prediabetes

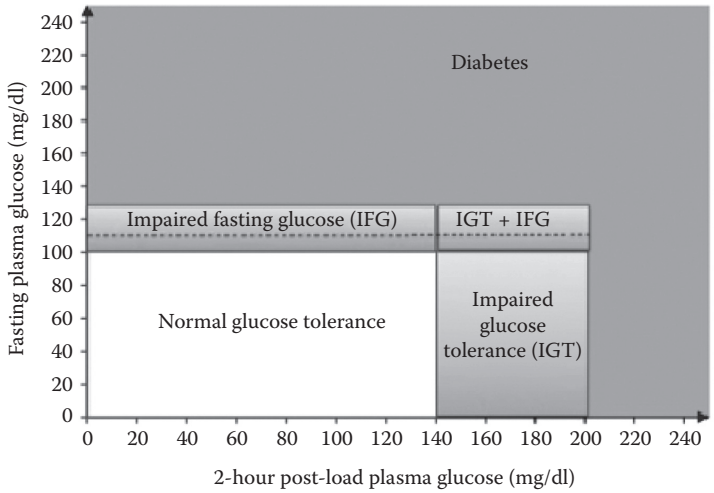


FIGURE 35.1 According to the definitions used by the American Diabetes Association, fasting plasma glucose levels of 100–125 mg/dl indicate impaired fasting glucose (IFG). A 2-hour post-load glucose of 140–199 mg/dl, as measured during an oral glucose tolerance test, indicates impaired glucose tolerance (IGT). IGT and IFG can occur in isolation or together. These two clinical phenotypes are known as prediabetes, a precursor for diabetes. Fasting or 2-hour glucose below these levels is considered normal; levels above IFG or IGT are diagnostic for diabetes. The dashed line indicates the definition for IFG used by the World Health Organization (110–125 mg/dl), a narrower range than that used by the American Diabetes Association.

Genetically susceptible population

	Pima indians living in the U.S.	Pima indians living in Mexico	General Mexican population
Diabetes prevalence	37.5%	8.0%	2.5%
Obesity rates	69.3%	13.2%	17.7%
Physical activity in hours/week	7.6	27.4	27.1

Low obesity, more physically active

FIGURE 35.2 Interaction between genetic susceptibility and lifestyle factors in type 2 diabetes risk: The Pima Indian Example. A healthier lifestyles can mitigate genetic risk for type 2 diabetes. (Adapted from Schulz, L.O. et al., *Diabetes Care*, 29, 1866, 2006; Weber, M.B. et al., *Am. J. Lifestyle Med*., 4, 468, 2010.)

and, with time, T2DM. Abnormalities of insulin secretion in persons with frank diabetes include reduced or absent first-phase responses to intravenous glucose,[34] delayed and blunted secretory responses to ingestion of a mixed meal,[35] alterations in the patterns of insulin secretion,[36] and increases in the plasma concentrations of proinsulin relative to those of insulin.[37]

While most individuals with diabetes or prediabetes have both impaired insulin secretion and impaired insulin action, and while hyperglycemia most often develops in people who already have insulin resistance phenotypes (e.g., overweight and/or sedentary), some slim, fit people also develop diabetes. Moreover, first-degree relatives of individuals with diabetes—those with NGT but at increased risk of developing diabetes—may exhibit insulin resistance and/or impaired insulin secretion.[38,39] Such observations have led to controversy as to whether insulin resistance or impaired insulin secretion is the "primary" cause of hyperglycemia in different individuals.[40] While such distinctions may not be essential for clinical management, they are important for both pathophysiological understanding and the development of health policies aimed at prevention. However, in part because of the lack of noninvasive methods to measure β-cell mass and function, at present we do not know whether the development of insulin resistance can "cause" β-cell failure over time in individuals whose β-cells were truly normal before insulin resistance developed. Regardless of the "primary" cause of hyperglycemia, the great majority of individuals with diabetes exhibit decreases in β-cell mass and function, leading to subsequent insulin deficiency.

Obesity increases insulin resistance via two mechanisms: (1) nonphysiological deposition of fat in visceral, hepatic, and

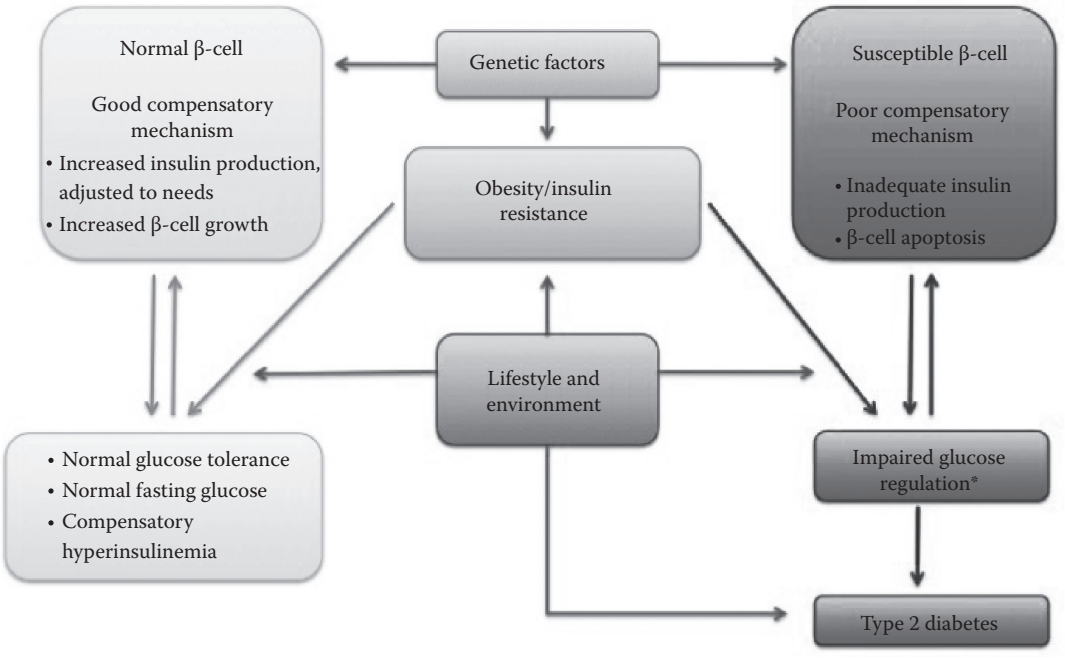
intramyocellular sites and (2) intracellular sequestration of GLUT4 glucose transporters in unexercised muscle, resulting in reduced glucose uptake.[41] Free fatty acids, produced more readily in visceral abdominal fat, decrease insulin sensitivity, impair vascular reactivity, and also increase endothelial dysfunction. "Toxic messages" from the adipose organ, such as free fatty acids, cytokines (e.g., an increase in tumor necrosis factor-α and a decrease in adiponectin), and oxidative stress, impair insulin action to restrain glucose production in the liver and promote glucose disposal in muscle.[42] The recent work of Shulman and colleagues has established increases in intracellular diacylglycerol (DAG) as an important mechanism of free fatty acid–induced insulin resistance in muscle,[39,43] disproving the "Randle hypothesis" of action via inhibition of pyruvate dehydrogenase.[44,45]

Reducing body weight and increasing exercise are key lifestyle factors to counter the effects of obesity on hyperglycemia. Diet and exercise can reduce adipose tissue and plasma concentrations of free fatty acids, improving glucose uptake. Exercise decreases concentrations of fatty acid metabolites (e.g., DAGs) to improve fatty acid–induced insulin resistance in humans.[39,46] In addition, exercise also stimulates the translocation of GLUT-4 to the plasma membrane, using signals that differ from the signals involved in insulin-induced GLUT-4 translocation.[41,47] As such, exercise improves glucose uptake and provides its own therapeutic benefit for those experiencing insulin resistance.[41,48]

The development of hyperglycemia (inadequate β-cell compensation for insulin resistance) reflects both impaired pancreatic β-cell function and loss of β-cell mass. The loss of β-cell mass is due to apoptosis, and β-cell mass is about 60% of normal in individuals with prediabetes, and 40% of normal in individuals with diabetes.[49] Accordingly, the extent to which lifestyle change to reduce insulin resistance can restore normoglycemia in individuals with prediabetes or diabetes depends on the β-cell defect, which is reflected by the clinical phenotype. As shown schematically in Figure 35.3, the highest insulin concentrations are required to promote glucose disposal into fat and muscle, the next highest to restrain glucose production in the liver, and the lowest to restrain lipolysis and ketogenesis. Thus, a mild β-cell defect presents as postprandial hyperglycemia, a moderate defect as fasting hyperglycemia, and a severe defect as ketoacidosis.

If the β-cell defect is mild, as in patients with prediabetes, lifestyle change to reduce insulin resistance can often restore normoglycemia and help prevent progression to diabetes. But if the β-cell defect is more severe, as in patients who are later in their natural histories and exhibit marked fasting hyperglycemia, lifestyle change is important to help control glucose excursions but may not restore normoglycemia, and pharmacological therapy will be needed. Lifestyle change also tends to improve postprandial hyperglycemia more than fasting hyperglycemia, because exercise can reduce insulin resistance in muscle (the major target of glucose disposal), but has less effect on the liver (the source of glucose production).

Different categories of prediabetes carry different risks of progression to frank diabetes. A 2004 study demonstrated that people with IGT are more insulin resistant than



*Impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)

FIGURE 35.3 Early susceptibility to impaired β-cell function and development of type 2 diabetes mellitus. Genetics, obesity, insulin resistance, lifestyle factors, and β-cell health interact to determine an individual's risk for developing type 2 diabetes. Normal β-cells are able to increase insulin secretion and maintain glucose homeostasis. On the other hand, β-cells that have poor compensatory mechanisms are unable to adjust insulin production in response to increased glucose levels or decreased insulin sensitivity, resulting in impaired glucose regulation and, eventually, frank type 2 diabetes. (Adapted from Kahn, S.E. et al., *Nature*, 444, 840, 2006.)

people with IFG and that IGT is more strongly associated with increases in cardiovascular disease[50]—an important distinction because IGT can only be identified through an OGTT, a test which is currently underutilized in the United States. Even within the category of IFG, people with FPG levels of 100–109 mg/dL have been shown to be at less risk of progression to diabetes than people with FPG levels of 110–125 mg/dL, likely because patients in the former category are earlier in their natural histories.[51] More studies are needed to see if lifestyle improvements can differentially impact those with IGT compared to IFG.

Thus, the development of glucose intolerance depends on both the degree of insulin resistance and the extent of β-cell reserve. Everyone who develops insulin resistance will not develop prediabetes, and everyone who develops prediabetes will not develop T2DM. However, because of the rising rates of obesity and sedentary activity and the resulting increase in insulin resistance, it is essential to emphasize healthy lifestyles to reduce insulin resistance and limit the development of glucose intolerance in individuals who are at risk, in order to minimize the effects of these conditions on the health of individuals and society. Furthermore, as glucose levels increase over the natural history of T2DM (insulin resistance to prediabetes to T2DM), β-cell mass and function decrease, making it harder for the body to sustain normal glucose. Accordingly, it is particularly important to utilize lifestyle change to "buy quality life-years of normoglycemia" early in the natural history of T2DM, via decreased insulin resistance and reduced β-cell challenge, since lifestyle change alone is less likely to restore normoglycemia later in the natural history.

LIFESTYLE INTERVENTIONS FOR DIABETES PREVENTION

Participation in lifestyle interventions that teach participants how to prevent diabetes and other chronic diseases through weight loss, increased physical activity, behavior change, and improvements in diet quality is related to significant decreases in T2DM incidence.[52–56] A meta-analysis of randomized, controlled, lifestyle intervention trials for T2DM prevention found that compared to control or placebo groups, lifestyle intervention participants had a 50% decrease in 1-year T2DM incidence (RR 0.55, 95% confidence interval: 0.44–0.69) and a 0.84 mmol/L decrease in 2 h plasma glucose (95% confidence interval: 0.39–1.29) compared to participants in the control or placebo groups.[57] Except in cases where there is an extreme weight loss (e.g., after bariatric surgery[58]), lifestyle modifications have shown little effect on fasting glucose, most likely because post-load, 2 h glucose reflects peripheral insulin resistance, while fasting glucose primarily reflects hepatic insulin resistance and a more severe β-cell defect.[59]

The Finnish Diabetes Prevention Study (DPS) and the U.S. Diabetes Prevention Program (DPP) showed a 58% reduction in diabetes incidence in study participants in the lifestyle group compared to those in the control group.[54,55] These studies were similar in several ways. Both were multicenter, randomized trials of diabetes prevention through lifestyle change, achieving weight loss (≥7% of baseline weight in the DPP and a ≥5% in the DPS) and increasing physical activity levels (at least 150 min of moderate physical activity per day in the DPP and ≥30 min/day of moderate physical activity in the DPS). However, there were key differences in the study design, participant goals, and lifestyle education curriculum between these two programs.

In the DPS, participants (522 middle-aged, overweight men and women with IGT from one of five study centers) were randomized to either the lifestyle intervention or usual care, and lifestyle participants were given additional dietary goals during the program: a reduction in dietary fat (total fat <30% of total energy, saturated fat <10% total energy) and an increase in dietary fiber (≥15 g/1000 kcal).[54] A nutritionist met with participants for seven individual sessions with phone calls between consultations to educate the participant on diet change (based on feedback from the participant's 3-day food record), physical activity, goal setting, and behavior change. In addition, participants were encouraged to attend voluntary group sessions (e.g., lectures, cooking classes, supermarket visits), and they were given the option of following a very low-calorie diet at months 6–7 to boost weight loss.

The DPP was a much larger study with 3234 overweight people, aged 25 years or older with IGT and IFG randomized to a placebo arm, metformin (850 mg twice daily), or an intensive lifestyle intervention. A troglitazone study arm was discontinued early due to potential liver toxicity associated with the drug. Diet change was not a primary goal of the DPP lifestyle intervention; however, participants were counseled on dietary fat reduction as a tool for weight loss. Participants in the lifestyle intervention met individually with a case manager once per week for 16 weeks followed by eight monthly maintenance sessions. Each lesson was individualized and culturally appropriate and covered topics including behavior change, goal setting, diet change (with a focus on fat reduction), and physical activity.[55,60]

Other studies have shown similar, albeit attenuated, results to the DPP and DPS. The Da Qing IGT and diabetes study,[53] another multicenter, diabetes prevention study for individuals with IGT, randomized participants by clinic to receive standard of care (control), diet education, exercise education, or both diet and exercise education. Depending on study arm, physicians counseled intervention arm participants to follow a low-fat diet with personal calorie and food group intake goals and/or taught participants to increase leisure-time physical activity by 1–2 units/day (units were defined as 30 min of mild-intensity exercise, 20 min of moderate-intensity exercise, 10 min of strenuous exercise, or 5 min of very strenuous exercise). Compared to the control group, individuals in the diet, exercise, and diet-plus-exercise groups had reductions in diabetes incidence of 31%, 46%, and 42%, respectively. Furthermore, the benefits of the lifestyle interventions were seen in all participants, even those who were not overweight at baseline.

Like the Da Qing IGT and diabetes study, the Indian Diabetes Prevention Programme (IDPP)[52] showed that lifestyle interventions are effective tools for diabetes prevention in low- and middle-income country settings. The IDPP included

531 subjects randomized to received standard health care advice (control), metformin, lifestyle advice, or metformin plus lifestyle advice. The lifestyle intervention in the IDPP had a lower effect on diabetes prevention than seen in the DPP or the DPS (28.5% reduction in diabetes incidence in the lifestyle arm compared to controls). In addition to the high rate of conversion to T2DM in the Asian Indian population and the lack of weight loss in study participants, this might be due to several key differences between the lifestyle curriculum in the IDPP and the other studies: (1) the IDPP was a worksite-based program while the other programs were community based, and participants might have been less motivated to make lifestyle changes; (2) IDPP participants with "active" jobs or who walked or biked to work were not counseled to increase their daily activity, so these people would not have done any added exercise; and (3) the IDPP was less intensive, with less frequent contact with study staff and dietary advice (maintain energy balance; reduce total fat, saturated fat, simple sugars, and refined carbohydrate intake; and increase fiber intake) was given only during monthly calls, which may not have been sufficient to lead to lasting behavior change. A pooled analysis of participants in the IDPP and the IDPP-2 studies showed that the lifestyle intervention was equally effective for T2DM risk reduction in participants with isolated IGT and those with both IGT and IFG.[61]

The Japan Diabetes Prevention Program[62] assessed the effectiveness of delivering lifestyle interventions in a primary care setting using existing resources. Patients aged 30–60 years with IGT were randomized to receive either standard of care treatment or group and individual diabetes prevention and lifestyle improvement education delivered by clinic staff. At 3 years, participants in the intervention arm had significant decreases in body weight and BMI and increases in insulin sensitivity (as measured by the Matsuda Index[63]), compared both to baseline and the control group. Although the relative risk reduction for T2DM was 53% for the intervention group compared to the control group, this reduction was not significant. These results show that clinic-based education can be beneficial for patients; however, the large loss to follow-up in this study (28%) is a reminder that maintaining motivation for lifestyle change in clinic patients is a challenge.

Continued follow-up of participants in lifestyle intervention trials show that the effects of lifestyle interventions on diabetes incidence are reduced but significant over the long term, even when participants gain back some of the weight lost during the intervention program.[53–55,64,65] After 7 year median follow-up in the DPS, the reduction in relative risk of diabetes was 36%[64], and in the Da Qing study, there was a 43% reduction in diabetes incidence in the combined lifestyle intervention groups compared to controls after 20 years of follow-up.[66] The reduction in the effectiveness over time might indicate that lifestyle interventions can only partially prevent or delay T2DM,[67] perhaps due to the inability of lifestyle inventions to affect β-cell function.[68] Over time, an age-related increase in insulin resistance might counteract the decrease in insulin resistance conferred by lifestyle change, allowing hyperglycemia to emerge because of the underlying β-cell defect. However, this does not detract from the importance of lifestyle change as a tool for increasing an individual's disability- and disease-free life-years and improving the general health of the population.

In addition to deducing diabetes risk, lifestyle interventions improve insulin responses,[69] whole body insulin sensitivity,[70] markers of inflammation (C-reactive protein [CRP], interleukin 6 [IL-6],[71] and plasminogen activator inhibitor[72]), aerobic capacity,[68] blood pressure, and plasma lipid levels.[73] Comparisons of data within and between studies of lifestyle interventions for diabetes prevention show that the beneficial effects of lifestyle change are consistent across gender, race/ethnic groups, and setting (e.g., see Refs. [52,55,68,73–75]) and are sustained in populations with increased diabetes risk (e.g., women with history of gestational diabetes[76] and participants with high levels of insulin resistance[77]). Furthermore, lifestyle interventions reduce diabetes risk and improve health behaviors in older participants and in people with normal BMI, populations often excluded in prevention trials. In the DPP, the reduction in diabetes incidence for those in the lifestyle intervention compared to the placebo group was greater for those in the oldest age group (71% for individuals aged 60 or more years, compared to 48% for those aged 25–44 years) and for individuals with the lowest BMIs (65% for people with BMIs of 22 to <30 kg/m^2, compared to 51% for those with BMIs of ≥35 kg/m^2).[55] The increased benefits for older populations are likely due to lifestyle interventions overcoming age-related increases in peripheral insulin resistance (as reflected by higher 2 h post-load glucose values).[78] The difference in effect based on BMI is probably attributable to the same percent weight loss having less effect on insulin resistance for people with more body fat than for individuals with less baseline body fat. Finally, lifestyle interventions can overcome genetic susceptibility to T2DM,[52,55] further supporting the importance of lifestyle change for diabetes prevention.[79]

It is important to note, however, that the large randomized trials of lifestyle interventions for diabetes prevention included participants with IGT or both IGT and IFG; none included participants with isolated IFG. Although it is yet to be seen if these results extend to all people with prediabetes, lifestyle participants in the DPP had an increase in fasting glucose over time that was significantly lower than the FPG increase in the placebo group,[55] indicating that lifestyle change might also be effective for individuals with IFG. Future studies will help to answer this question.

Diabetes is an economically costly disease; the estimated annual increase in expenditures attributed to diabetes for a person in the United States is $6649/year.[1] Conversely, lifestyle interventions, at various levels of intensity (from the very intensive DPP to the less intensive IDPP), are cost-effective for preventing diabetes.[80–82] For example, in the DPP, the cost of the lifestyle intervention from a societal perspective was $24,400 per case of diabetes delayed or prevented, less than the cost per case of diabetes prevented or delayed for metformin ($34,500); from the perspective of the health system, compared to placebo, the cost was $15,655 per case of diabetes prevented for the lifestyle intervention and $31,338 per case of diabetes prevented for metformin.[82]

Based on the findings of lifestyle intervention trials and other related studies, expert organizations, including the American Diabetes Association,[83] the International Diabetes Federation,[84] the European Society of Cardiology and the European Association for the Study of Diabetes,[85] and the Canadian Diabetes Association,[86] recommend lifestyle changes (e.g., increased physical activity, weight loss) for T2DM prevention.

Given the strong evidence for the effectiveness of existing lifestyle interventions for diabetes prevention, future research in this field should focus on translational research. Translational research seeks to bridge the gap between basic science and effectiveness studies and implementation of proven research in clinics and the community.[87–90] Several translation trials of lifestyle interventions for T2DM prevention are ongoing. The Finnish National Diabetes Prevention Program (FIN-D2D),[91] based on the DPS lifestyle intervention, seeks to prevent T2DM in the Finnish population with targeted strategies for high-risk individuals, early treatment, and population prevention. Participants in this diabetes prevention program for high-risk individuals who lost ≥5% of baseline weight (17.5% of the 2798 person sample) had a 69% reduction in diabetes risk and significantly greater improvements in blood pressure, plasma lipids, and lipoproteins compared to the group that maintained their baseline weight. The Diabetes in Europe—Prevention using Lifestyle, Physical Activity, and Nutritional Intervention (DE-PLAN)—is a European Union project to create a model to identify individuals at high risk for T2DM and establish the cost-effectiveness of translating T2DM prevention research into the existing health care systems of EU countries. Participants in the Greek study site,[92] which testing the translation of diabetes education at health clinics and worksites, had significant weight loss, and individuals at highest risk of converting to T2DM, those with both IGT and IFG, attended the most education sessions and lost the most weight of any subgroup in the study. Pilot studies of Diabetes Prevention Program translations in the United States, a faith-based program for African Americans held an African American church,[75] the Diabetes Education and Prevention with a Lifestyle Intervention Offered at the YMCA (the DEPLOY study),[93] and the PILI 'Ohana Project in Hawaii,[94] have shown promising results with participants displaying decreases in body weight, blood pressure, FPG, and total cholesterol and/or increasing in physical functioning. The Tehran Lipid and Glucose Study in Iran was a nonrandomized trial comparing community-based lifestyle education (nutrition education classes, public conferences, talks at mosques, distribution of educational materials, and the use of trained community health educators) and standard of care. Although loss to follow-up was high, participants in the lifestyle arm had lower increases in diabetes risk factors (e.g., weight, waist circumference, FPG) than controls, and there was a significant reduction in relative risk of T2DM in the intervention arm compared to the control (RRR = 65%, $p < 0.003$).[95]

LIFESTYLE INTERVENTIONS AND MANAGEMENT OF DIABETES

Similarly, T2DM patients receiving lifestyle interventions in community or clinical settings exhibit improvements in insulin sensitivity and resting energy expenditure and decreases in fasting glucose, HbA1c, body weight, BMI, low-density lipoprotein (LDL) cholesterol, and blood pressure.[96–102] In one trial, physicians counseled their T2DM patients on lifestyle changes at a baseline visit and over the phone in the following months. Patients who increased their levels of physical activity the most had improvements in health outcomes (significant reductions in weight, BMI, waist circumference, FPG, heart rate, and LDL; significant increases in high-density lipoprotein (HDL); and a 4%–5% reduction in 10-year coronary heart disease risk) and significant reductions in medical and indirect social costs related to T2DM.[103] However, these effects may be less pronounced in individuals with long duration of T2DM or poorly controlled T2DM. The Japan Diabetes Complications Study[104] randomized a hospital-based population of T2DM patients (N = 1304, mean duration of T2DM: 10.9 ± 7.2 years) to conventional treatment or a lifestyle intervention program delivered through individual counseling by medical professionals focusing on physical activity, adherence to diabetes treatment, and dietary habits. The goal of the study was to determine if a lifestyle intervention affected the incidence of T2DM-associated vascular complications. After 8 years of follow-up, the researchers found that the intervention had little effect on glycemic control and no appreciable effect on risk factors for secondary T2DM complications; however, participants in the intervention arm had a significantly reduced risk of stroke (HR 0.62, $p = 0.04$). Participants in the intervention arm (a group-care model for intensive lifestyle intervention for patients with T2DM) of the Rethink Organization to iMprove Education and Outcomes (ROMEO)[105] study had increased self-reported quality of life; improvements in plasma lipids, health behaviors, and diabetes knowledge; and decreased weight, BMI, HbA1c, FPG, blood pressure, and creatinine ($p < 0.001$ for all) compared to controls in individual care, indicating that group-based lifestyle education for T2DM patients may further improve diabetes management and reduce risk factors for secondary diabetes complications.

The Look AHEAD (Action for HEAlth in Diabetes)[106] study randomly assigned overweight and obese subjects with T2DM to receive either usual care or an intensive lifestyle intervention that focused on weight loss and increased physical activity. The lifestyle intervention included group-based classes, individual monthly meetings with a lifestyle counselor, calorie reduction through diet change and a liquid meal replacement plan, and increased physical activity. In addition, select participants were prescribed a weight loss drug, Orlistat. At 1 year, lifestyle intervention participants lost significantly more weight than those in the control group (6.15% weight loss vs. 0.7% ± 4.8% weight loss) and had significant improvements in insulin sensitivity, fasting glucose,

and free fatty acids and decreases in weight, body fat, and hepatic fat.[107,108] The odds of reaching the weight loss goal of 7% were highest for participants in the highest quartiles of physical activity, consumption of meal replacements, and attendance at study classes. High self-reported physical activity correlated strongest with weight loss.[108] At 4 years, the lifestyle intervention participants continued to show marked improvements in health compared to the controls, maintaining a greater percent weight loss (6.15% vs. 0.88%) and showing larger improvements in physical fitness level, blood pressure, HDL cholesterol, and triglyceride levels, and glucose control (HbA1c level decreased by 0.36% in the lifestyle group compared to 0.09% in the standard of care group).[109] Furthermore, spouses of Look AHEAD intensive lifestyle intervention participants had greater reductions in body weight, total energy and total energy from fat, and reported more low-fat and less high-fat foods in their homes than control participants' spouses.[110] Trials which are currently under way of lifestyle interventions for people with T2DM in the United States[111] and abroad[112] will add to the literature on the long-term effects of lifestyle interventions on diabetes care and prevention of secondary complications of T2DM.

COMMON COMPONENTS OF LIFESTYLE INTERVENTIONS PROGRAMS

The lifestyle interventions used in the randomized trials discussed earlier have several unifying features, which are summarized in Figure 35.4; in each, participants were counseled on (1) weight loss; (2) increasing physical activity; (3) a healthy, well-balanced diet; and (4) tools for behavior change.

Weight loss, changes in body fat distribution, and increases in physical activity (independent of weight loss) have been shown to be determinants of T2DM risk reduction in lifestyle intervention trials.[113–115] Excess weight and obesity are strongly correlated with T2DM risk.[116] Lifetime diabetes risk increases as BMI increases[117]; overweight- or obese-level BMIs are associated with increased T2DM risk[118]; and diabetes risk increases by 12% for each unit of BMI increase.[119] Conversely, a 10% weight loss reduces the risk of T2DM by 0.5%–1.7% (depending on gender, BMI, and age).[120] The Look AHEAD study, the DPP, and the DPS advised lifestyle arm participant to lose at least a 5%–7% of their baseline bodyweight.[54,60,111] In the DPP lifestyle intervention group, BMI, waist and hip circumference, weight, and waist-to-hip ratio predicted diabetes incidence in both sexes, and diabetes risk reduction in the lifestyle intervention arm was significantly predicted by weight, BMI, and waist reduction in women and by weight, BMI, waist-to-hip ratio, waist circumference, and subcutaneous and visceral fat reduction in men.[113] In Look AHEAD, among participants in the intensive lifestyle intervention, changes in weight and fat mass, as well as decreases in hepatic fat, best predicted improvements in peripheral insulin sensitivity.[107]

Weight loss is accomplished by inducing a calorie deficit through increasing physical activity, decreasing calorie intake, or, ideally, both. Most lifestyle interventions recommend at least 150 min/week of moderate- to vigorous-level physical activity.[53,113–115] An increase in moderate to vigorous physical activity is associated with a reduction in diabetes risk of 63%–65%,[114] and even short-term interventions that increase moderate-intensity exercise have increased participants' fitness level[121,122] and reduced cardiovascular[123–126] and diabetes[127,128] risk factors. Furthermore, the addition of resistance training exercises in T2DM patients and patients with IGT enhances insulin sensitivity compared to aerobic exercise alone.[98]

Even so, regular physical activity is low in the general population (only 49.7% of men and 46.7% of women in the United States engage in regular physical activity[129]) and in

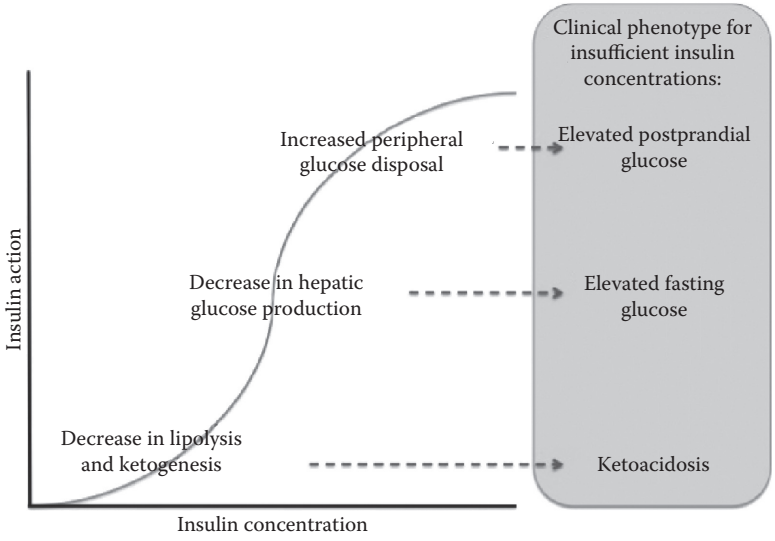


FIGURE 35.4 Degree of insulin deficit explains clinical phenotype. (a) The relative progression of insulin concentrations required for different actions of insulin and (b) the clinical phenotypes corresponding to insulin concentrations insufficient for that aspect of insulin action. (Adapted from Weber, M.B. et al., *Am. J. Lifestyle Med*., 4, 468, 2010.)

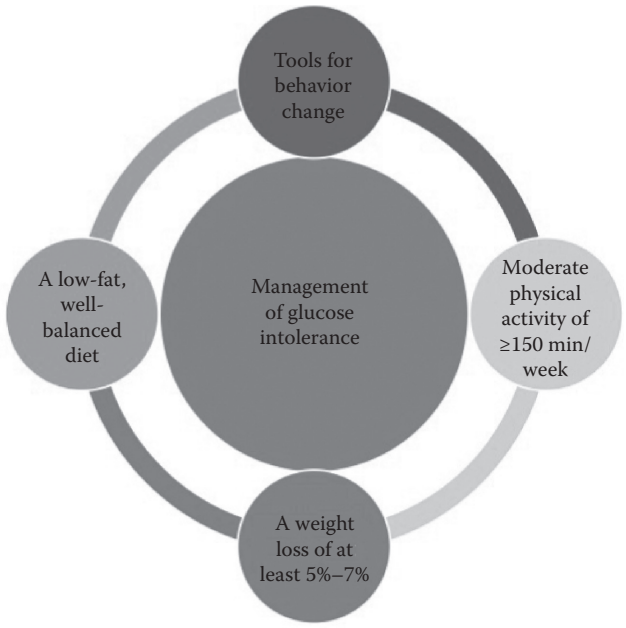


FIGURE 35.5 Components of successful lifestyle interventions for diabetes prevention and management. Randomized trials of lifestyle interventions for diabetes prevention and management include tools for behavior change based on established behavioral health theories; recommendations to participate in at least 150 min of moderate- to vigorous-level physical activity per week; a weight loss of at least 5%–7% of baseline weight; and advice to follow a well-balanced, low-fat diet.

individuals with T2DM.[130] For individuals who are reluctant to participate in an exercise program, gradually increasing exercise quantity will likely increase adherence and acceptability,[131] and programs including both endurance and resistance exercises increase compliance, probably because they increase interest by allowing participants to do a variety of exercises.[132] Simple tools, like pedometers, can be used to monitor and encourage activity. Pedometers have been shown to increase physical activity levels in T2DM patients.[96] In the Prediabetes Risk Education and Physical Activity Recommendation and Encouragement (PREPARE) Programme,[133] overweight or obese individuals with IGT were randomized to receive a control intervention or a single, group-based education program with or without pedometers. In the pedometer group, 2 h and fasting glucose decreased significantly at 3 and 12 months compared to both baseline levels and the control group. In the group with intervention only, there was no significant difference in fasting or 2 h glucose at any time point. Furthermore, self-reported overall moderate-to-vigorous activity and walking was significantly greater for the pedometer group compared to the control group at all time points.

Decreasing calorie intake and improving diet quality are important for diabetes prevention and management; specifically, individuals who wish to prevent diabetes or diabetes-related complications should consume a well-balanced diet rich in whole grains, fruit, and vegetables with <30% total fat and no more than 10% saturated fat. A prospective analysis of the Whitehall II cohort compared risk of cardiometabolic disease and mortality for several different diet patterns: an unhealthy diet pattern (full-fat dairy products, refined grains, processed meat, and fried foods), a sweet dietary pattern (high-fat dairy, dessert items, processed meats, and refined grains), a Mediterranean-like diet (fruits and vegetables, rice, pasta, and wine), and a healthy diet (low-fat dairy, whole grains, fruits and vegetables, and moderate alcohol). The analysis showed that the healthy diet, a low-fat diet rich in fiber, reduced the 15 year risk of diabetes and death from a coronary event or nonfatal myocardial infarction, compared with the unhealthy diet and only the healthy diet significantly reduced diabetes risk (HR 0.71, 95% confidence interval: 0.51–0.98).[134] Similarly, the DASH dietary pattern (a low-fat, high-fiber diet rich in vegetables, fruit, and low-fat dairy products) was inversely associated with diabetes risk.[135] In the DPS, consuming a low-fat, high-fiber diet had a dose-dependent affect on sustained weight loss and was also associated with reduced diabetes risk.[136] Diets low in saturated fat and high in unsaturated fat, fruit, vegetable, and fiber intake (e.g., the Mediterranean Diet) have also been shown to be beneficial for glucose control for patients with T2DM compared to diets with higher contents of simple sugars and carbohydrates.[137] The PREDIMED-Reus Nutrition intervention randomized trial[138] randomized healthy individuals aged 55–80 years old to one of three noncaloric restrictive diets: a low-fat diet or a Mediterranean-style diet (high intake of vegetables, beans, fruits, nuts, fish and olive oils with a low consumption of meat, high-fat dairy products, and processed foods) supplemented with either free extra virgin olive oil or mixed nuts. Even without significant changes in weight or physical activity in any group, incident diabetes was 51% lower in the olive oil group and 52% lower in the mixed nut group compared to the low-fat diet group; however, since only 21% of participants in the low-fat group reached the goal of reducing fat to <35% total energy, this group better represented a standard diet. In addition, diets reduced in glycemic index and glycemic load may also be useful in helping for preventing the development of T2DM,[139] and decreasing intake of simple sugars alone (without weight loss) results in improvements in glycemic control in obese T2DM patients.[140]

Dietary changes should also be made gradually over time starting with small behavior changes (e.g., eating fried foods only on occasion or switching from white to whole grain breads). Even gradual changes can be difficult if individuals do not have the tools to make lasting behavior changes. That is why successful programs, like Look AHEAD, the DPP, and the DPS, included information on health behavior change that is based on proven behavioral health theories (e.g., Prochaska's Stages of Change Model[141] and the Health Beliefs Model[142]).

In order to change behavior, individuals must have the ability to problem solve, a belief in their ability to succeed, and the tools to overcome barriers to behavior change. Self-efficacy, an individual's self-perception of his/her ability to change, is a mediator of behavior change.[143] In the DPP, exercise self-efficacy was significantly and positively correlated with mean leisure-time physical activity throughout the study.[144] Patients

with low self-efficacy for changing diet or increasing physical activity should be encouraged and provided with information or resources to aid them in their attempts at change. Also, health care providers should help patients to identify barriers and ways to overcome these barriers.[145] Social support, such as that provided in group-based weight loss programs or walking groups, is an effective tool to help people succeed in making and sustaining behavior changes[146] and could be used to help patients at greatest risk of failing in their attempts at lifestyle change. Research has indicated that patients with higher BMI, anxiety, depression, or stress might require extra support and encouragement to make and sustain behavior changes.[144] Finally, lifestyle messages should be culturally appropriate to improve acceptability and adherence. When people are approached in a culturally sensitive way, they are more receptive to health messages.[147,148] In addition, culturally appropriate advice can be easier to utilize immediately, as participants do not have to modify the advice on their own to account for common food and activity choices in their community.

Even though lifestyle interventions have been shown to be highly effective for reducing the risk of T2DM, they may not prevent the development of diabetes in individuals whose prediabetes involves a more severe β-cell defect. It is therefore vital that these patients be monitored closely. Furthermore, for these patients and in those who begin lifestyle change later in their natural history of glucose intolerance, glucose-lowering drugs might be needed earlier to complement the lifestyle interventions and to reduce insulin resistance. The American Diabetes Association recommends that individuals with both IFG and IGT and one additional risk factor for progression to diabetes (age <60 years, BMI ≥ 35 kg/m^2, family history of diabetes in a first-degree relative, elevated triglycerides, reduced HDL cholesterol, or HbA1c > 6.0%) be considered for treatment with metformin, in addition to lifestyle modification.[149]

CONCLUSION

T2DM is a global public health problem, brought on in large part by secular trends in lifestyle choices (decreasing physical activity and increasing body weight), which increase insulin resistance. Conversely, improvements in lifestyle, namely weight loss, behavior change, diet improvement, and increased physical activity, can effectively decrease insulin resistance leading to reductions in diabetes incidence in high-risk populations and improvements in disease management in people with T2DM. Successful lifestyle interventions should include tools for behavior changed based on existing health behavior models and recommendations to lose 5%–7% of baseline body weight, increase physical activity to at least 150 min/week, and follow a balanced, low-fat, high-fiber diet. Clinicians should advise patients at risk of developing T2DM and patients already diagnosed with T2DM to modify their lifestyle while continuing to monitor glucose levels to chart the patients' progress and identify deteriorations in glucose tolerance that might signal a need for pharmacological therapy.

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36 Lifestyle Approaches to the Metabolic Syndrome

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CONTENTS

Introduction 455
Metabolic Syndrome: Definition 456
Metabolic Syndrome: Pathophysiology 456
Metabolic Syndrome: Management of Components 457
Lifestyle Modification: Glucose Intolerance (Landmark Studies) 457
China Da Qing Diabetes Prevention Study 458
Finnish Diabetes Prevention Study 458
Diabetes Prevention Program 458
Lifestyle Modification: Obesity 459
Diet and Weight Loss 459
Physical Activity and Combination of Physical Activity and Diet 459
Lifestyle Modification: Hypertension 459
Weight Loss 459
Diet 459
Physical Activity and Combination of Physical Activity and Diet 461
Lifestyle Modification: Lipids, and Inflammatory and Prothrombotic Markers 461
Diet 461
Physical Activity and Combination of Physical Activity and Diet 462
Lifestyle Modification: Resistance Training 462
Alternative Strategies for Managing Metabolic Syndrome 462
Smoking Cessation 462
Botanicals 462
Pharmaceutical 463
Summary 463
References 463

INTRODUCTION

Metabolic syndrome refers to a clustering of traditional cardiovascular disease (CVD) risk factors that include insulin resistance, dysglycemia, abdominal obesity, atherogenic dyslipidemia, and hypertension, plus the nontraditional CVD risk factors such as proinflammatory and prothrombotic states.[1] Individuals with metabolic syndrome are five times more likely to develop type 2 diabetes and twice as likely to have CVD.[2,3] According to the National Health and Nutrition Examination Survey (NHANES) 2003–2006, ~34% of the adults in the United States have this syndrome.[4] The metabolic syndrome increases with age and body mass index (BMI); however, BMI appears to have a more dramatic effect.[4] Similarly, other countries have experienced an increased prevalence of the metabolic syndrome, suggesting the syndrome is a worldwide problem, possibly attributable to an increase in obesity and sedentary lifestyle.[5–10] This worldwide problem underscores the urgent need to develop therapeutic interventions for the prevention and treatment of this syndrome, thus reducing the societal burden of CVD and type 2 diabetes.

Pharmacological therapies targeted to treat the individual components of metabolic syndrome have been the conventional therapeutic approach. However, lifestyle interventions can be as effective as medication, but without the untoward side effects. In this review, the definition and pathophysiology of metabolic syndrome, and the numerous lifestyle interventions used to treat the syndrome will be discussed.

* William T. Cefalu's effort funded in part by P50AT002776-01 from the National Center for Complementary and Alternative Medicine and the Office of Dietary Supplements, which funds the Botanical Research Center of Pennington Biomedical Research Center and the Biotech Center of Rutgers University.

METABOLIC SYNDROME: DEFINITION

Due to the vague underlying pathophysiological processes leading to the metabolic syndrome's development and the perplexity between the numerous conceptual definitions, the syndrome continues to be a source of medical controversy. Throughout the years, several definitions for the metabolic syndrome have been proposed by various organizations such as the World Health Organization (WHO),[11] International Diabetes Federation (IDF),[12] American Heart Association and National Heart Lung and Blood Institute (AHA/NHLBI),[1] and National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).[13] Recently, a unified definition of the metabolic syndrome was proposed by the Joint Interim Societies (JIS) which includes the IDF Task Force on Epidemiology and Prevention, NHLBI, AHA, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity.[14]

All of the renowned health organizations concur with the decision to include the CVD risk factors, such as fasting glucose, obesity, blood pressure, triglycerides, and high-density lipoprotein cholesterol (HDL-C), in the definition of the metabolic syndrome. However, the groups differ in the combined risk factors that are used to diagnose the metabolic syndrome and the cutoff points for each risk factor. The various definitions of metabolic syndrome are compared in Table 36.1.

METABOLIC SYNDROME: PATHOPHYSIOLOGY

The concept of metabolic syndrome was first introduced as syndrome X by Dr. Gerald Reaven in 1988.[15] He proposed insulin resistance as the driving force of the syndrome.[15,16] Insulin resistance occurs when tissues cannot effectively respond to insulin, resulting in a decreased uptake of glucose into muscle and adipose tissues.[15] Insulin resistance is important in the natural history of type 2 diabetes and metabolic syndrome. Specifically, insulin resistance is a key pathophysiological parameter associated with both obesity and type 2 diabetes, as well as with other traditional and nontraditional CVD risk factors. Initially, insulin resistance exists in the prediabetic state and necessitates hyperinsulinemia in order to maintain normal glucose tolerance. However, if hyperinsulinemia is not compensated, insulin resistance can lead to progression from prediabetes to type 2 diabetes and CVD.[15,17–19] Since the metabolic syndrome may precede the development of type 2 diabetes, the

TABLE 36.1
Definitions of Metabolic Syndrome

	WHO	NCEP-ATP III	AHA/NHLBI	IDF	JIS
Required for diagnosis	Insulin resistance: type 2 diabetes, IFG (>110 mg/dL[a]), IGT (2 h > 140 mg/dL), or low insulin sensitivity[b]; plus ≥2 of the following risk factors	≥3 of the following risk factors	≥3 of the following risk factors	Central obesity (increase WC country/ethnic specific) plus ≥2 of the following risk factors	≥3 of the following risk factors
Obesity	W/H: men, >0.9; women, >0.85; and/or BMI >30 kg/m^2	WC: men, ≥102 cm, women, ≥88 cm	WC: men, ≥102 cm or women, ≥88 cm	Required (see previous text)	WC: country/ethnic-specific
Plasma glucose	Required (see previous text)	IFG (≥110 mg/dL[a]) or T2DM	IFG (≥100 mg/dL) or T2DM	IFG (≥100 mg/dL) or T2DM	IFG (≥100 mg/dL) or T2DM
Blood pressure	≥140/90 mm Hg or medication	≥130/85 mm Hg	≥130/85 mm Hg or medication	≥130/85 mm Hg or medication	≥130/85 mm Hg or medication
Triglycerides	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL or medication	≥150 mg/dL or medication	≥150 mg/dL or medication
High-density lipoprotein	Men, <35 mg/dL or women, <39 mg/dL	Men, <40 mg/dL or women, <50 mg/dL	Men, <40 mg/dL; women, <50 mg/dL; or medication	Men, <40 mg/dL; women, <50 mg/dL; or medication	Men, <40 mg/dL; women, <50 mg/dL; or medication

WHO, World Health Organization; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; IDF, International Diabetes Federation; JIS, Joint Interim Societies; BMI, body mass index; 2 h, 2 h post glucose load of 75 g; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; WC, waist circumference; W/H, waist–hip ratio.

[a] The 2001 definition identified IFG of ≥110 mg/dL as elevated. This was modified in 2004 to be ≥100 mg/dL in accordance with the American Diabetes Association's updated definition of IFG.

[b] Insulin sensitivity measured under hyperinsulinemic–euglycemic conditions; glucose uptake below lowest quartile for background population under investigation.

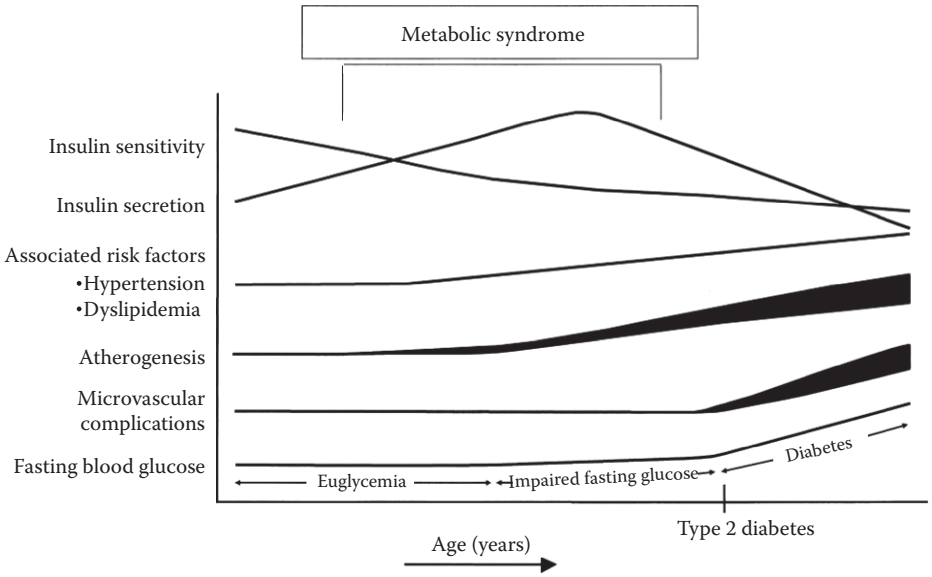


FIGURE 36.1 Schematic demonstrating the development of metabolic syndrome in the natural history of type 2 diabetes. As shown, with the development of metabolic syndrome, there is an increasing prevalence of the associated risk factors that are observed many years before the diagnosis of type 2 diabetes is made. In addition, the CVD risk is greatly accelerated during this time. Therefore, CVD risk is elevated many years prior to the diagnosis of diabetes in large part owing to the presence of metabolic syndrome. When the pancreas fails to compensate for the insulin resistance, hyperglycemia ensues, which also contributes greatly to CVD risk. (From Cefalu, W.T., Insulin resistance, *The Medical Management of Diabetes Mellitus*, Leahy, J. et al., eds., Marcel Dekker, New York, 2000, pp. 57–75. Reproduced with permission.)

presence of the syndrome may significantly contribute to the increase in CVD risk observed years prior to the diagnosis of type 2 diabetes (Figure 36.1). As early as 15 years prior to the diagnosis of type 2 diabetes, the relative risk for CVD is significantly increased and continues to increase particularly in the years closer to the diagnosis of diabetes.[20] The pathogenesis of the metabolic syndrome is complex and thus far incompletely understood.[21] To date, a single, central underlying mechanism has not been identified, although insulin resistance and central obesity have both been proposed as integral components in this process.[15,22] The most important dimension of the metabolic syndrome is its association with the risk of developing type 2 diabetes and CVD. Understanding of this complex set of risk factors is limited and warrants further research.

METABOLIC SYNDROME: MANAGEMENT OF COMPONENTS

The primary strategy for prevention and treatment of the metabolic syndrome is lifestyle modification through changes in diet and physical activity with the goal of improving risk factors for CVD.[23] The AHA's goals and recommendations for achieving diet and lifestyle change are provided in Tables 36.2 and 36.3.[24] Even in patients with established diabetes, intensive management of the metabolic syndrome will reduce the higher risk of CVD. Most individuals affected by the metabolic syndrome are overweight or obese; hence, weight reduction represents the principal goal of most intervention studies.[22,25] Weight loss is associated with significant improvement in the clinical abnormalities of the metabolic syndrome, such as blood glucose, lipid profile, and blood pressure.[26] Even a moderate weight reduction of 7% in 4 weeks can improve the metabolic syndrome despite persistence of a high BMI.[27] The greater the weight reduction, the greater the improvement in CVD risk factors. Likewise, effective lifestyle interventions should also increase insulin sensitivity and HDL-C levels, and decrease triglyceride, glucose concentrations, and blood pressure.

TABLE 36.2
AHA 2006 Diet and Lifestyle Goals for Cardiovascular Disease Risk Reduction

- Eat an overall healthy diet
- Achieve a healthy body weight (body mass index 18.5–24.9 kg/m^2)
- Achieve recommended lipid levels:
  Low-density lipoprotein cholesterol <100 mg/dL
  High-density lipoprotein cholesterol >50 mg/dL in women, >40 mg/dL in men
- Triglycerides <150 mg/dL
- Achieve a normal blood glucose level (≤100 mg/dL)
- Engage in physical activity
- Avoid use of and exposure to tobacco products

Source: Modified from American Heart Association Nutrition Committee, Lichtenstein, A.H. et al., *Circulation*, 114, 83, 2006.

Lifestyle Modification: Glucose Intolerance (Landmark Studies)

The effectiveness of lifestyle intervention in preventing the development of type 2 diabetes in high-risk individuals has

TABLE 36.3
AHA 2006 Diet and Lifestyle Recommendations for Cardiovascular Disease Risk Reduction

- Achieve or maintain a healthy body weight (balance calorie intake and physical activity)
- Eat a diet rich in vegetables and fruits
- Select whole-grain, high-fiber foods
- Eat fish, especially oily fish, at least two times a week
- Limit saturated fat intake to <7% of energy, *trans*-fat to < 1% of energy, and cholesterol to <300 mg per day
- Minimize intake of food and drinks with added sugar
- Select and prepare foods with little or no salt
- Consume alcohol only in moderation

Source: Modified from American Heart Association Nutrition Committee, Lichtenstein, A.H. et al., *Circulation*, 114, 88, 2006.

been demonstrated in three prominent studies: China Da Qing Diabetes Prevention Study,[28] Finnish Diabetes Prevention Study,[29] and Diabetes Prevention Program (DPP).[30] These studies targeted individuals with impaired glucose tolerance (IGT). Dietary modification (i.e., reduction in energy) and increased physical activity were the main lifestyle interventions, which resulted in subjects losing weight (approximately ≥5%). The progression from IGT to type 2 diabetes over a defined period (3–6 years) of observation in the intervention group versus a comparison group was the primary outcome for the studies.[28–30]

China Da Qing Diabetes Prevention Study

The Da Qing study is a major controlled trial that examined the effects of dietary modification, weight loss, and increased physical activity in preventing diabetes.[28] In this study, 577 Chinese adults with IGT were enrolled. The subjects were randomized to one of three treatment groups (diet only, exercise only, or diet plus exercise) or control group. The dietary group was encouraged to reduce their weight if BMI was ≥25 kg/m^2 (61% of all participants) aiming at a BMI of 23 kg/m^2. The exercise group had to increase their level of leisure-time activity by at least 1–2 units (i.e., 1 unit equaled 30 min slow walking, 10 min slow running, or 5 min swimming) per day. The subjects were evaluated every 2 years for 6 years. At year 6, the diet, exercise, and diet plus exercise groups had a reduction in developing type 2 diabetes (31%, 46%, and 42%, respectively). The Da Qing Study is important because it establishes the feasibility of implementing a successful lifestyle modification program in an outpatient clinic setting.

In 2006, a follow-up Da Qing Study was conducted in the subjects with IGT to assess the long-term effect of the lifestyle interventions on type 2 diabetes and other related health conditions.[31] Compared with control participants, those in the diet plus exercise lifestyle intervention group had a 43% lower incidence of type 2 diabetes up to 14 years after the 6 year (years 1986–1992) active intervention ceased. In addition, the diabetes onset was delayed an average of 3.6 years. There were no significant differences between the intervention and control groups for CVD incidence and mortality, and all-cause mortality. These results indicate that benefits from lifestyle intervention can be maintained long term after active intervention has been stopped.

Finnish Diabetes Prevention Study

Another key clinical trial is the Finnish Diabetes Prevention Study, which examined the effects of an intensive modification program in 522 middle-aged and overweight Finnish subjects with IGT.[29] Subjects were randomized to either intensive lifestyle intervention or a control group. The lifestyle intervention goals included reduction in weight of ≥5%, total fat intake <30% of energy, saturated fat intake <10% of energy, fiber intake ≥15 g/1000 kcal, and moderate exercise for ≥30 min/day (recommended aerobic and resistance training). After the first year, there were reductions in the clinical and metabolic variables from baseline for weight, waist circumference, glucose, insulin, triglycerides, and blood pressure in the intervention group. The body weight decreased on average 4 kg (5%) in the intervention group and 1 kg (1%) in the control group. At year 2, the lifestyle intervention group continued to have a greater weight loss than the control group. After 4 years, the cumulative incidence of diabetes was 11% in the intervention group and 23% in the control group. The risk of diabetes was significantly reduced by 58% in the lifestyle group. During the overall follow-up period of 7 years (4 years of active intervention), the incidence of diabetes rates were still lower in the intervention (4.3% per 100 person-years) versus control (7.4% per 100 person-years) groups.[32] This indicated a 43% reduction in the relative risk of diabetes. Most importantly, the beneficial effects of lifestyle intervention were maintained after discontinuation of the study.[32]

Diabetes Prevention Program

The DPP is the largest study in the United States that examined the efficiency of a lifestyle modification program to prevent or delay the development of type 2 diabetes in people with IGT.[30] This multicenter trial randomized 3234 subjects with IGT to one of three interventions (1082 to placebo, 1073 to metformin, and 1079 to the intensive lifestyle intervention). The goals of the intensive lifestyle intervention were at least a 7% weight loss (low-calorie and low-fat diet) and 150 min of physical activity per week (moderate intensity, such as brisk walking). The intensive lifestyle group received individual counseling and motivational support on an effective diet, exercise, and behavior modification. After an average follow-up of 2.8 years, the lifestyle intervention group reduced the incidence of diabetes by 58% when compared to the placebo group. DPP participants who took the oral diabetes medication also reduced their incidence of diabetes (31%), but not as much as those in the lifestyle intervention group. In addition, the lifestyle intervention group had a significantly greater average weight loss (5.6 kg) than the metformin (2.1 kg) and placebo (0.1 kg) groups. Thirty-eight percent of the lifestyle participants achieved at least a 7% weight loss and 58% met the physical activity goal.

Another important highlight of the DPP study was the impact of intensive lifestyle intervention, metformin, and

placebo on components of the metabolic syndrome which are risk factors for CVD.[33] When compared to metformin and placebo groups, the lifestyle intervention group had a reduction in the prevalence of dyslipidemia, LDL phenotype B (i.e., smaller, denser, and more atherogenic LDL particle), and hypertension. In addition, the intensive lifestyle group had decreased systolic and diastolic blood pressure (DBP) and triglyceride levels, and increased HDL-C when compared to the other groups. At the third year follow-up, there was a reduced need for antihypertensive and lipid-lowering medications among subjects assigned to the intensive lifestyle intervention.[33] This finding is in agreement with the well-known favorable effect of dietary modification and exercise on the regulation of the various components of the metabolic syndrome.

Ten years following the randomization in the DPP, the DPP Outcomes Study (DPPOS) found the diabetes incidence was reduced by 34% in the lifestyle intervention group and 18% in the metformin group compared with the placebo group.[34] The DPPOS's results indicated that high-risk individuals can delay or prevent developing type 2 diabetes by losing weight through regular physical activity and a diet low in fat and calories. The DPPOS's findings support other follow-up studies that found the beneficial health results from modifying lifestyle can be maintained long term.[31,32]

Lifestyle Modification: Obesity

Diet and Weight Loss

A weight loss of at least 7% can improve the metabolic syndrome.[27] Dansinger et al. compared four popular "fad" diets (i.e., Atkins, Ornish, Weight Watchers, and Zone) in a randomized trial of 160 overweight and obese participants with known hypertension, dyslipidemia, or fasting hyperglycemia.[35] The Akins diet restricted carbohydrates, the Ornish diet restricted fat, the Weight Watchers diet restricted calories, and the Zone diet had a macronutrient balance. CVD risk factor outcome measures were assessed at baseline, 2, 6, and 12 months. At 1 year, all four diets resulted in a moderate, statistically significant effect on weight loss, as well as other CVD risk factors such as total cholesterol (except Akins and Zone diets), low-density lipoprotein cholesterol (LDL-C; except Atkins diet), HDL-C (except Ornish diet), LDL-C/HDL-C ratio, insulin (except Atkins diet), and C-reactive protein (except Zone diet) (Table 36.4). Perhaps, this moderate effect was due to poor long-term compliance with the diets. The effect of a Mediterranean-style diet on body weight was evaluated by Esposito et al.[36] Seventy-five women who had a carbohydrate intake equal to or less than 50% (low-carbohydrate diet) were compared to 115 women who had a dietary intake of carbohydrate greater than 50% of energy (high-carbohydrate diet).[36] The women were followed for up to 2 years and those who consumed a low-carbohydrate diet significantly lost more weight and had a greater change in adiponectin and triglyceride levels than the women who consumed a high-carbohydrate diet.[36] Weight loss improves CVD risk factors; however, the benefits will not remain if the weight loss is not maintained. It is important to note that behavioral weight loss clinical trials, such as Trials of Hypertension Prevention Phase II (TOHP II),[37] STOP regain,[38]and Weight Loss Maintenance (WLM),[39] have been able to demonstrate the ability to maintain weight loss. Specifically, 30 months after the initial 6 month behavioral weight loss program, the WLM Randomized Controlled Trial found that 71% of the study participants remained at or below their entry level weight.[39] This weight loss was sustained by providing monthly brief personal contact sessions.

Physical Activity and Combination of Physical Activity and Diet

Independent of dietary changes, physical activity has been shown to decrease abdominal visceral and subcutaneous fat in healthy, overweight, and obese men and women.[40–44] Joseph et al. evaluated the effects of a 6 month weight loss (250–350 kcal/day caloric restriction) and low-intensity aerobic exercise (i.e., walking) program on body composition and metabolic parameters in obese postmenopausal women with and without the metabolic syndrome.[45]After the 6 month program, they found reductions in weight, fat mass, visceral and subcutaneous abdominal tissues, triglycerides, C-reactive protein, tumor necrosis factor α (TNF-α), and glucose concentrations in women with the metabolic syndrome. Resolution of the metabolic syndrome was best predicted by reductions in fat mass. Furthermore, the HERITAGE Family Study found that after 20 weeks of supervised aerobic exercise training (cycle ergometer), 30.5% of the obese subjects no longer had metabolic syndrome.[46] There were also decreases in their waist circumference and improvement in their metabolic profile (triglycerides, HDL-C, blood pressure, and fasting plasma glucose concentrations). Another significant study conducted by Lofgren in 70 overweight, obese premenopausal women found that 10 weeks of increased low-impact physical activity (walking) and consumption of a low-energy diet lead to significant reductions in weight, BMI, waist circumference, total fat mass, trunk fat mass, and insulin and leptin levels.[47] Importantly, after the intervention, some subjects with metabolic syndrome no longer had the syndrome.

Lifestyle Modification: Hypertension

Weight Loss

A small change of 2 mm Hg in DBP can have an impact on the risk of stroke (15% reduction) and coronary heart disease (6% reduction).[48] Weight gain has been reported to be strongly associated with the development of hypertension.[49] Multiple lifestyle modification, randomized trials have found that weight loss helps to lower blood pressure.[37,50–53] Particularly, a meta-analysis of 25 lifestyle intervention trials (n = 4874 subjects) found that a calorie-restricted diet, increased physical activity, or both resulted in a weight loss of 5.1 kg, which contributed to reduction in systolic blood pressure (SBP) and DBP of 4.44 and 3.57 mm Hg.[54]

Diet

A non-weight loss hypertension clinical trial reported a meta-analysis of 36 (n = 2635) randomized trials.[55] It concluded that

TABLE 36.4
Changes in Weight and Cardiac Risk Factors in Analysis in Which Baseline Values Were Carried Forward in the Case of Missing Data[a]

	Diet Group, Men Change (SD)				
Variable	Atkins (n = 40)	Zone (n = 40)	Weight Watchers (n = 40)	Ornish (n = 40)	p Value for Trend Across Diets
Weight (kg)					
2 Months	−3.6 (3.3)*	−3.8 (3.6)*	−3.5 (3.8)*	−3.6 (3.4)*	0.89
6 Months	−3.2 (4.9)*	−3.4 (5.7)*	−3.5 (5.6)*	−3.6 (6.7)*	0.76
12 Months	−2.1 (4.8)*	−3.2 (6.0)*	−3.0 (4.9)*	−3.3 (7.3)*	0.40
BMI					
2 Months	−1.3 (1.1)*	−1.3 (1.2)*	−1.2 (1.3)*	−1.2 (1.1)*	0.83
6 Months	−1.1 (1.7)*	−0.9 (2.4)**	−1.2 (2.0)*	−1.2 (2.3)*	0.65
12 Months	−0.7 (1.6)*	−1.1 (2.0)*	−1.1 (1.7)*	−1.4 (2.5)**	0.36
Waist circumference (cm)					
2 Months	−3.3 (3.1)*	−3.0 (3.5)*	−3.5 (4.2)*	−2.7 (3.2)*	0.37
6 Months	−3.2 (4.9)*	−2.9 (5.2)*	−3.5 (5.9)*	−2.5 (5.3)*	0.69
12 Months	−2.5 (4.5)*	−2.9 (5.3)*	−3.3 (5.4)*	−2.2 (5.5)**	0.89
Total cholesterol (mg/dL)					
2 Months	−1.8 (24)	−18.4 (25)*	−14.8 (26)*	−19.0 (28)*	0.01
6 Months	−0.9 (18)	−6.2 (19)**	−8.1 (21)**	−11.4 (26)*	0.03
12 Months	−4.3 (23)	−10.1 (35)	−8.2 (24)**	−10.8 (21)*	0.35
LDL cholesterol (mg/dL)					
2 Months	1.3 (18)	−9.7 (27)**	−12.1 (25)*	−16.5 (25)*	0.001
6 Months	−2.7 (14)	−6.7 (22)	−7.0 (24)	−10.5 (22)*	0.10
12 Months	−7.1 (24)	−11.8 (34)**	−9.3 (27)**	−12.6 (19)*	0.46
HDL cholesterol (mg/dL)					
2 Months	3.2 (6.2)*	1.8 (7.6)	−0.2 (11.8)	−3.6 (7.3)*	0.001
6 Months	3.8 (6.4)*	3.6 (10.5)**	2.4 (9.0)	−1.5 (7.0)	0.005
12 Months	3.4 (7.1)*	3.3 (10.3)**	3.4 (9.9)**	−0.5 (6.5)	0.06
Total/HDL cholesterol ratio					
2 Months	−0.36 (0.66)*	−0.66 (1.06)*	−0.49 (1.86)	−0.18 (1.01)	0.40
6 Months	−0.38 (0.68)*	−0.46 (0.93)*	−0.60 (1.57)**	−0.25 (1.07)	0.75
12 Months	−0.39 (0.69)*	−0.52 (1.04)*	−0.70 (1.67)**	−0.30 (0.96)	0.89
LDL/HDL cholesterol ratio					
2 Months	−0.18 (0.57)**	−0.33 (0.79)*	−0.42 (1.55)	−0.21 (0.67)	0.81
6 Months	−0.30 (0.55)*	−0.30 (0.74)*	−0.47 (1.37)**	−0.22 (0.70)	0.90
12 Months	−0.39 (0.81)*	−0.40 (0.81)*	−0.55 (1.39)**	−0.31 (0.68)*	0.92
Triglycerides (mg/dL)					
2 Months	−32.3 (66)*	−54.1 (105)*	−9.2 (39)	−0.4 (77)	0.01
6 Months	−10.6 (40)	−14.8 (57)	−1.5 (55)	−2.3 (71)	0.35
12 Months	−1.2 (84)	2.5 (147)	−12.7 (61)	5.6 (36)	0.93
Systolic BP (mm Hg)					
2 Months	−4.2 (13)**	−4.1 (14)	−4.8 (13)**	−1.3 (8.8)	0.19
6 Months	−3.7 (10)**	−3.9 (14)	−4.8 (14)**	−0.6 (8.7)	0.32
12 Months	−0.2 (12)	1.4 (15)	−2.7 (13)	0.5 (7.7)	0.71
Diastolic BP (mm Hg)					
2 Months	−4.2 (8.3)*	−4.8 (7.6)*	−3.1 (7.4)**	−2.5 (7.1)**	0.19
6 Months	−4.0 (6.5)*	−4.0 (9.1)*	−1.8 (6.9)	−0.3 (6.2)	0.01
12 Months	−1.4 (7.5)	−1.2 (9.5)	−1.7 (6.4)	0.2 (4.6)	0.40
Glucose (mg/dL)					
2 Months	−9.8 (30)**	−9.0 (29)	−5.5 (24)	−3.1 (23)	0.21
6 Months	−7.8 (26)	−8.2 (33)	−3.8 (22)	−5.1 (25)	0.50
12 Months	1.4 (30)	−4.2 (18)	−4.7 (19)	−4.1 (30)	0.34

TABLE 36.4 (continued)
Changes in Weight and Cardiac Risk Factors in Analysis in Which Baseline Values Were Carried Forward in the Case of Missing Data[a]

	Diet Group, Men Change (SD)				
Variable	Atkins (n = 40)	Zone (n = 40)	Weight Watchers (n = 40)	Ornish (n = 40)	p Value for Trend Across Diets
Insulin (μl U/mL)					
2 Months	−5.1 (13)*	−7.1 (12)*	−1.8 (6.0)	−1.7 (12)	0.06
6 Months	−2.3 (11)	−1.9 (16)	−2.5 (7.1)	−0.4 (18)	0.60
12 Months	−1.2 (6.7)	−5.4 (14)*	−2.6 (6.1)*	−3.0 (6.3)**	0.70
C-Reactive protein (mg/L)					
2 Months	−0.33 (1.6)	−0.22 (1.9)	−0.04 (1.2)	−0.61 (2.6)	0.61
6 Months	−0.71 (2.0)**	−0.42 (1.9)	−0.50 (1.5)**	−0.70 (2.8)	0.97
12 Months	−0.70 (2.1)**	−0.58 (2.1)	−0.58 (1.3)*	−0.88 (2.4)**	0.70

Source: Dansinger, M.L. et al., *JAMA*, 293, 48, 2005. Copyright © 2005 American Medical Association. All rights reserved. Reprinted with permission..

BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SI conversions: To convert glucose to mmol/L, multiply by 0.0555; HDL, LDL, and total cholesterol to mmol/L, multiply by 0.0259; insulin to pmol/L, multiply by 6.945; and triglycerides to mmol/L, multiply by 0.0113.

[a] For Atkins group, the actual numbers of records available were 31 at 2 months, 22 at 6 months, and 21 at 12 months; for Zone group, 33 at 2 months, 26 at 6 months, and 26 at 12 months; for Weight Watchers group, 33 at 2 months, 30 at 6 months, and 26 at 12 months; for Ornish group, 29 at 2 months, 21 at 6 months, and 20 at 12 months.

*$P < 0.01$ for difference from baseline within the group.

**$P < 0.05$ for difference from baseline within the group.

a low-sodium diet reduced blood pressure more in hypertensive (−4.8/−2.5 mm Hg; SBP/DBP) than non-hypertensive (−1.9/−1.1 mm Hg) patients. Further, a landmark trial of diet-based modification of blood pressure evaluated different levels of dietary sodium (high, 3.5 g/day; intermediate, 2.3 g/day; and low, 1.2 g/day) combined with the Dietary Approaches to Stop Hypertension (DASH) diet (fruits, vegetables, low-fat dairy products) versus a standard American diet (control) in 412 adults with prehypertension or stage 1 hypertension.[56] Compared to control, the DASH diet significantly lowered blood pressure at each sodium concentration. Likewise, in the PREMIER study, the addition of the DASH diet decreased SBP in metabolic syndrome individuals with prehypertension or stage 1 hypertension.[57] The Optimal Macronutrient Intake Trial to Prevent Heart Health (OmniHeart) compared three diets (diets rich in carbohydrates, protein, and unsaturated fat) in subjects with prehypertension and hypertension.[58] Relative to the carbohydrate group, the protein and fat diet groups exhibited a greater decrease in SBP and DBP, total cholesterol, and triglycerides despite no difference in weight loss among the three groups.

Physical Activity and Combination of Physical Activity and Diet

Like dietary treatment, increasing physical activity can also lower blood pressure. The beneficial effect of physical activity on blood pressure has been well documented.[59–61] Hypertension has a disproportionate effect on African Americans when compared to other ethnic groups. However, Rigsby found that 12 weeks of aerobic training (walking) resulted in improved control of blood pressure in African Americans.[62] Whelton et al. conducted a meta-analysis of 54 randomized clinical trials (n = 2419 subjects) that implemented aerobic exercises to treat blood pressure.[63] The results demonstrated a significant reduction in SBP and DBP (−3.84 and −2.58 mm Hg) in normotensive or hypertensive people who were normal weight or overweight. This blood pressure reduction was similar in trials that did not observe weight loss, thus suggesting that the effects of aerobic exercise on blood pressure may be independent of the change in body weight. A more profound reduction of SBP (14.83 mm Hg) and DBP (5.63 mm Hg) has been observed in a recent study among severe obese subjects after a 12-month moderate-intensity physical activity program (brisk walking) along with dietary changes.[64] In addition, physical activity (biking, walking, or jogging) along with dietary modifications has been shown to be associated with significantly greater reductions in both SBP (16.1 mm Hg) and DBP (9.9 mm Hg) when compared with only dietary adjustments among prehypertensive or stage 1 hypertensive patients.[65]

Lifestyle Modification: Lipids, and Inflammatory and Prothrombotic Markers

Diet

Low-carbohydrate diets have resulted in lower triglyceride concentrations and higher HDL-C levels than conventional

diets and the opposite effect has been documented with a high-carbohydrate diet.[66–70] Lipid effects with utilization of the DASH diet have yielded mixed results. The DASH diet has been reported to lower total cholesterol, LDL-C, and HDL-C with no effect on triglycerides and yet another randomized controlled trial resulted in higher HDL-C and lower triglycerides.[71,72] Besides the DASH diet, soy protein and the Mediterranean diet have also played a role in improving the lipid and inflammatory marker profiles. An increased consumption of soy protein (~47 g/day) has been shown to reduce total cholesterol (9.3%), LDL-C (12.9%), and triglycerides (10.5%) and increase HDL-C (2.4%).[73] A randomized trial using the Mediterranean-style diet or a regular control diet in 180 adults with metabolic syndrome was conducted by Esposito et al.[74] After 2 years, the intervention group had a lower body weight, highly sensitivity C-reactive protein, interleukin-6 (IL-6), IL-7, IL-18, and insulin resistance versus the control group. Furthermore, the intervention group had an improved endothelial function score.

Physical Activity and Combination of Physical Activity and Diet

Evaluation of the effect of daily aerobic exercise in combination with a diet low in fat and cholesterol while high in complex unrefined carbohydrates and fiber was reported by Beard et al.[75] This plan induced a reduction in LDL-C (20%), total cholesterol (20%), HDL-C (17%), triglycerides (26%), blood glucose (16%), and body weight (4%). Regarding HDL-C levels, a meta-analysis conducted by Leon and Sanchez found that ≥12 weeks of aerobic exercise increased HDL-C.[76] Reports by Ford and King et al. showed that after adjusting for several potential confounders, the time devoted to physical activity was inversely associated with C-reactive protein, plasma fibrinogen concentrations, and white blood cell count in adult participants in NHANES III (1988–1994).[77,78] Likewise, Abramson and Vaccarino reported that physical activity was associated with a lower probability of having elevated C-reactive protein levels, white blood cell count, and fibrinogen levels among healthy U.S. adults aged 40 years and older, independent of several confounding factors.[79]

Lifestyle Modification: Resistance Training

While there is considerable evidence on the effects of aerobic physical activity or training on individual CVD risk factors and metabolic syndrome as discussed earlier, less is known about the health effects of resistance training. Resistance training increases muscular strength and fat-free mass, and decreases fat mass and intra-abdominal adipose tissue.[80–82] In addition, resistance training can increase insulin sensitivity and decrease blood pressure, total cholesterol, LDL-C, and triglycerides in obese, hypertensive, and type 2 diabetic subjects.[83–87] Interestingly, studies have found that men with more muscular strength are less likely to develop the metabolic syndrome.[88,89]

ALTERNATIVE STRATEGIES FOR MANAGING METABOLIC SYNDROME

Smoking Cessation

Cigarette smoking is listed as one of the Framingham CVD risk factors.[90] Long-term prospective studies have clearly demonstrated the significant mortality risk reduction associated with smoking cessation.[91–94] Specifically, Critchley and Capewell conducted a meta-analysis of 20 smoking cessation studies that included 12,603 smokers with coronary heart disease at baseline. There was a 36% relative risk reduction of mortality in those patients with coronary heart disease who quit smoking versus those who continued to smoke.[91] Likewise, Gerber et al. have also shown that subjects with CVD improved their survival with smoking cessation. In this study, 1521 patients (≤65 years) with a first acute myocardial infarction were followed for a mean of 13.2 years. Relative to the persistent smokers, the odds of dying were lower for the never smokers (hazard ratio: 0.57), pre-acute myocardial infarction quitters (hazard ratio: 0.50), and post-acute myocardial infarction quitters (hazard ratio: 0.63). In addition, persistent smokers who reduced their number of daily cigarettes had an 18% decline in mortality risk for every five cigarettes decreased after being diagnosed with acute myocardial infarction.[94]

Botanicals

It is estimated that ~38% of adults use complementary and alternative medicine in pursuit of achieving good health and well-being.[95] Specifically, the most commonly used complementary and alternative medicine therapies are non-vitamin, non-mineral, and natural products (especially derived from botanicals) because they are perceived to be less toxic with fewer side effects than synthetic products.[95] Botanicals have been proposed as therapeutic agents for the treatment or prevention of the metabolic syndrome. These plant-derived therapeutics often contain many biologically active compounds with numerous mechanisms of action that are postulated to augment each other's activity synergistically, thus providing a greater benefit than a single chemical compound. Graf et al. reviewed a number of botanicals that have been commonly associated with treatment of the metabolic syndrome.[96] These botanicals consisted of cinnamon, Russian tarragon, bitter melon, fenugreek, blueberries, grape seed, hawthorn, and hoodia. These plant-derived therapeutics have been shown to exhibit antidiabetic, antihypertensive, antiobesity, and cholesterol-lowering effects in several reports (Table 36.5).[96] Specifically, Stull et al. found that 6 weeks of supplementation with blueberry smoothies improved insulin sensitivity when compared to consuming a placebo smoothie in obese and insulin-resistant (prediabetes) adults.[97] However, specific and precise validation for each botanical in prevention and treatment of the metabolic syndrome and the associated risk factors is still lacking and recommendations for general use for this purpose cannot be determined at this time.

TABLE 36.5
Selected Plant-Derived Therapeutics and Their Effects on Disease Risks Associated with Metabolic Syndrome

Botanical	Scientific Name	Therapeutic Effect	References
Cinnamon	*Cinnamomum cassia and Cinnamomum verum*	↑IS; ↓G; ↓BP; ↓LDL; ↓TG	Anderson, 2004, 2008; Kim, 2006; Dugoua, 2007; Crawford, 2009; Khan, 2003; Altschuler, 2007; Blevins, 2007; Preuss, 2006; Ziegenfuss, 2006; Qin, 2010; Mang, 2006
Russian tarragon	*Artemisia dracunculus*	↑IS; ↓G	Ribnicky, 2006; Logendra, 2006; Wang, 2008; Govorko, 2007; Cefalu, 2009; Ribnicky, 2004, 2010; Defronzo, 1979
Bitter melon	*Momordica charantia*	↑IS; ↓G; ↓LDL; ↓TG	Leung, 2009; Ahmad, 1999; Grover, 2001, 2002, 2004; Rathi, 2002; Ahmed, 2001; Chaturvedi, 2005; Fernandes, 2007; Jayasooriya, 2000; Senanayake, 2004
Fenugreek	*Trigonella foenum-graecum*	↑IS; ↓G; ↓LDL; ↓TG	Srinivasan, 2006; Gopalpura, 2009; Kassaian, 2009
Lowbush blueberry	*Vaccinium angustifolium*	↓BP; ↓G; ↓W	Watson, 1928; Grace, 2009; Vuong, 2009; Prior, 2010; Shaughnessy, 2009; Kalea, 2009, 2010; Lazze, 2006; Xu, 2004; Erlund, 2008
Grape seed	*Vitis vinifera*	↓BP; ↓LDL	Peng, 2005; Sivaprakasapillai, 2009; Jones, 2004; Aldini, 2003; Fitzpatrick, 2000, 2002; Quesada, 2009
Hawthorn	*Crataegus laevigata, Crataegus monogyna, Crataegus curvisepala (Crataegus oxyacantha) and Crataegus tanacetifolia*	↓BP; ↓LDL	Pittler, 2008; Asgary, 2004; Walker, 2006; Brixius, 2006; Laccaille, 2001; Tadic, 2008; Kocyildiz, 2006; Kim, 2000; Shanthi, 1994, Rajendran, 1996
Hoodia	*Hoodia gordonii*	↓W	MacLean, 2004; Shukla, 2009; Avula, 2008

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BP, blood pressure; G, blood glucose; IS, insulin sensitivity; TG, triglycerides; W, body weight; LDL, low-density lipoprotein.
↑ means an increase and ↓ means a decrease.

Pharmaceutical

Lifestyle interventions are well-established strategies that improve the metabolic syndrome. However, it should be noted that although lifestyle changes can provide many benefits for the management of the syndrome, sometimes these changes are difficult to implement and maintain. When lifestyle modifications are unsuccessful, pharmacological interventions that are capable of reducing blood pressure, lipids, and glucose concentrations, weight, and other abnormalities related to the metabolic syndrome become pertinent. Therefore, pharmaceutical treatments including metformin and thiazolidinediones are able to increase insulin sensitivity.[98] A single or combination therapy using a statin and/or a fibrate can reduce atherogenic dyslipidemia and also angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers can effectively treat hypertension.[99,100] In addition, pharmacotherapy such as sibutramine, rimonabant, and orlistat have been documented to have weight loss and lipid-lowering effects in an overweight and obese population.[101–105] A more aggressive therapy for weight loss is bariatric surgery which includes gastric banding, gastric bypass, gastroplasty, and biliopancreatic diversion or duodenal switch.[106]

SUMMARY

Lifestyle modification plays a pivotal role in managing the metabolic syndrome. The syndrome is a complex condition that involves treatment of multiple CVD risk factors. The evidence briefly reviewed in this chapter demonstrates the efficacy of modifying diet and increasing physical activity to reduce CVD risk factors, primarily mediated through weight reduction. Incorporating dietary and physical activity changes to induce modest weight loss exerts beneficial effects on the CVD risk factors of the metabolic syndrome. However, the current challenge is the long-term maintenance of the lifestyle changes because only long-term changes can reduce the morbidity and mortality of the metabolic syndrome. In order to achieve successful interventions, physicians and health care professionals must be willing to incorporate lifestyle change as part of their medical practice and encourage their patients to adapt those lifestyle changes to prevent or treat the metabolic syndrome.

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Part VIII

Lifestyle Issues in the Prevention and Treatment of Cancer

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37 Lifestyle Interventions in the Prevention and Treatment of Cancer

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CONTENTS

Introduction 471
Lung Cancer 471
Colon and Rectal Cancer 472
Breast Cancer 474
Prostate Cancer 475
Skin Cancers 476
Conclusion 477
References 478

INTRODUCTION

No longer is there any doubt that human behavior is a factor in many health-related issues that mankind must endure. It is clear that smoking, diet, and physical activity all have a causal relationship to heart disease, still the number one cause of death in the United States. For more than 40 years, evidence has been accumulating that cancer, the number two cause of death in this country (soon to surpass heart disease in that regard), also has those same lifestyle factors as etiological factors for many diseases classified as "cancer." With cancer accounting for more than one-half million Americans dying each year, researchers have intensified efforts to identify which cancers are significantly influenced by lifestyle issues and what other controllable behaviors are responsible for adding to the risk of one succumbing to cancer.

Since diet and physical activity have such a bearing on one's weight, the accumulation of excess body fat is one lifestyle-related factor that has become of major significance in the development of certain cancers. In fact, it is predicted that as tobacco control measures continue to reduce the overall use of tobacco products that obesity will soon become the number one etiologic factor for most cancers.

In this chapter, five of the most common cancers which in one or another way are impacted by lifestyle are described and certain interventions that are either explicit or inferred that can alter either the incidence of the cancer or in some instances the severity or types of specific cancer are discussed.

In order of the magnitude of deaths in the United States, the following cancers are presented: lung, colon and rectal, breast, prostate, and skin (with special emphasis on malignant melanoma).

LUNG CANCER

Lung cancer is the leading cause of cancer-related death in the United States, comprising 31% of cancer deaths in men and 25% of cancer deaths in women. An estimated 215,020 new cases of lung cancer will have been diagnosed in this country in 2008 and 161,840 deaths will be attributed to lung cancer in the year 2008.[1] Approximately 85%–90% of lung cancers are related to tobacco use.[1] Furthermore, approximately half of all patients with lung cancer have quit smoking before their diagnosis.

Worldwide, nearly a billion men are cigarette smokers, including ~35% of men in developed countries and 50% of men in developing countries. Worldwide, ~250 million women are smokers, including 22% of women in developed countries and 9% of women in developing countries. Currently, in the United States ~25% of the adult population is smokers, or ~46 million adults.

There has been significant interest in evaluating risk of lung cancer in both smokers and nonsmokers. Approximately 1 in 10 lifelong smokers will develop lung cancer. The risk of lung cancer increases with duration of smoking and with the number of cigarettes smoked daily.?

Approximately 1.6% of lung cancer cases are attributable to secondhand smoke. Authors have found a relative risk of 1.14 to 5.20 in persons who never smoked but who resided with a smoker.[2,3] Furthermore, exposure to secondhand smoke in childhood has been found to carry a relative risk of lung cancer in adulthood of 2.6.[4]

A role for genetic susceptibility for the development of lung cancer includes data that show that only ~10% of smokers will develop lung cancer. Additionally, studies demonstrate clustering of lung cancer within certain families.

Li and Hemminki[5] reported a germ-line epidermal growth factor T790M sequence variation in a family with multiple cases of lung cancer. Bailey-Wilson et al.[6] reported the results of a genome-wide linkage study of 52 families demonstrated a new major susceptibility locus influencing lung cancer risk at 6q23-25p. Hung et al.[7] reported a locus at chromosome 15q25 associated with lung cancer. In this analysis of 3502 lung cancer case patients and 7377 controls, the risk of lung cancer was 30% higher for people with one copy of the marker at chromosome 15q25 and 70%–80% higher for persons with two copies of the marker. The region where the marker resides contains three genes that encode subunits of the nicotine acetylcholine receptor.

The field of molecular epidemiology focuses on evaluation of susceptibility to environmental carcinogens. Within this field, a number of investigators have evaluated the role of genetic variability in susceptibility to the carcinogenic effects of nicotine. One such gene is the *CYP2D6*, a gene in the cytochrome P450 family which plays an important role in the metabolism of many common drugs and activates tobacco smoke–derived nitrosamine.

Studies by Spitz et al. show that 90% of the U.S. population are extensive metabolizers, increasing their risk for lung cancer. This is related to the enzyme's high risk of activating tobacco carcinogens. The remaining 10% of the population are poor metabolizers, with a lower associated risk of lung cancer due to a lower ability to activate tobacco carcinogens.

Another gene that may affect genetic susceptibility to lung cancer is the glutathione *GSTM1* gene.[8] This gene belongs to a large family of genes that facilitate the detoxification of a variety of carcinogens, including polycyclic aromatic hydrocarbons present in tobacco smoke.

Individuals who have the GSTM1 enzyme are able to detoxify carcinogens using this metabolic pathway, while those individuals lacking this enzyme are less able to detoxify carcinogens and therefore have a higher lung cancer risk.

Diets that are rich in fruits and vegetables have been suggested to have a protective effect against the development of lung cancer, possibly due to their rich antioxidant content.[9,10] Researchers have hypothesized that micronutrients protect against oxidative damage to DNA, thereby conferring a protective effect against cancer.[11] Early studies by Bjelke suggested a protective effect of vitamin A against lung cancer.[12] However, randomized studies evaluating the effects of β-carotene and retinoids (vitamin A derivatives) have not demonstrated protective effects against lung cancer.[13–15]

At least 21 studies have demonstrated a protective effect of exercise against lung cancer risk.

A Norwegian study[16] demonstrated a 25%–29% reduction in the risk of lung cancer in men who engaged in moderate exercise (at least 4 h/week) compared to sedentary men; this effect was demonstrated after controlling for tobacco use. Another study[17] reported results from the Harvard Alumni Health Study which followed 13,905 men for up to 16 years. After accounting for tobacco use, men who engaged in light, moderate, and strenuous amounts of exercise on a regular basis were shown to have, respectively, a 13%, 24%, and 39% reduction in lung cancer risk.[17] It should be noted that many of these studies are cohort studies conducted in Caucasian populations of higher socioeconomic status.

Smoking prevention and cessation are of critical importance in the prevention of lung cancer and in improving outcomes of lung cancer patients. Evidence from the Copenhagen Health study demonstrated that smoking cessation reduces the risk of development of lung cancer by 50%. Primary prevention of tobacco use has also been demonstrated to be a successful strategy in reducing lung cancer incidence rates in states such as California which have strong antitobacco legislation.

Data also demonstrate that smoking cessation is associated with improved survival after a diagnosis of lung cancer and improved treatment efficacy.[18,19] Gritz et al. reported that in a population of 840 patients with diagnosis of stage I non-small cell lung cancer, 40% of patients who were smokers at the time of diagnosis subsequently quit smoking.[20]

Ongoing tobacco use can adversely affect outcomes of surgery, radiation, and chemotherapy.[18,19] The incidence of postoperative complications is increased in smokers; this rate is decreased in patients who have quit smoking prior to surgery.[18] Continued smoking may also decrease the efficacy of chemotherapy for lung cancer. There is evidence that nicotine increases the metabolism of multiple drugs via the induction of hepatic enzymes which may decrease the efficacy of certain chemotherapy agents.[21] Smoking cessation at the time of diagnosis furthermore decreases the rate of subsequent lung cancers.[22,23]

COLON AND RECTAL CANCER

The concepts of preventing colon cancer and upper gastrointestinal malignancies through lifestyle changes have evolved over time, with inconsistent recommendations. The data obtained were derived from the multitudes of prospective and retrospective trials, reanalyzed in a meta-analytical fashion.

Due to its high incidence, and its impact on human morbidity, mortality, and health dollar expenditure,[24] colon cancer prevention ranks high on the importance list of cancers to prevent. In a population, individuals also have a vested interest in preventing colon cancer due to its mostly sporadic incidence.

Dietary habits are known to contribute to or improve the risk of colon cancer[25–27]; thus, it would make sense to modify dietary behavior in order to reduce risk. In doing so, researchers have looked at intake of animal fat, red meat, fruits, vegetables, and fiber, as some of the many dietary factors may influence the risk of colon cancer.

Among the studies that have looked at the dietary content of red meat and the risk of colon cancer, a large European population study[28] looked at intake of red meat, poultry, and fish, and prospectively followed the incidence of cancer. There was an increased risk of colon cancer in the group that consumed more than 180 g/day of red meat compared to those who consumed less than 20 g/day (hazard ratio of 1.35). Interestingly, the hazard ratio for high fish intake

was 0.80, and the risk for poultry intake was not significantly different than that of the average population. In another case–control study,[29] red meat intake was associated with a near 85% increase in colorectal cancer in subjects who ate red meat seven times per week compared to three times per week. Several other studies,[30–32] at least one of which was a prospective,[33] have corroborated the relationship between red meat intake and colon cancer.

It is not clear whether the risk is due to the heme, animal fat, or carcinogens generated during the meat preparation.[34,35] It may very well be a combination of all three. To date, however, no studies have explored the impact of changing red meat content on colon cancer incidence. It is also unclear if the impact occurs at a young age or later in life.

Dietary fiber and the intake of fruits and vegetables have also been looked at extensively. No conclusive benefit can be drawn from the available data. A pooled analysis of 13 prospective cohort studies showed no advantage to increased dietary fiber intake when other dietary risk factors were taken into consideration.[36] Several other studies seem to corroborate these findings. Some smaller studies have shown a protective impact against colon cancer in people who consume more fruits. One large European study showed a reduction of the incidence of colon cancer when comparing the upper and lower quintile of fiber intake.[37] This benefit was limited to colon cancer but not to rectal cancer. Most of the studies evaluating the impact of dietary fiber on the incidence of adenomatous polyps showed no significant reduction in polyp formation.[38–40] There was, however, no disadvantage to the consumption of fruits, vegetables, and other fiber-rich foods on the incidence of colon cancer.

Dietary supplementation as a means of disease prevention is a widely used practice among the public, mainly due to a perceived benefit carried down over generations of folklore. Solid data behind such practices are nearly absent, more so in the cancer prevention arena. In order to make evidence-based recommendations, several studies, both retrospective and prospective, have been conducted looking at the effect of such supplements on the incidence of cancer. Calcium intake in the form of dairy products has been shown to reduce the risk of colon cancer.[40,41] But high calcium levels may be associated with increased risk of prostate cancer.[42–44] The benefit-to-risk ratio has been postulated to be optimal at lower rather than higher doses, but this is subject to dispute. It may be appropriate to take into consideration the individuals risk for either cancer when deciding on calcium supplementation. The benefit from calcium occurs at high doses that are usually unattainable with regular consumption of dairy products and thus require high dose supplements.

Vitamin D may have an effect on colonic mucosal cells,[45,46] and in turn a protective effect against colon cancer.[47,48] The data are inconclusive and in some studies no benefit was demonstrated except in very high dose supplementation.[49] It is important to note that the beneficial effect of sun exposure to improve vitamin D levels can be negated by the increased risk of skin cancer.[50]

Antioxidants have a very solid rational as protective agents against the mutagenic effect of free radicals, which can affect malignant transformation[51,52] although some investigators theorize that reactive oxygen species are part of the cellular signaling mechanisms, and thus, loss of such species may also lead to malignant transformation.[53] The evaluation of several antioxidants, including omega-3 fatty acids, vitamin C, and vitamin E did not conclusively demonstrate a protective effect against several cancers including colorectal cancers.[54,55] It is also not clear if supplemental multivitamins in general offer any benefit over a well-balanced diet.[56]

Moderate to intense exercise seems to have a favorable impact on the risk of developing colon cancer. In one systematic review of published literature,[57] a definite inverse relation was observed between increased physical activity and the risk of colon cancer. A near 50% reduction in incidence of colon cancer was observed in those undertaking the highest level of activity. This benefit was maintained even with multivariate analysis accounting for other variables such as diet and weight.[58] The benefit was evident in colon cancer more so than rectal cancer.[59,60]

In a recent study presented by McClain at the AACR 7th Annual International Conference on Frontiers in Cancer Prevention,[61] the investigators found that, at least in women, the beneficial impact of exercise was negated by the lack of sufficient sleep. In that trial, around 6000 women were queried regarding their exercise and rest patterns. Investigators assessed the physical activity energy expenditure (PAEE) and the duration of sleep. During a 10 year follow-up, the subjects were monitored for the incidence of breast and colon cancer. Of the 604 women with either breast or colon cancer, those who slept less than 7 h/day had a higher incidence of breast and colon cancer, negating most of the beneficial effect derived from vigorous physical activity.

Exercise was also found to prevent relapse of resected stage 3 colon cancer. This was found upon analysis of the data from a large randomized trial looking at two different chemotherapy regimens administered in the adjuvant setting. The benefit of exercise was found to be independent of sex, body mass index, number of positive lymph nodes, age, baseline performance status, or chemotherapy received.[62] The mechanism by which physical activity and rest affect a change in malignant transformation is not clear. The effect of exercise on hormonal, immune, and weight changes may impact the inflammatory and proliferative environment that could lead to abnormal and eventually malignant cell growth.

Chemoprevention, in the form of nonsteroidal anti-inflammatory agents (NSAIDs), and more specifically aspirin have been shown to reduce the incidence of colonic polyps and the risk of colon cancer.[63–65] In several large randomized and observational trials, there was a benefit to using aspirin; however, the data were not clear as to which dose was most beneficial. Some of the data implied a dose–response effect with higher doses resulting in less incidence of polyps and malignant lesions.[66] The duration of therapy was also very important. Most of the benefit became evident after 10 years of therapy. Some population-based

observational trials were analyzed after 5 years of NSAID therapy and were found to be negative.[63]

Due to the potential complications of NSAID therapy, including hemorrhagic gastritis, increased risk of bleeding, and renal complications, caution should be exercised when utilizing these agents to prevent colon cancer and should be limited to very specific high-risk groups such as patients with familial adenomatous polyposis (FAP). When evaluating the available data, the U.S. Preventative Services Task Force (USPSTF) concluded that the risks of using NSAIDs at the dose and for the durations required to prevent colon cancer outweigh their benefits and thus should not be used in the general population.[67]

BREAST CANCER

In 2008, about 180,000 new cases of breast cancer were diagnosed in the United States, and 40,000 women died due to advanced breast cancer. Five-year survival for early stage breast cancer is 98% and drops to 89% for all stages together.[68] There are an estimated 2 million breast cancer survivors in the United States today and thus the implications of lifestyle modifications are enormous.

Though diet and lifestyle have been associated and often implicated in the risk of developing breast cancer, there is very little known about its effect on breast cancer survival.

Understanding the consequences of diet and lifestyle on breast cancer survival is extremely important to breast cancer survivors who want to make appropriate choices to improve not only their lifespan but also the quality of life.

There are only two published studies that have looked at the relationship between diet after breast cancer diagnosis and long-term survival. Although the results are promising, it is too early to tell if these results will be confirmed over time. The Nurses Health Study[69] examined diet after breast cancer diagnosis and its impact on survival. In this study, 1982 women with breast cancer were followed for an average of 13 years. Of that total, 1237 of the women did not develop metastatic disease. Women in this group who ate the largest amounts of poultry, total protein, and omega-3 fatty acids had a statistically significant lower risk of death compared to women who ate the least amounts of these foods and nutrients. Women who ate more fiber, fish, and vegetables also had a lower risk of death than women who ate less of these. The association of diet with survival was different for the 745 women whose did develop metastasis. Women who ate the largest amounts of dairy products and had high levels of calcium in their diets had a significantly lower risk of death. In addition, women with metastasized tumors who ate more protein had a lower risk of death. There are no published studies that have examined the effect of eating soy products on breast cancer survival.[70,71] Studies of women eating soy products daily have shown that soy-containing foods can act like estrogen and can cause cell proliferation in the breast. This could have a negative effect on breast cancer survival. Phytoestrogens in soy have also been reported to both oppose and complement the effects of tamoxifen in breast cancer cells. More study is needed in this area. At this time, it is a good idea for breast cancer survivors to avoid soy supplements and use soy-containing foods in moderation.

Some foods or nutrients were associated with as much as a 50% decrease in the risk of death. If these results prove to be correct, they could be quite important, as diet after diagnosis is something over which cancer survivors have control. It is important to recognize that these studies report associations and are not to be considered as recommendations.

The foods may just be representative of the women's lifestyle in general. Poultry products, like chicken and turkey, are often viewed as healthier choices than red meat. Women who ate more poultry may also have been making other efforts toward a healthier lifestyle.

Likewise, eating more hydrogenated oils may have been something done by the women who ate more processed baked foods (where these oils are found) and who were less concerned with healthy lifestyles.

Currently, it is unclear if specific diets before diagnosis affect breast cancer survival. Twelve studies have examined the effect of diet before breast cancer diagnosis on various aspects of survival. Four studies reported no association of survival with dietary fat consumption before diagnosis, but five studies reported that eating high levels of dietary fat was associated with a statistically significant increase in the risk of death. Some of these studies also examined the intake of vitamins A, C, and E from dietary food, not supplements, and showed differing results. Thus, no conclusions regarding the use of vitamins can be made at this time.

Although obesity at the time of diagnosis has been associated with decreased survival, it is unclear if weight gain after breast cancer diagnosis affects survival.[72,73] Weight gain is common in breast cancer patients after diagnosis and in 50%–96% of all early stage breast cancer patients receiving chemotherapy.[74] Two studies did not show any association between weight gain and an increased risk of cancer recurrence, but two other studies did report a possible association. Several studies have reported that weight gain is psychologically troubling and reduces the quality of life of breast cancer patients and thus negatively impacts long-term outcome.[73,74]

The effect of low body weight at the time of diagnosis and weight loss following diagnosis has been studied less often. Three studies have reported poorer survival for women of low body weight at the time of diagnosis; two of these reports saw this effect only in women with advanced breast cancer. One study reported that the loss of 11 or more pounds in women of any body size was associated with poor survival.

The effect of exercise on breast cancer survival is not known.[75,76] It may improve the quality of life of breast cancer survivors but no studies have directly examined how exercise after cancer diagnosis affects survival. An Australian study that followed 412 women with breast cancer for an average of 7 years showed no association of recreational exercise before diagnosis and survival.

Increasing physical activity, even if started later in life, reduces overall risk of developing breast cancer by 20% across women of all risk categories, including those

considered to be high risk. Consistent physical activity is more important than how strenuous an activity is. Inducing a "negative energy balance"—where less energy is taken in than is spent—by eating a low-calorie diet or increasing exercise can decrease postmenopausal risk of breast cancer associated with obesity.

Several studies have reported associations between exercise and improvements in the quality of life of breast cancer survivors, including improved mood, self-esteem, and sleep patterns and less nausea and fatigue.[77] These studies differed greatly in their study design, so comparisons between the studies are difficult. The results, although currently early, show promise. A reasonable suggestion for exercise would be that recommended by the U.S. Surgeon General, who recommends that everyone participate in moderate physical activity for at least 30 min 5 days a week.

Although smoking has been associated with numerous health problems, its effect on breast cancer survival is, as yet, not resolved.[78] Well-conducted studies have demonstrated an association between smoking and an increase in the risk of death but others show no association with the risk of death from breast cancer. Smokers may be at increased risk for the spread of cancer.[79] Two studies have reported an increase in the metastasis of tumors from the breast to the lung in smokers. Survival of women who have stopped smoking has been examined in one study and found to be similar to that of women who never smoked.

Drinking alcoholic beverages is considered to be a risk factor for getting breast cancer. However, most but not all studies have reported no association between drinking alcoholic beverages and breast cancer survival.[80]

It currently appears that group psychological therapy does not affect the survival of women with metastatic breast cancer. A recent, well-designed study, along with two other studies, disagrees with an early study that found that group therapy increased the survival of women with metastatic cancer.[81] Studies examining group psychological therapy for patients with other types of cancer have also reported mixed results. Yet, the support of fellow survivors and the encouragement to express concerns and feelings during group psychological therapy have been shown to have positive effects on breast cancer survivors' quality of life.

Alternative medical practices have not been studied sufficiently to determine whether they can affect breast cancer survival.[82,83] Few epidemiological studies or clinical trials have examined alternative therapies for breast cancer survivors. Over 30% of the women diagnosed with breast cancer report using alternative treatments including relaxation methods and spiritual practices; alternative medicines such as megavitamins, herbal medicines, and homeopathy; and healing therapies such as massage, chiropractic, acupuncture, and energy healing. More study is needed of these practices. To this end, the National Institutes of Health has established a National Center for Complementary and Alternative Medicine (http://nccam.nih.gov/) to fund and encourage the study of alternative medicine in various areas including cancer treatment.

The preliminary studies looking at diet and lifestyle after breast cancer diagnosis are encouraging and support the concept that diet and lifestyle choices can make a difference for breast cancer survival, as well as help these women feel better. There is limited evidence on specific diet and lifestyle behaviors that women can use to increase survival, but living a healthy lifestyle is a sensible choice for breast cancer survivors.

PROSTATE CANCER

The effects of obesity, energy expenditure, and specific nutrients are being vigorously studied in both the development and the outcomes of prostate cancer. In fact, countries with historically lower incidences of prostate cancer are now beginning to recognize increases in its diagnosis as their lifestyles become more "Westernized."[84]

With one in three adults in the United States being considered obese,[85] it is clear this epidemic could have a very marked effect in the way we think about prostate cancer. Even though obesity by itself is not clearly associated with an increased risk of developing prostate cancer, it has been linked to the diagnosis of more advanced prostate cancer, higher risk of dying of prostate cancer, and progression after prostatectomy.[86–88] The mechanism for this is not clear, but difficulties in examining the prostate, inaccurate nodal staging during prostatectomy, lower PSA values in obese patients, a low testosterone–high estradiol environment, leptin, adiponectin, and insulin-like growth factor have all been implicated as potential contributors to these findings.

Obese patients have increased caloric and fat intake. The increased intake of calories has been prospectively linked to an increased prostate cancer mortality.[89] Conversely, increased physical activity does not appear to have either a positive or a negative correlation.[90] Preadulthood height and obesity may indeed be associated with the previously mentioned risk in mortality.[91]

This implies that efforts to control the effect of obesity on cancer mortality should start during childhood and adolescence.

The U.S. diet is rich in linoleic acid, a fatty acid commonly found in corn oil. In vitro studies show that androgen-sensitive prostate cancer cell lines exhibit increased growth when exposed to this ubiquitous fatty acid.[92] Again, there is no apparent relationship to fat intake in terms of prostate cancer incidence[93] yet one study linked the consumption of saturated fat to increased relapse rates after prostatectomy.[94]

The Western diet, in addition to being rich in calories and saturated fat, may lack certain specific nutrients. Particular attention has been paid to those that may have antioxidant properties, under the hypothesis that excessive oxidative damage to nucleic acids is likely to lead to carcinogenesis and cancer progression.

Particular attention has been paid to lycopene, an antioxidant commonly found in tomatoes.

Most of the U.S. intake of lycopene is derived from tomato sauce consumption. Results from a 2004 meta-analysis initially

showed a possible decrease in incidence of 10%–20%.[95] However, a recent analysis from the Prostate, Lung, Colorectal and Ovarian Screening trial shows no relationship between this nutrient and prostate cancer incidence. Moreover, consumption of β-carotenoids, a related group of antioxidants, was associated with an increased risk of aggressive prostate cancer in the same study.[96]

Selenium has received much attention as well. This stems from an initial trial of selenium supplementation in skin cancer patients residing in areas with low dietary selenium. As a secondary endpoint, it was noted that there were fewer prostate cancers in subjects assigned to selenium.[97,98] The possible preventive role of selenium has been recently investigated by the National Cancer Institute in the SELECT trial, where 35,533 subjects were given placebo, selenium, and/or vitamin E for up to 7 years. After a negative planned second interim analysis, the Data and Safety Monitoring Committee recommended the discontinuation of these supplements.[99]

High milk consumption has been associated with increased risk of prostate cancer. In order to test whether this was related to calcium intake and vitamin D levels, the Health Professionals Follow-up Study assessed 47,750 males. The results showed that high calcium intakes of more than 1500 mg/day were associated with the development of high-grade prostate cancer, but not of low-grade, organ-confined, prostate cancer. In addition, those patients with an intake of more than 1500 mg/day did indeed have lower levels of circulating vitamin D. This led to the hypothesis that lower levels of vitamin D may impair the differentiation of prostate cancer cells toward a less aggressive, more confined cancer.[100]

With respect to diet, review of the published evidence does not support the viewpoint that the development of prostate cancer is the direct result of increased caloric intake, fat intake, or nutritional deficiencies. However, the studies indicate that our dietary habits may modify the biological behavior of preexistent foci of less aggressive prostate cancers. The implications are that this impact will be noted mostly in terms of detection of aggressive cancers, rates of relapse after curative treatment, and ultimately, in the risk of death.

At this point, it is impossible to make evidence-based recommendations toward the ingestion or avoidance of any specific nutrient. But based on the information presented on caloric and fat intake, it would appear wise to support a dietary regimen that would avoid obesity and excess fat as early as possible in one's life.

SKIN CANCERS

Worldwide, the incidence of melanoma is increasing at a rate faster than any other malignancy.

One in five Americans will develop skin cancer during their lifetime. An estimated 1 in 63 Americans will develop melanoma and this risk is 1 in 33 if in situ melanomas are included.[101]

Melanoma incidence is increasing across all age groups. It is now the second most common cancer in women in their 20s and third most common cancer in men in their 20s.[101] More than 1 million new skin cancers will be diagnosed this year in the United States, but actual numbers are likely higher and underreported. It is estimated that $500 million is spent annually in the treatment of skin cancers in the United States.[101]

Ultraviolet (UV) radiation has been demonstrated to be both mutagenic and carcinogenic in in vitro and in vivo studies. Its damaging effects on molecules and cellular structures have been well demonstrated. Skin cancer develops because DNA is altered after exposure to UV radiation.[102] UVB radiation has a long-accepted role in the development of skin cancers. UVB radiation, by virtue of its short wavelength (<320 nm), is absorbed throughout the epidermis, including proteins and DNA.[103] The carcinogenic effects of UVB radiation occur through direct absorption of photons, but it is also known that UVB radiation damages proteins and cell membranes, in addition to generating oxidative stress.[104,105]

The role of UVA radiation in the development of malignancy and immunosuppression has recently become more clear.[105,106] UVA radiation, with its longer wavelength (320–400 nm) more easily penetrates the skin, even reaching the basal layer of the epidermis, including dermal fibroblasts. The integrity of the genetic code is maintained by DNA repair mechanisms, which allow damaged bases or altered gene sequences to be eliminated and replaced via base and nucleotide excision repair pathways.[103] If DNA damage gets to a certain point, and repair enzymes are saturated, and signaling pathways can be stimulated; hyperproliferation of abnormal cells and subsequent tumor development may occur.[103,107,108]

The more common skin cancers, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), most commonly occur on sun-exposed areas of skin. The risk is highest among those who burn easily.[109–111] Skin cancer risk is highest among those with fair skin. These individuals are more sensitive to exposure at wavelengths 290–320 nm.[112]

The incidence of skin cancer worldwide is highest in those areas with above average annual UV radiation.[113] Mortality rates from melanoma in the United States and Canada have also been shown to directly correlate with ambient UV exposure, and this correlation is even higher when ambient UVA (320–400 nm) radiation is included.[114,115]

There is a direct correlation with BCC and SCC incidence and latitude, as demonstrated by Scotto et al. There is a strong inverse correlation between latitude and incidence of BCC and SCC for both men and women.[116] Long-term chronic UV exposure seems to increase the risk of nonmelanoma skin cancer, where the opposite (acute intermittent UV exposure) increases the risk of melanoma.[117] The incidence of melanoma is also higher in high-altitude regions, possibly related to higher UV fluencies (measured in J/cm^2) in these areas.[118]

A complex study by Fears et al. demonstrated that when lifetime residential history was coupled with levels of mid-range UV radiation (UVB flux) to provide a measure of individual exposure to sunlight, a 10% increase in annual UVB flux was associated with a 19% increased risk of melanoma. Even in women who could tan easily, a 10% increase in

hours outdoors was associated with 5.8% increase in melanoma incidence.[119] The influence of sun exposure in early life appears to be greater than exposure at a later age. Migration studies of people born in Australia demonstrate an increased risk of skin cancer compared to native Northern Europeans who migrated to Australia at age 10 years or older.[120] Nevertheless, UV exposure at later age also contributes to the risk of developing skin cancer. In patients before and after age 15 years, investigators demonstrated a similar upward gradient of melanoma related to the frequency of sunburns. Importantly, more than five sunburns doubled the melanoma risk, regardless of age at which the sunburns occurred.[121]

In areas of the skin consistently exposed to UV, such as the head and neck, the density of skin cancer is highest. In rarely exposed areas such as the scalp and buttocks, skin cancer development is rare.[122] In women, melanoma is more common on the lower extremities, where there tends to be more UV exposure, than in men.[123] Individuals with higher number of nevi (personal nevus count) have a higher risk of melanoma.[124]

Protection from UV exposure can lower subsequent skin cancer risk.[125] Sunscreens offering broader spectrum protect skin better from UV-induced neoplasia. In fact, daily use of broad-spectrum sunscreens significantly reduces UV-induced skin damage.[126] In children who regularly used sunscreens, lower nevus counts were found than in children who used less sun protection, thus suggesting that sun protection during childhood does reduce subsequent melanoma risk.[127]

A meta-analysis of 11 studies of melanoma risk and sunscreen use showed only a small protective advantage.[128] However, when more recent studies are included where high sun-protection factor sunscreens were available, a protective effect is identified, and other inherent flaws associated with retrospective studies may be responsible for protection not being noted.[129] It is important that development of future sunscreens incorporate a full range of UV protection.[130]

In addition to sunscreen, patients are advised to wear protective clothing and avoiding sun exposure during peak (midday) hours when UV intensity is greatest. These interventions, coupled with regular sunscreen use, have the greatest impact in lowering skin cancer risk.[131]

According to the National Institutes of Health states, "exposure to sunlamps or sunbeds is known to be a human carcinogen."[132] In a case–control study, the incidence of SCC and BCC was significantly associated with the use of any tanning device.[133] In a prospective cohort study of over 100,000 Scandinavian women, a 55% increased melanoma risk was demonstrated in those who used tanning devices at least once a month between the ages of 10 and 39 years, compared to those who rarely or never used such devices.[134]

There are over 50,000 tanning facilities in the United States, generating revenue of approximately $5 billion.[135] Of the 1 million people who use tanning salons every day, 70% are females between the ages of 16 and 49 years.[136] Tanning beds emit both UVA radiation and UVB radiation.[137] In fact, the UVA irradiation emitted by some tanning beds may be 10–15 times higher than that of the midday sun. The idea that "controlled" salon tanning, while touted as being safer than "uncontrolled" beach tanning, is inaccurate.[137]

According to the International Agency for Research on Cancer, the use of tanning beds was positively associated with melanoma, particularly if first exposure occurred before the age of 35 years.[138] In a recent survey of non-Hispanic white teenagers (ages 13–19 years), 24% of respondents reported using a tanning facility at least once in their lives and 28% of American teenage girls report having used tanning salons three or more times during their lives.[136] Among children ages 11–18 years, 10% reported using indoor tanning sunlamps within the past year.[139] Twenty-eight states have regulations limiting teenagers' access to tanning facilities. In 2007, 16 more states introduced similar bills.[140] In some states, written parental consent is required for minors using commercial tanning beds. The Colorado House rejected a Senate-passed bill prohibiting anyone under the age of 18 years from using a tanning bed without a doctor's prescription, notarized parental consent, or parents present at the salon. In California, laws were recently passed prohibiting those ages 14–18 years from using any UV tanning device without written parental consent. In that state, tanning bed use under the age of 14 years is already banned.[141]

The Indoor Tanning Association, a vehement industry group, states that its mission is to "protect the freedom of individuals to acquire a suntan, via natural or artificial light. When it involves a suntan, the State has no business inserting itself between child and parent. This notion that government knows more about child rearing than parents is preposterous."[142,143] The International Agency for Research on Cancer,[137] American Academy of Pediatrics,[144] World Health Organization,[145] American Medical Association,[146] and American Academy of Dermatology[147] have all issued position statements against the use of tanning beds.

CONCLUSION

The main aim of the fight against cancer is to decrease mortality from the disease. This can be achieved by better treatments or by decreasing the incidence of cancer. Treatment of cancer has reached new horizons over the last two decades resulting in cure of several types of cancer, increase in survival of patients living with cancer, and improvement in quality of life. A universal cure for all types of cancer is still not in the foreseeable future.

Decreasing the incidence of cancer can be achieved by modulation of known causes of cancer. In this regard, changes in lifestyle, e.g., adhering to a healthy diet, regular exercise, and avoiding smoking and excessive exposure to UV radiation, can decrease the incidence of cancer.

Yet another way of controlling one's lifestyle that can lead to a decrease in the incidence of cancer is by following medical recommendations related to screening for cancer. That includes screening for breast cancer with mammograms, for cervical cancer with Papanicolaou smears, for prostate cancer with digital rectal examination and serum prostate-specific

antigen (PSA), and for colon cancer with colonoscopies.[148] Screening can lead to early detection of cancer or precancerous lesions. This is important, because early detection of cancer can lead to early medical intervention and a higher chance of cure. The detection of precancerous lesions can help in preventing the development of cancer by removing these lesions or by starting the affected individual on chemoprevention medications. There is clear evidence that if a breast precancerous lesion is detected, the use of chemoprevention medications may reduce the chance of breast cancer developing in that individual.[149,150]

Know your genes. Our lifestyle has to accommodate our genes. Over the last decade, many inherited gene mutations that may predispose one to cancer have been discovered. Testing for carrier status of susceptibility genes for breast and colon cancers is commercially available.[151]

Those tested and found to be carriers should focus their lifestyle around their susceptibility to that certain cancer and should seek counseling with regular physician visits and appropriate screening. Additional considerations for such an individual may include chemoprevention and an awareness of the impact of inherited genes on their personal family planning. The U.S. congress recently passed the genetic information nondiscrimination act (GINA law) which protects an individual carrier of an identified genetic mutation from work and insurance discrimination.[152] It is hoped that this legislation will result in a wider use of genetic testing for individuals with a strong family history of cancer.

While the molecular basis for most cancers is now well known, the inciting process for many has yet to be defined. However, what is clear is that certain controllable human behaviors often may be the trigger mechanism and changes in lifestyle may be one's best protection from becoming another victim of some very preventable diseases.

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38 Obesity and Cancer

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CONTENTS

Breast Cancer 484
Colon Cancer 484
Endometrial (Uterine) Cancer 485
Esophageal and Gastric Cancer 485
Kidney Cancer 485
Prostate Cancer 485
Other Cancers 485
Physical Activity 485
Diet 486
References 487

Cancer is a group of diseases that result from uncontrolled growth and spread of genetically altered cells. Cancers are caused by both external factors (tobacco, infectious organisms, radiation, chemicals) and internal factors (inherited mutations, hormones, immune conditions, metabolic abnormalities). Interactions among these causative factors are thought to lead to genetic changes that transform normal cells into those that no longer respond to the normal homeostatic mechanisms enjoyed by normal tissue. At least two external factors are controllable, and if they were to be eliminated, a large number of cancers could be prevented. The use of tobacco products and excessive body fat contributes greatly to the incidence of several of the most serious forms of cancer.

For more than half a century, it has been appreciated that a causal relationship between cigarette smoking and lung cancer exists [1]. Of interest, it was German scientists during the 1930s under Adolph Hitler who were the first to link smoking to lung cancer [2]. Beginning in the mid-twentieth century, investigators began identifying other malignancies that are associated with smoking [3], and medical professionals have become accustomed to advising their patients who smoke to discontinue that particular lifestyle. From those efforts and from a number of government [4] and nongovernmental initiatives, the number of Americans who continue to smoke has significantly decreased [5,6]. Between 1965 and 2004, cigarette smoking among adults aged 18 and older declined by half from 42% to 21%. By 2007, that rate diminished to 20%. Thus, a considerable reduction in the incidence of tobacco-related diseases, including several cancers, has occurred [7].

As numerous efforts to eliminate smoking appear to be effective, that lifestyle factor is declining [7], but unfortunately the other controllable lifestyle factor, being overweight or obese, is doing just the opposite. Many sources have substantiated the fact that there is a frightening rise in the number of Americans, including children, who are obese [8,9]. And while there has long been an association of obesity with heart disease and other noncancerous medical conditions, only during the past 10–20 years has the etiologic relationship between obesity and cancer been fully appreciated [10,11]. In fact, some authorities feel that obesity and lack of physical activity have or soon will surpass tobacco use as the leading cause of cancer [12,13]. Not rare cancers, but some of the more common and serious forms of cancer including colon, breast (postmenopausal), endometrial, renal, and esophagus [11]. In addition, some studies have also reported links between obesity and cancers of the gallbladder, ovaries, and pancreas [12].

This chapter will describe what is known about the relationship between obesity and cancer and examine the possible etiologic factors that research has uncovered in this most troubling, yet potentially controllable, situation. Since obesity and a sedentary lifestyle have, for all practical purposes, a cause and effect relationship, much of the reported evidence relating obesity and cancer refers as much to the lack of physical activity as to body weight or body mass index (BMI).

The National Health and Nutrition Examination Survey (NHANES), a program within the Centers for Disease Control and Prevention, reported that in the year 2008, approximately 34% of U.S. adults over the age of 20 were overweight and more than one-third (33.8%) were classified as obese [9]. In 2008, 16.9% of children, 2–19 years of age, were overweight, more than triple the number two decades earlier [8]. A startling statistic reported by NHANES is that since 1976, the percentage of adult Americans with BMI values above 30.0 (“obese”) has doubled. Studies have shown that being overweight or obese directly relates to both a lack of physical activity and the ingestion of a high caloric and/or fatty diet.

In 2001, the International Agency for Research on Cancer of the World Health Organization convened a group

of experts to evaluate the evidence for the role of physical activity and weight control in cancer prevention. The group concluded that being overweight or obese increases the risk of breast cancer (postmenopausal) and cancers of the colon, endometrium, kidney (renal cell), and esophagus (adenocarcinoma) and possibly thyroid cancer. And, by losing weight, one may reduce his or her risk of developing these cancers, but there is insufficient evidence to definitively conclude that such is the case. These experts determined that physical activity plays a significant role in preventing cancers of the colon and breast. Taken together, they concluded that excess body weight and physical inactivity account for approximately a quarter to one-third of cancers of the colon, breast, endometrium, kidney (renal cell), and esophagus (adenocarcinoma). Thus, lack of physical activity and being overweight or obese appear to be the most important lifestyle factors causing these cancers [12].

More than 150 epidemiologic studies of physical activity and cancer risk have been carried out. Several possible biological mechanisms relating physical activity and cancer have been proposed, including changes in androgen, estrogen, and metabolic hormone levels and various growth factors, decreased BMI, and possibly changes in immune function. Excess weight and central adiposity have been implicated in promoting metabolic conditions that relate to carcinogenesis [13,14].

One of the most in-depth studies to estimate the number of obesity-related cancers in the United States was reported in 2008 [10]. Using published meta-analyses and/or large cohort studies, it was estimated that 33,966 new cancers (4% of all cancers) in males and 50,535 (7% of all cancers) in females, diagnosed in 2007, or 6% of all cancers, may be attributable to obesity.

Regarding mortality, if the correlation between obesity and cancer is indeed causal, it was estimated that in 2004, obesity accounted for one in seven (14%) cancer deaths in American men and one in five (20%) cancer deaths in American women, or a total of 17% of all cancer deaths in the United States [11]. More recent data would suggest that as many as one-third of the 562,340 cancer deaths in 2009 were related to overweight or obesity, physical inactivity, and poor nutrition. Reflecting on the relationship between tobacco use and cancer, the American Cancer Society reported that in 2009, approximately 30% of all cancer deaths in the United States were related to the use of tobacco [15]. If these numbers are factual, then obesity may have passed tobacco use as the number one cause of cancer in the United States.

What follows is a more in-depth narrative of the relationship between being overweight or obese and certain cancers that are causally linked to this lifestyle factor.

BREAST CANCER

There is rather irrefutable evidence that obesity increases the risk of a woman developing breast cancer and depends upon a woman's menopausal status. Premenopausal women who are obese actually have a lower risk of developing breast cancer than nonobese premenopausal women [16–19]. Women who are postmenopausal and obese are those who have an increased risk of developing breast cancer, as much as 1.5 times that of women with healthy weights [16,17,20].

While the evidence is not conclusive, studies suggest that the distribution of the adipose tissue in obese women may have significance. Women with abdominal distribution of fat are at greater risk of developing breast cancer than those whose fat is predominantly deposited over the hips, buttocks, and thighs [21,22].

It is believed that the increased risk of breast cancer in obese women is due to their having higher levels of estrogen. While the main source of estrogen is the ovaries, adipose tissue is also a producer of this female hormone and becomes the main source of estrogen in the postmenopausal state. Obese postmenopausal women produce nearly twice the level of estrogen as postmenopausal women with healthy weights [18]; therefore, estrogen-sensitive tissues such as estrogen-responsive breast cancers are more apt to be stimulated to grow.

An additional statistic related to obesity and breast cancer is the observation that death rates for this disease are higher in overweight women. Experts believe that this can be attributed to a delay in detecting a palpable tumor mass in the obese breast, thus leading to a later stage of disease at diagnosis [19].

While being overweight does not seem to confer a greater risk of developing the disease in African American women, these women, obese or not, have a greater likelihood of having a more advanced stage of disease at diagnosis [23]. Hispanic women who are overweight have a higher risk of breast cancer, irrespective of menopausal status [24].

COLON CANCER

While there is strong evidence for a relationship between obesity and the risk of developing colon cancer, this has been consistently reported for men [25–28], but not for women [25,28,29].

Just as with breast cancer, the distribution of adipose tissue appears to be a factor in those who are obese and at risk for developing colon cancer. Since men with high BMI are generally obese with an increase in abdominal fat, and women with high BMI are more likely to have their adipose tissue distributed around hips, buttocks, and thighs, the risk of colon cancer appears to relate to abdominal fat [27,28].

The mechanism responsible for the increased risk of colon cancer, especially in obese males, is not determined; however, there is some evidence that high levels of insulin or insulin-related growth factors may enhance adenomatous growth in the colon and thereby lead to the evolution of a cancerous tumor [30].

An additional comparison to breast cancer and obesity is the possible causative factor of estrogen. Unlike for breast cancer and uterine cancer (see the following), the presence of estrogen appears to be protective for colon cancer in women [31]. However, obese women who also take estrogenic

hormone replacement therapy, regardless of menopausal status, increase their risk of developing colon cancer not dissimilar to the risk seen in obese men [32].

ENDOMETRIAL (UTERINE) CANCER

Obesity accounts for more than a third of all cases of endometrial (uterine) cancers [33]; and, obese women have nearly a four times greater risk of developing uterine cancer than women with healthy weights, irrespective of menopausal status [34–37].

Evidence suggests that high levels of estrogen and higher than normal levels of insulin in overweight or obese women may account for this increased risk [34–36].

ESOPHAGEAL AND GASTRIC CANCER

There is an increase in esophageal and gastric cancer of a particular histology, specifically adenocarcinoma, and location (distal esophagus and gastric cardia at the esophageal–gastric juncture) in obese individuals [38–42]. Obesity confers two times greater risk of developing one of these cancers than for individuals who have healthy weights [38–40].

Since it is known that gastric reflux may lead to the development of Barrett's esophagus, a precancerous condition affecting the distal esophagus, reflux has been postulated to be the mechanism that is responsible for the increased risk of adenocarcinoma of the esophagus. However, the evidence is inconclusive, and a precise mechanism has not been determined [41].

KIDNEY CANCER

Obese women are at increased risk of developing kidney cancer (renal-cell carcinoma) [43–47]. This risk may be as high as four times that for women who are not overweight. For men, there does not seem to be this association between obesity and renal cell carcinoma [43]. Like other cancers associated with obesity, the exact mechanism is uncertain, but estrogen exposure certainly has been considered an etiologic factor since the risk is gender related.

PROSTATE CANCER

While the overall risk for obese men developing prostate cancer appears to be no greater, perhaps even slightly less, than for men with healthy weights, obese men appear to be at greater risk of developing the more aggressive forms of prostate cancer [48–51].

The observation that obese men may have lower rates of prostate cancer than thinner men may not reflect an actual lower risk, but a lower rate of early detection through prostate cancer screening. Using data from three U.S. government health surveys, researchers found that among men who underwent prostate cancer screening with a prostate-specific antigen (PSA) blood test, obese men generally had lower PSA levels than thinner men. They were also less likely to have their PSA test followed up with a biopsy to rule out or confirm prostate cancer. Of obese men who had ever had PSA screening, 4.6% had undergone a biopsy versus 5.8% of normal-weight men [52].

Furthermore, mortality studies have yielded conflicting data, at least one such study suggesting that obese men may in fact have a better prognosis than nonobese men with prostate cancer [53].

OTHER CANCERS

An association between obesity and ovarian cancer has not been delineated [54,55]; however, one study described an increased incidence of this cancer in women who were overweight or obese during adolescence or young adulthood [56].

Obesity as a risk factor for pancreatic cancer has been reported in one study [57], but such an association was not confirmed in other reports [58]. It has been suggested that persons who exhibit physical inactivity are at increased risk of developing pancreatic cancer [59].

Women who are obese are at increased risk of developing cancer of the gall bladder [60,61]. Obesity is associated with a high frequency of gallstones, and the relationship between gall bladder cancer and gallstones is a recognized phenomenon.

PHYSICAL ACTIVITY

While caloric intake is the most important determinant of BMI, not to be overlooked in the variables that contribute to one's BMI is the amount of physical activity that an individual undertakes. Clearly, when there is a high intake of calories accompanied by a sedentary lifestyle, the chance of one becoming overweight or obese is greatly increased. Therefore, one may conclude that those cancers that are associated with obesity as a causative factor might become less common in a population that exhibits regular physical activity.

In fact, with colon cancer, such has been observed. Even with moderate levels of physical activity, the risk of developing colon cancer was reduced by 50% [62,63].

With respect to breast cancer, most studies have looked at the effects of physical activity in postmenopausal women where it has been shown that moderate levels of physical activity (e.g., walking approximately 30 min each day) reduced the risk of developing breast cancer by nearly 20%, the greatest benefit experienced by women who were not overweight, with no benefit seen in obese women [64].

The beneficial effects of increased physical activity as it relates to other cancers with a known association with overweight and obesity are unknown. Virtually no controlled studies to examine this question have been undertaken.

A summary of the foregoing information relating to the causality of obesity and certain cancers and data relating to proposed mechanisms and the relationship of physical activity to the respective cancer is shown in Table 38.1.

TABLE 38.1
Obesity: A Causality Factor for Certain Cancers and Related Data

Cancer	Overweight/ Obesity Related	Population at Risk	Proposed Mechanism of Relationship	Physical Activity Related
Breast	+++++	• Obese postmenopausal • Obese Hispanic women	• Estrogen	++ • Postmenopausal women • Women with healthy weight
Colon	+++++	• Obese men • Obese women on hormone replacement therapy	• Abdominal fat • Insulin • Insulin-related growth factors	+++
Uterine	++++	• Obese pre- and postmenopausal	• Estrogen • Insulin	Not studied
Kidney	+++	• Obese women	• Estrogen	Not studied
Esophageal	++	• Obese men and women • Distal esophagus	• Gastric reflux	Not studied
Gastric	++	• Gastric cardia	• Gastric reflux	Not studied
Gall bladder	++	• Obese women	• Gall stones	Not studied
Ovarian	+	• Obesity during youth or early adulthood	• Unknown	Not studied
Pancreatic	+	• Obese men and women	• Decreased physical inactivity	Not studied
Prostate	+	• Obese men with aggressive form	• Unknown	Not studied

+++++, Conclusive evidence; ++++, strong evidence; +++, moderate evidence; ++, inconclusive evidence; +, weak evidence.

DIET

Evidence is rather compelling that dietary patterns and dietary elements are etiologic factors for several types of cancer. As many as 35% of cancer deaths may be related to dietary factors [65]. Research shows that diets low in fat and high in fiber, fruits, vegetables, and grains are associated with reduced risks for certain cancers.

Diets high in fat have been linked to breast, colon, and prostate cancers and possibly to pancreas, ovary, and endometrial cancers [66]. The average U.S. diet is estimated to contain nearly 40% of calories from fat, which is significantly higher than that needed to meet the physiological needs for energy and essential fatty acids. The major sources of fat in the American diet are added fats and oils used as spreads, cooking fats, and salad oils as well as the fat in meats and whole milk dairy products.

Because dietary fat intake is highly correlated with calorie intake, there is the issue as to whether fat intake or caloric intake is the major dietary factor affecting cancer risk. Several studies have looked at the importance of fat intake versus caloric intake and suggest that both have independent effects. Since dietary fat is the most concentrated source of energy of all the nutrients and supplies (9 cal/g compared to 4 cal/g from either carbohydrate or protein), a reduction in dietary fat intake is accompanied by a decrease in total calorie intake and body weight [67,68].

Evidence suggests that diets high in fiber are associated with a reduced risk for cancer, especially cancer of the colon [69]. This may also be true for cancers of the breast, rectum, oral cavity, pharynx, and stomach [70].

With respect to fruits and vegetables, it has been observed that populations whose diets are rich in fruits and vegetables have a lower risk for cancers of the lung, colon and rectum, breast, oral cavity, esophagus, stomach, pancreas, uterine cervix, and ovary. Fruits, vegetables, and grains contain a number of nutrients, including carotenoids, vitamin A, and vitamin C. For most cancer sites, especially those of the respiratory and digestive tracts, persons with low fruit and vegetable intake had about twice the risk of cancer as those with high intake [71].

The current dietary recommendation is for five servings of fruit and vegetables a day, and Americans fall somewhat short of this goal. Only approximately 20% of the population is achieving this goal with the average daily intake of only three and a half daily servings of fruits and vegetables [72].

In addition to vitamins A and C and the carotenoids, fruits, vegetables, and grains contain other vitamins and minerals associated with a protective effect against cancer.

Vitamin E has inhibited tumors in experimental animals and been linked to reduced risks of oral, stomach, and other cancer in epidemiologic studies. Selenium also may have a protective effect. In a recent randomized large-population trial testing the effectiveness of vitamin/mineral supplementation among persons in high-risk areas of China, those who received daily supplements with a combination of beta-carotene, vitamin E, and selenium for 5 years had

a significantly lower cancer death rate [73]. The findings do not automatically translate to Western populations—in that the Chinese population studied was chronically deficient in a number of nutrients—but offer a hopeful sign that certain vitamins and minerals may lower risk of some cancers. However, two other recent large randomized trials of supplements, one testing the effect of supplemental beta-carotene or alpha-tocopherol in the prevention of lung cancer among smokers and the other testing the effect of supplemental beta-carotene and vitamins C and E in the prevention of adenomatous polyps (a precursor lesion for colorectal cancer), suggest that supplemental use of these nutrients does not reduce the risk of either lung or colorectal cancer [74,75]. In the study of the effect of beta-carotene or alpha-tocopherol on lung cancer among smokers, dietary intake of these nutrients from foods was associated with a reduced risk for lung cancer [74]. Some studies suggest that calcium may play a protective role in colon cancer. A 19 year prospective study in men showed that the risk for colon cancer was lower in those with the highest calcium intake [75]. In addition to dairy products, certain vegetables are good sources of calcium, notably roots, okra, and dark green leafy vegetables such as collard greens.

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39 The Role of Physical Activity across the Cancer Survivorship Continuum

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CONTENTS

Overview of Cancer 491
Definition of a Cancer Survivor 491
Physical Activity and Cancer Survivorship 492
Benefits of Physical Activity for Cancer Survivors 495
Physical Activity and Bio-Physiological Health 495
Physical Activity and Psychosocial Health 496
Physical Activity Guidelines for Cancer Survivors 496
Physical Activity Prevalence across Tumor Groups 497
Potential Cancer-Specific Barriers to PA 498
Evidence-Based Behavior Change Strategies 498
Limitations and Future Directions 499
Practical Strategies for Practitioners 500
Concluding Remarks 501
References 501

OVERVIEW OF CANCER

In the United States alone, over 1.6 million new cases of cancer (excluding skin cancer) are expected to be diagnosed in 2012, and just over 577,000 Americans are expected to die from the disease [1]. Cancer is the second most common cause of death in the United States after heart disease. The four most common cancers—prostate, breast, colorectal, and lung—account for over 55% of all new cancer cases and over 50% of all new cancer deaths each year [1]. The population of cancer survivors is growing as there are approximately 12 million individuals with a history of cancer alive today in the United States [1].

It is estimated that the overall cost of cancer in the United States in 2007 was just over $227 billion [1]. Cancer is now viewed as a major public health burden not just in the United States but worldwide. The 5-year relative survival rate in the United States across all cancers and disease stages is 67% [1], although this survival rate varies substantially by cancer type and stage. For example, the 5-year relative survival rate for breast cancer is now 90% (99% if the cancer is local and has not spread to other parts of the body outside the breast). In contrast, the 5-year relative survival rate for lung cancer that is localized (i.e., early stage) is 52%, but only 16% when all stages are considered. Despite the high death rates, for certain cancers, more individuals are surviving their cancer.

DEFINITION OF A CANCER SURVIVOR

There are several definitions used to describe a cancer survivor. For some, an individual receiving their first diagnosis of cancer may be considered a survivor, instead of "survivorship" starts from diagnosis. Alternatively, an individual may not be labeled "survivor" until the completion of primary and systemic treatments (including but not limited to surgery, chemotherapy, and radiotherapy). Others define survivors as those with a cancer history who live 5 or more years beyond their diagnosis [2]. The National Cancer Institute (NCI) maintains that an individual is a cancer survivor from the time of diagnosis through the balance of his or her life [3]. In support of this definition, a cancer control continuum was developed that defines six phases of the cancer trajectory ranging from prevention and early detection to diagnosis, treatment, survivorship, and end-of-life [2]. Individuals in each phase of the continuum have unique needs related to their cancer that affect their overall health and quality of life. One mechanism known to help improve many aspects of health and quality of life across the cancer control continuum is physical activity (PA).

PA is a well-documented strategy that can be effective in improving physical, biological, and psychosocial health during cancer survivorship. Courneya and Friedenreich [4] extended the cancer continuum and developed the Physical Activity and Cancer Control (PACC) framework for understanding

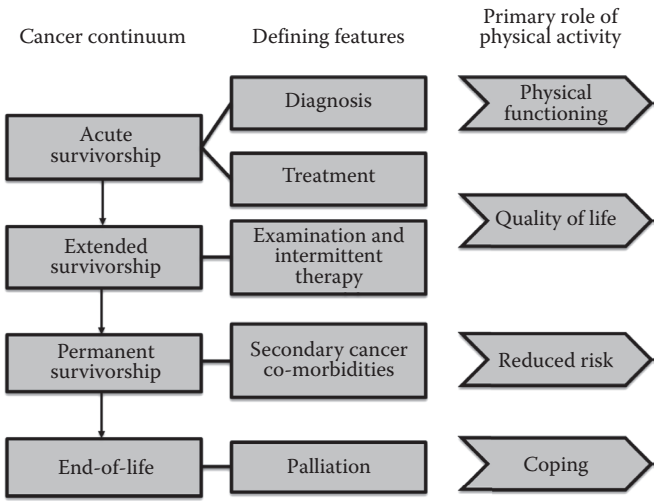


FIGURE 39.1 Cancer Survivorship and Physical Activity (CSPA) Schema.

PA as a facilitator of cancer prevention and cancer recovery. The PACC framework has been used as a template to help organize, focus, and stimulate research and initiatives related to PA and cancer [4], as well as the development of PA guidelines for cancer survivors [5]. Synergizing PA and the cancer continuum has helped foster public health efforts aimed at helping more individuals with a history of cancer initiate and maintain PA. These efforts have also helped guide research on the determinants and outcomes of PA among cancer survivors. In Figure 39.1, we provide a modified model that adapts the PACC framework and the NCI cancer continuum and summarizes the literature to provide an overview of the association between PA and cancer survivorship.

The Cancer Survivorship and Physical Activity schema (CSPA; Figure 39.1) details different stages of cancer survivorship, which spans diagnosis to end-of-life. The CSPA defines features of each phase drawing on Mullan [6]: acute survival (a period dominated by diagnosis, diagnostics, and treatments), extended survival (postsystemic treatment, dominated by constant examination and intermittent therapy), and permanent survival (a period following the "cure," dominated by potential for secondary effects of cancer treatment and long-term risk). We also include an end-of-life phase in the model as consistent with cancer survivor definitions and frameworks. Although regular PA is important during each of these stages of survivorship for a number of reasons, the most important role for each phase is illustrated in Figure 39.1. For acute survivorship, PA can help improve physical functioning and reduce treatment side effects. In the period of extended survivorship, PA can help improve quality of life, which is defined broadly as having physical (e.g., body composition, fatigue), psychological (e.g., mood, stress and anxiety), and social (e.g., social support and connectedness) dimensions [7,8]. For the period of permanent survivorship, PA is likely to help reduce the risk of recurrence of some cancers such as breast and colon [e.g., 9–12], and to help protect against comorbidities such as cardiovascular disease, hypertension, diabetes, overweight, and obesity [13]. Finally, the primary role of PA in the end-of-life stage is to help individuals manage their emotions and cope with the predominant symptoms associated with persistent fatigue, low energy, and anorexia–cachexia conditions [14,15].

As illustrated in Figure 39.1 and in this chapter, we focus on the effects of PA during the extended and permanent survival periods of cancer survivorship (the period that spans posttreatment to end-of-life). We also present research examining PA promotion strategies for cancer survivors. Based on the research presented, we provide health care practitioners with some strategies that can be discussed with survivors to facilitate PA.

PHYSICAL ACTIVITY AND CANCER SURVIVORSHIP

Researchers and clinicians are increasingly interested in understanding the role PA in promoting the health of cancer survivors. This has yielded a large body of evidence linking various aspects of PA to biopsychosocial outcomes [16]. Evidence of the growing body of literature is reflected in the several reviews and meta-analyses synthesizing evidence from observational and experimental studies that have now been published [5,16–20]. These reviews have varied in regards to the search terms used, inclusion/exclusion criteria applied, types of studies reviewed, and health-related outcomes examined. For example, some reviews focused on certain cancer types (e.g., breast), whereas others reviewed studies where various tumor groups were included. Some reviews summarized studies with individuals at various phases of the cancer continuum and others chose a specific phase. One recent systematic review identified 64 randomized controlled trials (RCTs) postdiagnosis (i.e., both during and after treatments) across various cancer groups [16]. Properly conducted and well-designed RCTs provide the best evidence of the efficacy of a treatment or health care intervention [21]. This review of RCTs, and other meta-analyses and systematic reviews, provides mounting evidence suggesting that PA both during and after cancer treatments may improve multiple health outcomes. Table 39.1 presents an overview of existing review articles examining associations between

TABLE 39.1
Summary of Published Reviews and Meta-Analyses Investigating Health-Related Outcomes of Physical Activity for Cancer Survivors

Reference	Types of Studies Reviewed	Number of Published Studies Reviewed[a,b]	Samples	Health-Related Outcomes Measured	Physical Activity Details
Brown et al. [22]	Experimental studies (RCT)	44	Breast; prostate; lymphoma; leukemia; colorectal cancer; mixed diagnoses	Cancer-related fatigue	The assessment and prescription of physical activity, in terms of type, intensity, frequency, duration, were varied
Courneya [20]	Observational and experimental studies (RCT, pretest-posttest with no control group, pretest-posttests with matched controls)	14	Breast; prostate; head and neck; colorectal; mixed diagnoses	Anxiety; body composition; depression; exercise capacity; functional capacity; hemoglobin concentration; immune system; lymphedema; mood; muscular strength; natural killer cell cytotoxic activity; number of monocytes; physical appearance; physical fitness; physical well-being; quality of life; satisfaction with life; self-esteem	Within the observation studies reviewed, the common method used to assess physical activity was self-report questionnaires, though monitoring devices (e.g., heart rate monitors, motion monitors) were used. Within the experimental studies reviewed, the prescribed physical activity was generally for aerobic activity (alone or in combination with different types) of moderate to vigorous intensity, three to five times per week, for 30 min per session, and sessions were supervised
Craft et al. [23]	Experimental studies (RCT)	7	Breast; colorectal; breast, colorectal and ovarian; mixed diagnoses	Depression	
Cramp and Daniel [24]	Experimental studies (RCT)	12	Breast; breast or prostate; colorectal; mixed diagnoses	Aerobic capacity; affect; anger; anxiety; arm volume; body composition; body esteem; cardiovascular fitness; confusion; depression; emotional functioning; energy; fatigue; flexibility; happiness; health-related quality of life; peak oxygen consumption; physical fitness; mood; physical function; quality of life; satisfaction with life; self-esteem; self-perception; symptom stress; tension; vigor; well-being (physical, emotional, social/family)	
Ferrer et al. [25]	Experimental studies (RCT, pretest-posttest with no control group, pretest-posttests with matched controls)	13	Breast; prostate; colorectal; endometrial; head and neck; lymphoma; ovarian; mixed diagnoses	Quality of life	

(*continued*)

TABLE 39.1 (continued)
Summary of Published Reviews and Meta-Analyses Investigating Health-Related Outcomes of Physical Activity for Cancer Survivors

Reference	Types of Studies Reviewed	Number of Published Studies Reviewed[a,b]	Samples	Health-Related Outcomes Measured	Physical Activity Details
Knols et al. [19]	Experimental studies (RCT, CCT)	12	Breast; breast, colon, ovarian, non-Hodgkin's, brain and lung; colon; mixed diagnoses	Aerobic capacity; affect; anxiety; arm circumference; blood pressure; body composition; body mass index; body weight; cardiopulmonary changes; depression; fasting insulin; fatigue; happiness; glucose; insulin-like growth factors and binding proteins; insulin resistance; mood; muscle strength; natural-killer cell cytotoxic activity; physical capacity; physical strength; quality of life; self-esteem; sum of skinfolds; walking distance	
McMillan and Newhouse [26]	Experimental studies (RCT)	5	Breast; colorectal; mixed diagnoses	Aerobic fitness; fatigue	
McNeely et al. [18]	Experimental studies (RCT)	6	Breast	Body composition; body fat; body mass index; body weight; fatigue; lean mass and body fat muscular fitness; quality of life; sum of skin folds; upper and lower extremity strength, volume and circumference; VO2peak; 6-min walk test	
Pekmezi and Demark-Wahnefried [27]	Experimental studies (RCT)	12	Breast; colorectal; mixed diagnoses	Adiponectin; body fat; bone mineral density; central adiposity; fatigue; fitness; health; hip circumference; hot-flash frequency and severity; insulin; insulin-like growth factors and binding proteins; joint dysfunction; lean mass; leptin; lymphedema; oxidative DNA; pain; perceived appearance; quality of life; relationship functioning; side effects; sleep disturbance; sexuality; social functioning; upper and lower body strength; vigor	
Schmitz et al. [17]	Experimental studies (RCT, pretest-posttest with no control group, pretest-posttests with matched controls)	12	Breast; colon; lung; ovarian; lymphoma; testicular; sarcoma; other	Affect; anger; anxiety; arm volume; avoidance; body dissatisfaction; body image; body size; cardiovascular fitness; confusion cognitive functioning; communication; depression; fatalistic; fatigue; family well-being; flexibility; fighting spirit; happiness; hopelessness; hostility; leukocytes; lymphocytes; mononuclear cells; natural killer cells; neutrophils; pain; physical fitness; problems with activities at home and in community; quality of life; satisfaction with life; self-esteem; sick leave; social well-being; spiritual well-being; strength; T-cells; tiredness; vigor; vitality; white blood cells, work status	

TABLE 39.1 (continued)
Summary of Published Reviews and Meta-Analyses Investigating Health-Related Outcomes of Physical Activity for Cancer Survivors

Reference	Types of Studies Reviewed	Number of Published Studies Reviewed[a,b]	Samples	Health-Related Outcomes Measured	Physical Activity Details
Schmitz et al. [5]	Observational and experimental studies (RCT, CCT, UCT)	64	Breast; prostate; colon; hematologic; gynecologic	Aerobic fitness; anxiety; balance; blood lipids; body composition; body mass index; body size; body weight; bone health; cancer recurrence; cancer-related mortality; depression; energy; fatigue; flexibility; hemoglobin; immune functioning; incontinence; inflammation; insulin-like growth factor; lymphedema; muscle mass; muscular strength; overall mortality; oxidative stress; pain; peripheral neuropathy; physical function; quality of life; sexual functioning; sleep; vigor; vitality	
Speck et al. [16]	Experimental studies (RCT, CCT)	49	Breast; colon; lung; ovarian; leukemia; lymphoma; prostate; sarcoma; stomach; testicular; other	Aerobic fitness; anger; anxiety; arm volume; body image; body mass index; body size; body weight; cholesterol; confusion; fat mass; fatigue; flexibility; glucose; immune functioning; insulin; insulin-like growth factor; lean mass; mood; pain; physical condition; physical functioning; quality of life; satisfaction with life; self-esteem; sexual attractiveness; symptoms/side effects; upper and lower body strength; vigor; vitality; waist circumference; weight concerns	
Winter-Stones et al. [28]	Experimental studies (CCT, UCT)	3	Breast	Bone mineral density; bone remodeling	

RCT, randomized controlled trials; CCT, controlled clinical trials; UCT, uncontrolled clinical trials.
[a] Only studies reviewed including survivors post-treatment were considered in this summary.
[b] Studies reviewed including multicomponent interventions are excluded from this table.

PA and cancer survivorship [5,16–20,22–28]. Given the outcomes identified from the reviews presented in Table 39.1, and the overview of benefits in Table 39.2, PA is associated with numerous physical, biological, and psychosocial health outcomes among cancer survivors. This evidence supports the potential value of interventions and public health programs aimed at increasing PA.

BENEFITS OF PHYSICAL ACTIVITY FOR CANCER SURVIVORS

Physical Activity and Bio-Physiological Health

The evidence presented in Table 39.1 (i.e., outcomes examined in the studies reviewed in the meta-analyses and review articles) and benefits summarized in Table 39.2 show the breadth of biophysiological benefits associated with PA among cancer survivors. Many of these benefits are important for improved health and may help in the prevention of secondary cancers and comorbidities such as cardiovascular disease, hypertension, diabetes, and osteoporosis. The biophysiological benefits span immune function adaptations and protective effects for chronic inflammation, improvements in markers of cardiovascular disease and risk, and prevention of bone loss and improved bone mineral density. Also, reduced cancer-related fatigue may be a positive outcome of a physically active lifestyle [29]. Brown et al. [22] reported that PA may be effective in reducing fatigue during survivorship for individuals diagnosed with various cancer types, cancer stages, and treatments endured. Similarly, Speck et al. [16] suggest there is a moderate relationship between PA and fatigue across various cancer types posttreatment. Additional benefits of PA may include

TABLE 39.2
Summary of Physical Activity Benefits for Cancer Survivors

Improvements	Reductions
• Survival rates	• Rates of all-cause mortality
• Natural killer cell cytotoxic activity	• Rates of cancer-related mortality
• Physical, functional, and mental health	• Cancer recurrence
• Cardio-respiratory fitness	• C-reactive protein
• Muscle strength/mass	• [3H] thymidine uptake by peripheral blood lymphocytes
• Flexibility	• Cancer-related fatigue
• Immune function	• Body weight
• Body composition	• Fat mass
• Sexual functioning	• Bone loss
• Sleep quality	• Incontinence
• Balance	• Pain
• Healthy hemoglobin levels	• Systolic blood pressure
• Diastolic blood pressure	• Resting heart rate
• Quality of life	• Depression
• Mood and happiness	• Anxiety
• Body image	• Stress
• Self-esteem	• Tension
• Perceptions of sexual attractiveness	• Cognitive disorganization
• Posttraumatic growth	• Emotional irritability
• Personality functioning	• Confusion
• Locus of control	
• Perceptions of social support	
• Feelings of connectedness	

improved sexual functioning, reduced incontinence, improved sleep, reduced pain, improved balance, and healthy hemoglobin levels, blood pressure, and resting heart rate [5,16,30]. Related to these latter benefits, PA has been clearly linked to improved cardiorespiratory fitness, muscular strength, and flexibility [5,16,17,31,32].

The evidence presented in a variety of cohort studies also suggests that PA may protect cancer survivors from premature death and/or death due to their cancer [10–12,33,34]. Furthermore, it appears that PA postdiagnosis plays a more important role in reducing risk of mortality than lifetime PA prediagnosis [11]. That is, PA started after a survivor is diagnosed may exert a greater influence on mortality than PA engaged in prior to being diagnosed, even if the survivor was previously inactive.

Physical Activity and Psychosocial Health

Table 39.1 provides a detailed description of systematic reviews and meta-analyses exploring the associations between PA and psychosocial health among cancer survivors. To summarize, several reviews provide strong support for the role of PA in facilitating psychosocial health among cancer survivors [16–18,23,35]. For controlled studies conducted posttreatment, significant weighted effect sizes were observed for overall quality of life, physical condition, mood disturbance, confusion, body image, and fatigue [16]. Given the expanding evidence-base, systematic reviews and meta-analyses are beginning to target specific psychosocial outcomes. For example, the first systematic review and meta-analysis exploring the effects of PA specifically on depression symptoms among cancer survivors has recently been published [23]. Overall, 15 RCTs comparing PA with usual care and assessing depressive symptoms both pre- and post-intervention were reviewed. PA was significantly associated with reduced depression symptoms. In light of these reviews, clinically relevant and exciting evidence continue to emerge that supports the role of PA as a safe and effective intervention to facilitate favorable physical and psychosocial health outcomes among various cancer survivor groups. Furthermore, while most of the evidence to date has focused on the more adverse or negative psychosocial effects of cancer and the association with PA, it is expected that studies and reviews on the promotion of positive effects (e.g., posttraumatic growth [36]) through PA will be introduced in the literature shortly.

Finally, cancer survivors continue to have needs for social support beyond the active treatment phase, and these support needs change as survivors move along the cancer continuum [37]. The association between PA and social support is an overlooked area of research among cancer survivors. Thus far, the studies exploring the role of PA in fostering social support among cancer survivors have mostly been focused on dragon boating for breast cancer survivors [36,38]. The evidence suggests that group-based PA is beneficial in helping these women gain support by providing them with a forum to discuss cancer (and noncancer) related concerns. More work is needed to ascertain the role of PA in improving social benefits during cancer survivorship.

PHYSICAL ACTIVITY GUIDELINES FOR CANCER SURVIVORS

The biological, physiological, psychological, social, and recurrence and survival benefits of PA for cancer survivors are summarized in Table 39.2, and are discussed in detail by Sabiston and Brunet [39]. De Backer and Colleagues [40] also provide a review of the specific benefits associated with resistance training. With the variety of health benefits observed following PA programs or participation, one must ask the questions "Do all cancer survivors who lead physically active lifestyles experience these benefits?" As part of an effort to improve cancer survivors' health and well-being, guidelines have been formulated for cancer survivors based on existing evidence drawn mostly from studies with survivors of breast, prostate, colorectal, hematologic, and gynecologic cancers. Regularly cited guidelines in the literature include those from the American Cancer Society [41,42] and the American College of Sports Medicine [5]. The most recent American Cancer Society guidelines suggest that cancer survivors should engage in at least 30 min of moderate-to-vigorous PA, above usual activities (i.e., those that are done regularly as part of one's daily routine), on 5 or more days of the week, although 45–60 min of PA is preferable. The type of PA being recommended is not specified.

There are three main modes of PA. These include aerobic activity, strength training, and flexibility training [41,43]. Aerobic (or endurance) activity refers to any activity that uses large muscle groups, can be maintained continuously for a long period of time, and is rhythmic in nature. Examples include walking, jogging, running, cycling, dancing, skating, swimming, aerobics classes, and household chores (e.g., vacuuming, sweeping, mopping, raking). Resistance (or strength) training refers to any activity that uses resistance methods (e.g., free weights, an individual's own weight, machines, elastic bands) to increase one's ability to exert or resist force. These activities involve concentric (i.e., lifting and pushing/pulling) and eccentric (i.e., controlled lowering/returning) muscle contractions and are done for each major muscle group (i.e., quadriceps, hamstrings, hip adducters/abductors, upper/lower back, abdomen, chest, shoulders, biceps/triceps, and neck). Flexibility training refers to activities that lengthen muscles to increase range of motion around the joints. These activities can be static (i.e., stretch is held for a period of time), dynamic (i.e., fluid motion such as tai chi), or active (i.e., hold stretch while balancing such as yoga) [41,43].

More recently, the importance of delineating the different types of PA has been recognized. Consequently, guidelines have been modified to specify that all three types of PA should be undertaken [5,43]. The American College of Sports Medicine convened an expert committee consisting of clinical and research experts in the field to review existing evidence on the safety and efficacy of PA during and after adjuvant cancer therapy [5]. This panel of experts developed PA guidelines for cancer survivors to include engaging in aerobic activity, musculoskeletal or strength training, and flexibility training [5]. These guidelines recommend that cancer survivors engage in: (a) aerobic activities at a *moderate* intensity (i.e., heart rate and sweating increases, can still maintain a conversation) for a total of 150 min/week, (b) *vigorous/strenuous* intensity activity (i.e., fast and hard breathing, heart rate increases considerably, cannot maintain a lengthy conversation) for 75 min/week, or (c) some combination of moderate and vigorous activities. Recommendations for strength training suggest cancer survivors should perform activities that work the major muscle groups of the lower and upper body two or three times per week. Finally, guidelines suggest stretching major muscle groups when aerobic and strength training activities are performed. There are insufficient data available to conclude what the optimal intensity and volume for each type of activity is for cancer survivors. The guidelines indicate that these are the minimum amounts of PA cancer survivors should strive to meet and that additional benefits will likely result if frequency and duration is increased.

PHYSICAL ACTIVITY PREVALENCE ACROSS TUMOR GROUPS

The overwhelming majority of cancer survivors do not achieve the dose of PA suggested in the guidelines [44–47]. These data suggest that from the time an individual is diagnosed with cancer, PA substantially decreases. The most substantial change occurs from prediagnosis to the treatment phase in the cancer continuum. While PA rates improve after treatment is completed, PA rates after treatment remain significantly lower than prediagnosis rates [48–51]. Total PA, moderate and vigorous PA, and sports or recreational PA substantially decrease from prediagnosis, to during treatment, and through to postdiagnosis phases.

Evidence comparing rates of PA between cancer survivors and individuals who have never received a cancer diagnosis is equivocal [52–54]. Some studies have documented that cancer survivors are less active than noncancer controls [44,55], whereas other have found no differences [45,56–58]. Regardless, large population-based studies have documented the low PA behavior rates among cancer survivors such as in the American Cancer Society's Study of Cancer Survivors-II (ACS SCS-II) [44]. The ACS SCS-II is a United States national cross-sectional survey that includes over 9000 survivors from six different cancers. Data from this survey show that the minority of breast (37.1%), prostate (43.2%), colorectal (35.0%), bladder (36%), and uterine (29.6%) cancer survivors were meeting the American Cancer Society's recommendations for PA (i.e., accumulate at least 150 min of moderate to strenuous PA or 60 min of strenuous PA per week). Studies with large Canadian and Australian samples of cancer survivors have yielded similar results. For example, the Canadian Community Health Survey data from cancer survivors demonstrated the minority of prostate (23.9%), breast (16.6%), and colorectal (17.1%) cancer survivors were achieving PA levels that were consistent with public health recommendations [46]. From the Australian National Health Survey, only 28% of the 968 cancer survivors were meeting Australian PA guidelines (i.e., accruing 150 or more minutes of PA over at least five sessions per week) [56]. Taken together, there may be small differences in the rates of PA across cancer sites but more research is needed to understand the mechanisms associated with these differences. For example, Blanchard et al. [44] demonstrated that survivors of uterine cancer were least likely and survivors of skin melanoma and prostate cancer were most likely to meet the PA guidelines. Bellizi et al. [59] reported that survivors of prostate cancer were most likely to meet PA guidelines whereas survivors of lung, larynx, and pharynx cancer were among the least likely to meet PA guidelines. Given these PA rates, increasing PA levels among all cancer survivors should remain a high research and public health priority worldwide.

Until now, most research pertaining to the PA behavior levels of cancer survivors has utilized self-report measures. Recently, two studies have implemented PA data using accelerometers [60,61]. Accelerometers are small devices providing objective, gold standard PA information and provide the researcher with individuals' activity counts, vector magnitude, energy expenditure, steps taken, and activity intensity level. The data examined in these studies are drawn from two waves of the National Health and Nutrition Examination Survey (2003–2004 and 2005–2006), where

accelerometer data were available for a heterogeneous sample of self-reported cancer survivors. Among 111 breast cancer survivors from the NHANES database, Lynch et al. [60] reported that survivors were engaging in an average of only 3.7 min of moderate-to-vigorous intensity PA (MVPA) per day. Similarly, among 103 prostate cancer survivors, the average time per day spent engaging in MVPA was 6.0 min [61]. These NHANES studies indicate PA behavior rates of cancer survivors derived from self-reported measures may be substantially inflated.

Regardless of how the PA estimate is obtained, the prevalence of PA among cancer survivors is very low, and it is important to better understand the reasons for these low rates of participation. One way to understand the prevalence of PA is to examine the cancer-related barriers that may impede participation among survivors.

POTENTIAL CANCER-SPECIFIC BARRIERS TO PA

Survivors likely report the common PA barriers identified by researchers studying individuals of all ages (e.g., lack of time, motivation, money, knowledge or information, competence and skill, and/or social support, among many others [64,65]). However, there are unique cancer-specific barriers to PA an individual may experience as they go through diagnostic steps and treatments compared to when he or she has finished treatments and are returning to work or various life roles. This is another reason why it is beneficial to distinguish survivorship phases (see Figure 39.1) as this may help inform targeted efforts aimed at understanding and reducing the PA barriers. Table 39.3 identifies main cancer-specific barriers to PA across the cancer continuum.

TABLE 39.3
Potential Cancer-Related Barriers to Physical Activity across the Cancer Continuum

Cancer Continuum Phase	Potential Barriers to Physical Activity
Acute survivorship	
Diagnosis	Other life priorities, time management, negative affect and emotions, anxiety, fear of exacerbating condition
Treatment (early effects)	Seroma, ascites, peripheral edema, short-term pain after treatment, dry and sore skin, mouth and throat sores, swelling, and lymphedema, fatigue, hair loss, nausea and vomiting, immunosuppression and fear of compromising immunity to postpone treatment, myelosuppression, body image disturbance, depression
Extended survivorship	
Treatment (late effects)	Fibrosis, cardiovascular and pulmonary toxicities, hypertension, atherosclerosis, lymphedema, hematologic abnormalities, avascular necrosis, thrombocytopenia, neuropathy, dyspnea, fatigue, joint pain, body image disturbance, depression
Permanent survivorship	Recurrence of another type of cancer, second cancers, cardiac dysfunction, weight gain or loss, bone loss, lymphedema, arthralgias, cognitive dysfunction, menopausal symptoms, reduced health-related quality of life, fatigue, joint pain, body image disturbance, lack of social support, lack of PA knowledge, and psychosocial distress
End-of-life	Weight loss (e.g., cachexia), motivation, pain, fatigue, cognitive deficits, decreased balance, impaired fine and gross motor skills, shortness of breath, lowered aerobic capacity, deconditioning, muscle atrophy

EVIDENCE-BASED BEHAVIOR CHANGE STRATEGIES

Identifying and understanding the cancer-specific barriers that may impede PA participation is one step in helping to optimize PA opportunities among cancer survivors. Additionally, evidence-based initiatives focused on PA among cancer survivors can be used to help advance research and clinical practice. Approximately 12 million cancer survivors may possibly benefit from evidence-based, well-designed PA programs [5]. Moreover, many cancer survivors are interested and opportunistic in pursuing PA programs and receiving PA counseling [52]. Few interventions, however, have been developed and evaluated to facilitate PA initiation and maintenance among cancer survivors. Physician counseling on PA may be one targeted strategy to increase PA among cancer survivors [66,67]. Yet, the limited guidelines put forward to assist practitioners and PA programmers in providing PA recommendations to cancer survivors have resulted in PA counseling being done on a sporadic and infrequent basis [43,68]. The Oncologist Recommendation to Exercise (ONCORE) Trial was one trial that examined the effects of two oncologist-centered interventions on self-reported PA behavior in breast cancer survivors beginning treatment using an RCT design [67]. During their initial treatment consultation, participants were randomized to receive either (a) an oncologist's recommendation for PA, (b) an oncologist's recommendation for PA plus a referral to a Kinesiologist, or (c) usual care (i.e., no recommendation). Results of this study indicated that participants receiving one of the exercise recommendations reported total PA amounts that were significantly higher than those receiving usual care (i.e., approximately 30 min/week).

However, given the amount of information that is given during an initial treatment consultation, and not to mention the distress an individual might experience during their treatment consultation, it is unclear whether the treatment consultation represents the opportune time to recommend PA. As the authors indicated, participants may have only been concerned with critical information regarding prognosis and treatment. This contention is supported in that only 59% of individuals correctly recalled the group they were randomly

assigned to. Nonetheless, this trial suggests that advocating a physically active lifestyle via an oncologist's recommendation may be an easy and efficient form of promoting PA among breast cancer survivors.

Researchers are also starting to engage in PA promotion efforts by exploring targeted tools and resources that can facilitate PA adoption and maintenance in this population. To provide an example, Vallance et al. [69] evaluated the role of PA print resources and step pedometers in facilitating PA behavior among breast cancer survivors. *Exercise for Health: An Exercise Guide for Breast Cancer Survivors* was a 62-page PA resource designed for breast cancer survivors. Developed within the Theory of Planned Behavior framework [21], the development of this resource along with evidence supporting the suitability, appropriate readability, and theoretical merit of the resource has been documented [69]. Messages within this resource were based on theoretical beliefs (e.g., attitudes, norms) and PA programming preferences previously elicited from breast cancer survivors [70,71]. The *Exercise for Health* resource consisted of 10 chapters and included activities that were designed to facilitate positive attitudes (i.e., instrumental and affective attitudes), subjective norms (i.e., injunctive and descriptive norms), perceived behavioral control (i.e., self-efficacy and controllability), and implementation intentions (e.g., goal-setting, planning) related to PA.

The *Act*ivity Promot*ion* (ACTION) trial was a four-group RCT designed to determine the effects of the *Exercise for Health* resource, a step pedometer, or their combination, on PA behavior, health-related quality-of-life (HRQoL), and fatigue in breast cancer survivors compared to survivors receiving a verbal recommendation for PA that was consistent with current PA guidelines [72]. At the 3-month postintervention assessment, the *Exercise for Health* resource and the step pedometers were effective strategies for increasing PA behavior (both independently and in combination), HRQoL, and reducing fatigue symptoms in breast cancer survivors. Overall, PA increased by about 40–60 min/week (equivalent to one or two extra PA sessions) in the three intervention groups compared to the verbal PA recommendation group. A significant change was also observed for brisk walking across all intervention groups when compared to the recommendation group. Brisk walking was increased by 60–90 min/week, which is equivalent to 2–3 more days of PA per week. Finally, the intervention group receiving both the print resource and pedometer also reported significantly improved HRQoL and reduced fatigue symptoms compared to the verbal PA recommendation group.

The usefulness and effectiveness of telephone counseling for facilitating PA behavior change among cancer survivors has also been examined. In one of the largest experimental studies, Morey et al. [73] randomized 641 older, overweight, long-term cancer survivors to receive either telephone counseling or mailed print materials based on PA and diet or to a wait-list control group. Results from this study suggested that receiving telephone counseling and mailed print resources facilitated overall HRQoL including physical and mental health, pain, vitality, and social functioning when compared to survivors in the control group. Survivors in the intervention group also reported significant increases in the duration and frequency of strength and endurance training. Significant reductions in body weight and body mass index were also reported in the intervention group. In Australia, Eakin et al. [74] conducted an RCT with newly diagnosed breast cancer survivors (receiving treatment at baseline) evaluating an 8-month PA intervention delivered by exercise physiologists over the telephone. In this trial, survivors receiving telephone counseling were two times more likely to be engaging in at least 180 min/week of PA 6 months after surgery and two times more likely 12 months after surgery compared to baseline. Also, survivors were over eight times more likely to be engaging in resistance training 6 months after surgery and over three times more likely 12 months after surgery. Continued development and evaluation of modes in which to communicate and potentially facilitate PA behavior among cancer survivors is critical. Such programs and opportunities may facilitate longer survival and better quality of life for millions of cancer survivors.

LIMITATIONS AND FUTURE DIRECTIONS

The evidence linking PA to health outcomes in cancer survivors is mounting, and there are important considerations for advancing this line of inquiry. Based on the reviews and meta-analyses outlined in this chapter, one of the common criticisms is that much of the information available derives from studies that have been conducted with breast cancer survivors. Survivors of certain cancer types are underrepresented (e.g., lung, testicular, head/neck, colorectal, gynecologic, hematological), which reduces opportunities for determining the effects of PA in these sub-populations. Homogeneous samples of survivors drawn from underrepresented cancer types are needed to better understand cancer-specific responses to PA. Similarly, homogeneous samples within specific phases of the cancer continuum should be used to understand unique needs and effects of PA to better target intervention and clinical practice guidelines. Currently, some investigations have included solely cancer survivors as defined in this chapter (i.e., individuals who completed primary treatment) and other studies and reviews have included both patients and survivors.

There is also a lack of comparability in the methods used to assess PA and the health-related outcomes between studies that prevent researchers from being able to make comparisons across studies. Furthermore, there are few studies aimed at understanding the mechanisms that link PA to health-related outcomes. Identifying the pathways through which PA influences cancer survivors' health represents one area of future research needed to better understand how PA can promote health. In addition to understanding mechanisms, there are also limited studies looking at the long-term effects of PA. The majority of studies reviewed in this chapter implemented short-term interventions (i.e., <6 months) and few included

long-term follow-up measures, which makes it difficult to ascertain the long-term or delayed effects of PA.

Further, the mode of delivery differs greatly across studies. Some investigations have used unsupervised/home-based or supervised/facility-based protocols for the delivery of interventions, with some studies utilizing both approaches. Despite the fact that unsupervised/home-based interventions may be more sustainable long-term, monitoring whether participants follow the prescribed intensity and volume of PA is more difficult when the intervention is unsupervised, unless monitoring devices are used to assess adherence. Also, there are inconsistent PA parameters included in the tested interventions across the different studies. For instance, different types (i.e., aerobic, resistance, flexibility), intensities (i.e., lifestyle, light, moderate, vigorous), frequencies (i.e., times per week), and durations (i.e., session length) of PA have been prescribed; however, the types, intensities, and volume of PA that are most beneficial for cancer survivors are unknown since most studies have examined the links between PA and health-related outcomes rather than the dose–response effects of PA on short- and long-term outcomes. Finally, given new objective PA data suggesting the PA prevalence among cancer survivors is much lower than previously thought [60,61], researchers should rely on more objective assessments of PA (e.g., accelerometers, step pedometers). Such efforts will provide a more accurate and precise estimate of how much PA cancer survivors are engaging in.

PRACTICAL STRATEGIES FOR PRACTITIONERS

All practitioners working with cancer survivors are encouraged to refer to the *American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors* [5]. Overall, this panel concluded that there appears to be consistent evidence that PA is safe during and after cancer treatment. The panel recommended that cancer survivors should engage in an overall volume of weekly PA equivalent to 150 min of at least moderate intensity PA. If the survivor is engaging in vigorous intensity PA, the recommendation can be achieved by accruing 75 min per weak. The 150 min should include 2–3 days of strength training as well as stretching activities.

It is difficult to provide guidelines that are individually tailored since there is considerable variation in cancer survivors' pathophysiology and treatment(s) received. Many cancer survivors experience adverse effects months and/or years after treatment(s) are completed (e.g., cardiovascular and pulmonary toxicities, hypertension, atherosclerosis, lymphedema, hematologic abnormalities, neuropathy) that can decrease their capacity to engage in certain types of PA. These negative side effects can result in fatigue, pain, decreased balance, impaired motor skills, shortness of breath, lowered aerobic capacity, deconditioning, muscle atrophy, and general performance limitations. For example, cancer survivors experiencing shortness of breath may find it difficult to engage in certain aerobic activities, whereas survivors experiencing pain may find it difficult to engage in weight bearing activities. In addition, since cancer is an advancing age disease there are likely other aging health concerns (e.g., chronic obstructive pulmonary disease, osteoporosis) that may occur alongside cancer-related comorbidities and interfere with PA.

Accordingly, the presence of these medical comorbidities and/or negative side effects of treatment may be significantly debilitating and affect cancer survivors' ability to tolerate and/or engage in PA. This highlights the need for practitioners to be attentive of these issues and help survivors chose activities that are appropriate, safe, and feasible (e.g., seated activities for survivors reporting loss of balance). Thus, although the guidelines discussed above are useful, PA prescriptions should be tailored for survivors based on their PA levels prediagnosis and current health status. Programs for survivors who have always been inactive and experience negative treatment side effects will differ from programs for survivors who have always been active and are without encumbering side effects. Nevertheless, all cancer survivors should be encouraged to resume activity gradually and should see the PA guidelines presented above as a long-term goal.

The first step in facilitating PA behavior change is to communicate to and educate cancer survivors about benefits of regular and sustained PA and provide them with clear guidelines. To support PA behavior change among patients, practitioners may also want to encourage survivors to engage in intermittent bouts of activity throughout the day until they are able to complete a continuous longer bout of activity [43]. Participating in shorter bouts of PA (i.e., at least 10 min in duration) has been shown to facilitate adherence to PA [75]. For survivors that are unfamiliar with how to initiate and maintain a PA program, practitioners could promote *lifestyle-based* physical activities. These activities are planned or unplanned activities that are part of everyday life such as leisure, occupational, household, and/or care-giving/childcare activities. Practitioners could encourage their patients to at least perform these lifestyle-based activities at a moderate intensity. During moderate intensity PA, there should be an increase in heart rate, light sweating, and the individual may need to catch their breath if they are talking during the activity. If the individual is going for a walk, walking as if one was late for an appointment is one example of moderate intensity PA. The lifestyle approach may be particularly beneficial for survivors who are reluctant to begin a traditional PA program because they fear that intense activity may exacerbate their cancer-related symptoms (e.g., fatigue, pain, nausea).

Additionally, practitioners must recognize the unique disease and treatment-related PA barriers that survivors may face (see Table 39.3) in addition to the "traditional" barriers that healthy adults report (e.g., lack of time, lack of motivation, financial burden) [43]. One common suggestion practitioners can provide is for their patients to engage in PA when fatigue levels are lowest (e.g., morning), for shorter durations, lower intensities, and perform interval training (i.e., alternate activity and rest bouts). While the majority of cancer survivors are able to safely participate in regular PA, practitioners should still consider individual factors (e.g., body size, functional limitations, treatment received) and provide PA recommendations that are suitable, appropriate, and allow the survivor the

highest likelihood to experience success. Practitioners should involve and engage their patients in the discussion regarding PA and ways PA guidelines can be achieved. There is good evidence that providing individuals choices for PA is indeed associated with greater participation [76]. This is an important consideration when discussing PA among cancer survivors.

For practitioners who are unfamiliar or uncomfortable with discussing PA with their patients, there are several avenues where patients can seek assistance. The practitioners may refer the patient to a local Certified Exercise Specialist or fitness trainer. There are a number of exercise specialists also now achieving the ACSM Cancer Exercise Trainer certification [5], and there are published tips for proper training for some cancer survivor groups, such as breast cancer [77]. Practitioners can also refer their patients to a local Young Men's Christian Association (YMCA) or other local wellness centers offering appropriate PA programs delivered by qualified instructors. Several cancer centers and hospitals now offer PA and/or rehabilitation programs for cancer survivors. As the evidence-base continues to grow and support the role of PA across the cancer survivor context, practitioners should be prepared to discuss PA and refer their patients to available PA opportunities and pursuits.

CONCLUDING REMARKS

There is now unquestionable merit in encouraging and fostering PA throughout the cancer continuum. Overall, the data suggest there are many biopsychosocial benefits associated with regular and sustained PA participation, and these benefits are observed among cancer survivors as defined in this chapter. Unfortunately, most cancer survivors fail to meet established PA guidelines, and their long-term health and well-being may be at risk. It is important that survivors realize that PA is beneficial. With the assistance and guidance from physicians, health professionals, and qualified PA personnel, more cancer survivors may realize the benefits associated with PA.

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40 Nutrition and Cancer

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CONTENTS

Epidemiology 505
Fruits, Vegetables, and Cancer 505
Antioxidants and Cancer 506
Calcium and Cancer 506
Soy, Garlic, Tea, and Cancer 507
Nutrition and Breast Cancer 508
Nutrition and Colorectal Cancer 508
Nutrition and Prostate Cancer 509
Nutrition and Endometrial Cancer 509
Nutrition and Ovarian Cancer 509
Nutrition and Pancreatic Cancer 509
Nutrition and Gastric Cancer 509
Summary 509
References 511

Among the several lifestyle activities affecting cancer risk that humans have within their control, such as the use of tobacco products, overexposure to cosmic irradiation, physical activity and diet, one would think that the most easily controlled is the one that relates to what one eats and how much one eats. The National Cancer Institute estimates that at least 35% of all cancers have a nutritional connection.

As reflected in Chapter 38, the subject of the relationship between being overweight or obese and one's risk of developing cancer is addressed. Strong evidence exists that obesity is a causal factor for certain cancers, including breast cancer, colon cancer, uterine cancer, and others. In that chapter, there is a brief reference to diet and how the intake of dietary components are or may be related to the reason those cancers may evolve. This chapter will inform the reader of more detail about how nutrition has a bearing on these and other cancers and which dietary nutrients may have a significant role in that process.

EPIDEMIOLOGY

Epidemiologic evidence that nutrition plays a role as an etiologic factor for several cancers is compelling. There is considerable evidence that nutrition significantly affects the development of certain cancers, including cancers of the colon, pancreas, kidney, breast, ovary, endometrium, and prostate [1].

Both epidemiologic studies and laboratory experiments have provided evidences that dietary factors have a role in carcinogenesis. In 1982, the Committee on Diet, Nutrition, and Cancer of the National Research Council conducted a comprehensive evaluation of this evidence. That assessment suggested that a high fat diet is associated with increased susceptibility to cancer of different sites, particularly the breast and colon, and to a lesser extent, the prostate, and that dietary fiber may have a protective effect against colon cancer.

In epidemiologic studies, consumption of certain fruits and vegetables, especially citrus fruits and carotene-rich and cruciferous vegetables, is associated with a lower incidence of some cancers. It is not clear which specific components of these foods are responsible for these effects, although the epidemiologic evidence appears to be most consistent for an effect of beta-carotene on lung cancer and less so for vitamins A and C and various cancer sites [2].

With respect to geography, studies on migrant populations have supported the concept that diet and nutrition as risk factors for human cancers relate to dietary habits. Reduction in gastric cancer and an increase in colon cancer incidences have been observed in immigrants moving from Japan to the United States via Hawaii with concurrent change in dietary habits. In this population, high fat consumption has been linked to increased incidence of breast and colon cancer, and increased intake of dietary fiber (or some specific component of it) may be associated with diminished risk of colorectal cancer [3].

FRUITS, VEGETABLES, AND CANCER

Epidemiologic evidence of a protective role for fruits and vegetables in cancer prevention is substantial. Current U.S. fruit and vegetable intake averages about 3½ servings per day.

The strength of the scientific evidence guides U.S. policy-making in diet and health issues and facilitates community and local programs that address national dietary goals to increase fruit and vegetable consumption.

The types of vegetables or fruit that appear to be protective against cancer are raw vegetables, followed by allium vegetables, carrots, green vegetables, cruciferous vegetables, and tomatoes. Substances present in fruits and vegetables that may help protect against cancer include the group of phytochemicals such as dithiolethiones, isothiocyanates, indole-3-carbinol, allium compounds, isoflavones, protease inhibitors, saponins, phytosterols, inositol hexaphosphate, lutein, beta-carotene, lycopene, flavonoids, D-limonene, and other nutrients that have been known for some time such as vitamin C, folic acid, selenium, vitamin E, and dietary fiber [4].

While most studies have shown a protective effect of high consumption of fruits and vegetables, one large study of more than 142,000 men and 335,000 women, conducted by the European Prospective Investigation into Cancer and Nutrition (EPIC), during 1992–2000, revealed only a very small inverse association between intake of total fruits and vegetables and cancer risk, and the reduced risk was restricted to women [5].

ANTIOXIDANTS AND CANCER

Antioxidants are substances that may protect cells from the damage caused by unstable molecules known as free radicals. Due to their highly chemical reactivity, free radical damage may lead to cancer. Antioxidants interact with and stabilize free radicals and may prevent some of the damage free radicals might otherwise cause. Examples of antioxidants include beta-carotene; lycopene; resveratrol; vitamins C, E, and A; and selenium. Considerable laboratory evidence from chemical, cell culture, and animal studies indicates that antioxidants may slow or possibly prevent the development of cancer.

In the 1990s, several large randomized trials examining the effect of antioxidants on cancer were reported, with inconsistent conclusions. One large study examining the effect of beta-carotene, vitamin E, and selenium on cancer in Chinese men and women at high risk for gastric cancer showed a significantly reduced incidence of both gastric and cancer and cancer overall [6].

Examining the effects of beta-carotene and vitamin E on the incidence of lung cancer, the Alpha-Tocopherol (vitamin E)/Beta-Carotene Cancer (ATBC) Prevention Study, reported in 1994,demonstrated that lung cancer rates of Finnish male smokers increased significantly with beta-carotene supplements and were not affected by vitamin E [7]. Another 1994 study, the Beta-Carotene and Retinol (vitamin A) Efficacy Trial (CARET), also demonstrated a possible increase in lung cancer associated with antioxidants supplements [8]. The 1996 Physicians' Health Study I (PHS) found no change in cancer rates associated with beta-carotene and aspirin taken by U.S. male physicians [9]. Taken together, these results suggest there is no convincing evidence of a benefit of antioxidants for overall cancer risk.

CALCIUM AND CANCER

Some studies have suggested that high calcium intake may decrease the risk of one or more types of cancer, whereas other studies suggest that a high calcium intake may actually increase the risk of prostate cancer.

In one study, a randomized trial that included nearly 1200 healthy, postmenopausal Nebraska women, participants in the study were randomized to receive daily calcium supplementation alone (300–600 mg elemental calcium), calcium supplementation (300–600 mg elemental calcium) combined with vitamin D supplementation (1000 IU), or a placebo for 4 years [10]. The incidence of all cancers combined was approximately 60% lower for women who took the calcium plus vitamin D supplements compared with women who took the placebo. A lower risk of all cancers combined was also observed for women who took calcium supplements alone, but this finding was not statistically significant.

Several studies have suggested that a high intake of calcium may increase the risk of prostate cancer. In 2008, The European Prospective Investigation into Cancer and Nutrition reported an increased prostate cancer risk among more than 142,000 men consuming a high intake of protein or calcium from dairy products. Calcium from nondairy sources, however, was not associated with increased risk [11]. Another study, a prospective analysis of dairy product and calcium intakes among more than 29,000 men participating in the National Cancer Institute's (NCI) Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial showed increased risks for prostate cancer associated with high dietary intakes of calcium and dairy products, but not from calcium supplements [12]. In contrast, results from the NIH-AARP Diet and Health Study showed no increased risk of prostate cancer associated with total calcium, dietary calcium, or supplemental calcium intakes [13].

Ovarian cancer may be less frequent in women consuming calcium from dairy products [14]. The Nurses' Health Study found that higher intakes of calcium reduced the risk of breast cancer among premenopausal, but not postmenopausal women [15,16]. This was seen only with calcium-containing dairy products as nondairy sources were not associated with the reduction in risk [15].

There is also evidence that high calcium intake may confer protection from developing colorectal cancer, and while the exact mechanism by which calcium may reduce the risk of colorectal cancer is unclear, it is known that calcium binds to bile acids and fatty acids in the gastrointestinal tract to form insoluble complexes known as calcium soaps. It is speculated that this process may reduce the ability of the acids (or their metabolites) to damage cells in the lining of the colon. Calcium also may improve signaling within cells and cause cancer cells to differentiate and/or die [17].

SOY, GARLIC, TEA, AND CANCER

"Soy" comes from the soybean, a legume native to Northern China. It is often called a complete protein because it is the most complete protein source from vegetables comparable in that regard to animal protein derived from meat products. Soy protein contains many essential nutrients, and human populations that regularly include soy in their diets and decrease meat protein intake are generally healthier. In a meta-analysis of 8 studies among Asian women and 11 studies among low soy consuming Western women, a reduction in risk of breast cancer was observed among Asian women with high (≥20 mg/day) versus low (<5 mg/day) soy consumption. In contrast, no such benefit was observed among Western women whose range of soy consumption was significantly lower (from 0.8 to 0.15 mg/day). A meta-analysis of eight prostate cancer cohort and case control studies examining the effect of dietary soy consumption revealed a reduction in prostate cancer risk with increased soy consumption [18]. In addition to these very common cancers, colorectal cancer and lung cancer also seem to be less frequent in these populations. In a case control study examining lung cancer risk and phytoestrogen intake, a 46% risk reduction was observed among those in the highest quartile of phytoestrogen consumption from food sources [19]. These benefits were observed both in nonsmokers and current smokers. The effectiveness of soy appears to be due to the presence of phytochemicals, chemicals derived from plant products. One such chemical, phytate is an organic acid that is the storage form of phosphorus, a substance that binds iron and calcium in the intestines. Other constituents of soy include saponins that protect DNA from damage, a process known to result in cancer transformation, and protease inhibitors, which are important in their property of inhibiting protein digestion. Finally, isoflavones, natural estrogenic-like chemicals unique to soybeans, have been shown to impede cell proliferation and cancer growth in vitro. However, because these specific compounds are plant estrogens, more research is needed to end the controversy regarding the safety of soy foods for women with breast cancer.

Garlic is a vegetable (*Allium sativum*) that belongs to the allium class of bulb-shaped plants. Other vegetables in this class include onions, chives, leeks, and scallions. Garlic is used for flavoring in cooking and is unique because of its high sulfur content, the source of its characteristic odor and flavor, created when allicin is formed when garlic bulbs are chopped, crushed, or damaged [20]. Garlic also contains arginine, oligosaccharides, flavonoids, and selenium, all of which may be beneficial to health [21].

Several population studies have shown an association between increased intake of garlic and reduced risk of certain cancers, including cancers of the stomach, colon, esophagus, pancreas, and breast. An analysis of data from several studies showed that the higher the amount of raw and cooked garlic consumed, the lower the risk of stomach and colorectal cancer [22].

In another large prospective study investigating whether diet, distribution of body fat, and other risk factors are related to cancer incidence, findings showed a strong association between garlic consumption and colon cancer risk. Women in that study who consumed the highest amounts of garlic had a 50% lower risk of cancer of the distal colon compared with women who had the lowest level of garlic consumption [23].

Other population studies have found that frequent consumption of garlic and various types of onions and chives was associated with reduced risk of esophageal and stomach cancers [24].

Evidence also suggests that increased garlic consumption may reduce pancreatic cancer risk. A study conducted in the San Francisco Bay area found that pancreatic cancer risk was one-half that for people who ate larger amounts of garlic compared with those who ate lower amounts [25].

Tea, among the oldest and most popular beverages in the world, is composed of polyphenols, alkaloids (caffeine, theophylline, and theobromine), amino acids, carbohydrates, proteins, chlorophyll, volatile organic compounds (chemicals that readily produce vapors and contribute to the odor of tea), fluoride, aluminum, minerals, and trace elements [26]. The polyphenols, a large group of plant chemicals that includes the catechins, are thought to be responsible for the health benefits that have traditionally been attributed to tea, especially green tea [27]. The most active and abundant catechin in green tea is epigallocatechin-3-gallate (EGCG).

Among their many biological activities, the predominant polyphenols in green tea, EGCG, and others, and the theaflavins and thearubigins in black teas have antioxidant activity [28]. These chemicals have substantial free radical scavenging activity and may protect cells from DNA damage caused by reactive oxygen species [29]. Tea polyphenols have also been shown to inhibit tumor cell proliferation and induce apoptosis in laboratory and animal studies [30]. In other laboratory and animal studies, tea catechins have been shown to inhibit tumor cell invasiveness [30]. In addition, tea polyphenols may protect against damage caused by ultraviolet (UV) B radiation [31], and they may modulate immune system function [32]. Green teas have been shown to activate certain enzymes such as glutathione S-transferase and quinone reductase that may help protect against tumor development [32]. Although many of the potential beneficial effects of tea have been attributed to the strong antioxidant activity of tea polyphenols, the precise mechanism by which tea might help prevent cancer has not been established [30].

More than 50 epidemiologic studies of the association between tea consumption and cancer risk have been published since 2006. While inconclusive and inconsistent, the results of these studies have linked tea consumption to reduced risks of cancers of the colon, breast, ovary, prostate, and lung [33–37]. The inconsistent results may be due to variables such as differences in tea preparation and consumption, the types of tea studied (green, black, or both), the methods of tea production, the bioavailability of tea compounds, genetic variation in how people respond to tea consumption, the concomitant use of tobacco and

alcohol, and other lifestyle factors that may influence a person's risk of developing cancer, such as physical activity or weight status.

NUTRITION AND BREAST CANCER

Many studies indicate that a diet high in vegetables and fruits may protect against breast cancer and, given the observed variations in incidence rates with this disease among geographically differing populations, it has been strongly considered that diet is a risk factor for breast cancer.

In one large study of premenopausal women 40 years of age or older, identified through pathology records from hospitals in Western New York, it was shown that intake of vegetables appeared to decrease premenopausal breast cancer risk. Fruits were weakly associated with a reduction in risk. In this study, intake of vitamins C and E and folic acid taken as supplements did not influence risk and no single dietary factor explained the favorable effect [38].

Data on intake of specific carotenoids and breast cancer risk are limited. Furthermore, studies of vitamins A, C, and E in relation to breast cancer risk, not limited to premenopausal status, are inconclusive. In a cohort of more than 80,000 women (aged 33–60 years in 1980) who were participating in the Nurses' Health Study, 2697 incident cases of invasive breast cancer (784 premenopausal and 1913 postmenopausal) were identified. In this large analysis, intakes of beta-carotene from food and supplements, lutein/zeaxanthin, and vitamin A from foods were weakly associated with a reduction in breast cancer risk, but only in premenopausal women and in those premenopausal women who consumed five or more servings per day of fruits and vegetables. Moreover, this association was stronger among those who had a positive family history of breast cancer [39].

Most of the foregoing evidence that an intake of vegetables and fruits protects against developing breast cancer comes from case control studies. A more recent analysis in which a prospective study was employed casts some doubt that there truly is a protective effect from consuming these nutrients. This study included 285,526 women between the ages of 25 and 70 years, participating in the European Prospective Investigation Into Cancer and Nutrition (EPIC) study, in which each participant completed a dietary questionnaire in 1992–1998 and subsequently followed for incidence of cancer until 2002. During 1,486,402 person-years (median duration of follow-up, 5.4 years), 3659 invasive incident breast cancer cases were reported. No significant associations between vegetable or fruit intake and breast cancer risk were observed. Although the period of follow-up, at the time of publishing the results was limited, the results suggested that total or specific vegetable and fruit intake is not associated with risk for breast cancer [40].

There is no clear association between the intake of red meat and breast cancer. In the Nurses' Health Study II, red meat intake in premenopausal women between ages 26 and 46 was assessed with subjects being questioned regarding intake in 1991, 1995, and 1999 with follow-up in 2003. During the 12 years of follow-up of 90,659 premenopausal women, greater red meat intake was strongly related to elevated risk of breast cancers that were estrogen and progesterone receptor positive, but not to those that were estrogen and progesterone receptor negative. Thus, higher red meat intake may be a risk factor for premenopausal women who develop estrogen and/or progesterone positive breast cancer [41].

NUTRITION AND COLORECTAL CANCER

While there is clear evidence of genetic predisposition to colon cancer, dietary habits also appear to be a significant risk factor. Some data suggest that vegetables are associated with a lower risk of colon cancer; and, fiber content in the diet does not alone seem to account for this association. In both men and women, red meat consumption appears to be associated with increased risk; however, evidence would suggest that this is not explained solely by its fat content. Mutagenic compounds, particularly heterocyclic amines, produced when meat protein is cooked, may explain the meat association. On the contrary, certain microconstituents of the diet, including folate and calcium may be associated with reduced risk. Rectal cancer is less well studied than colon cancer but, at present, there are few data to suggest that the dietary risk factors are markedly different [42].

With respect to dietary fiber, this nutrient has received considerable attention as a factor that may reduce the risk of colorectal cancer. Potential mechanisms for a protective effect include dilution of fecal carcinogens, reduction of transit time of feces through the bowel, production of short chain fatty acids, which promote anticarcinogenic action, and binding of carcinogenic bile acids [43]. Inconsistent findings from observational studies have continued the controversy over the effects of dietary fiber on these cancers. One large meta-analysis, in which 13 prospective cohort studies were examined, over 700,000 men and women were followed for 6–20 years. In this pooled analysis, dietary fiber intake was inversely associated with risk of colorectal cancer. However, after accounting for other dietary risk factors, high dietary fiber intake as an independent variable did not appear to be solely responsible for the reduced risk of colorectal cancer [43]. In yet another large meta-analysis of 25 reported studies, it did appear that a high intake of dietary fiber, in particular cereal fiber and whole grains, was associated with a reduced risk of colorectal cancer [44].

With respect to fish consumption and colorectal cancer, epidemiologic studies have been inconsistent. Animal studies

have shown favorable effects of n-3 fatty acids (omega-3) on inflammation and cancer, thus the potential that this nutrient, abundant in certain fish, may reduce the risk of colorectal cancer has been studied in a very limited manner. In one large analysis of cohort studies, fish consumption was shown to slightly reduce colorectal cancer risk, but as noted, few data are available addressing this association [45].

NUTRITION AND PROSTATE CANCER

There is considerable evidence that prostate cancer is the result of both inherited as well as environment influences. African American men have the highest incidence of prostate cancer in the world, while Asian men have the lowest. As men from the Far East migrate to the United States and as Western cultural influences, such as diet, are being adopted in that part of the globe, those who immigrate and those who more frequently consume a Western diet appear to be at greater risk of developing prostate cancer [46].

Such epidemiologic studies combined with animal model and in vitro experiments indicate that natural components of the diet, including n-3 PUFA, the carotenoid lycopene, and the trace element selenium, may serve as chemopreventive agents that suppress the growth and dissemination of neoplastic prostate cells [47].

Soyfoods are a unique dietary source of isoflavones, which have both hormonal and nonhormonal effects relevant to prostate cancer prevention. The in vitro studies have shown that the main soybean isoflavone protein, genistein, inhibits prostate cancer cell growth; in animals, some studies show isoflavone-rich soy protein and isolated isoflavones inhibit prostate tumor growth. Although limited epidemiologic data indicate soy intake reduces prostate cancer risk, results from one trial suggest isoflavones may be beneficial to prostate cancer patients [48].

Several case control and large prospective studies have suggested that the intake of tomatoes and tomato products may reduce one's risk of having prostate cancer and that lycopene, one of the compounds in tomato products, may confer that protection. Other carotenoids and phytochemicals in tomato products may also contribute to the proposed health benefits. Since only randomized controlled studies would provide a definitive answer to this hypothesis, such studies are unlikely due to the fact that tomato products are such a common part of the American diet and the duration of these trials would make them very difficult. As noted, numerous other potentially beneficial compounds are present in tomatoes, and, conceivably, complex interactions among multiple components may contribute to the anticancer properties of tomatoes [49–50].

NUTRITION AND ENDOMETRIAL CANCER

Endometrial cancer is the most common gynecologic cancer in the United States. While the relationship between obesity and endometrial cancer is quite well established, there is limited evidence that nutritional factors influence the incidence of this cancer. Case control studies have suggested an inverse association between fruit and vegetable consumption and endometrial cancer [51]; however, cohort studies have failed to substantiate this relationship [51,52]. Essentially, the same conclusion has been reached for dietary fiber, red meat, and antioxidant intakes [53,54].

NUTRITION AND OVARIAN CANCER

For ovarian cancer, the second most common gynecologic cancer in the United States, there are no recognized nutritional risk factors [55]. A somewhat detrimental relationship exists for obesity and limited physical activity [56]; however, additional controlled studies are needed to confirm such associations.

NUTRITION AND PANCREATIC CANCER

Pancreatic cancer is the fourth leading cause of cancer mortality in the United States and while there is substantial evidence that tobacco smoking and type 2 diabetes increase the risk of developing pancreatic cancer, there is limited evidence that dietary factors such as increased red meat and decreased intake of fruit and vegetables affect the incidence of this cancer [57,58].

NUTRITION AND GASTRIC CANCER

While somewhat uncommon in the United States, cancer of the stomach is the second leading cause of death from cancer worldwide [59]. Even though a relatively rare cancer in the United States, the overall incidence of this cancer appears to be increasing, an observation that may be related to gastric reflux into the lower esophagus due to abdominal obesity [60]. Numerous studies have shown that a diet of increased fruit and vegetables reduces the risk of developing gastric cancer, whereas a diet of increased salt and salt-preserved foods is associated with an increased risk [61,62].

SUMMARY

"The scientific study of nutrition and cancer is highly complex, and many important questions remain unanswered (Table 40.1). It is not presently clear how single nutrients, combinations of nutrients, over-nutrition, and energy imbalance, or the amount and distribution of body fat at particular stages of life affect a person's risk of specific cancers. Until more is known about the specific components of diet that influence cancer risk, the best advice is to consume a mostly plant-based diet that limits red and processed meats and emphasizes a variety of vegetables, fruits, and whole grains, legumes, nuts, seeds, herbs, and spices. A special emphasis should be placed on controlling total caloric intake to help achieve and maintain a healthy weight" [63].

TABLE 40.1
Relationships between Nutritional Factors and Certain Cancers

Cancer Site	Dietary Influences
Breast	• High dietary fat consumption has been linked to an increased incidence [3] • Higher intakes of calcium-containing dairy products reduced the risk in premenopausal, but not postmenopausal women [15,16] • High consumption of soy (≥20 mg/day) has been associated with a reduction of risk in Asian women. More research is needed to end the controversy regarding the safety of soy foods for women with breast cancer [18] • Increased intake of raw or cooked garlic is associated with a reduced risk [22] • While inconclusive and inconsistent, the results of studies have linked tea consumption to a reduced risk [33–37] • Total or specific vegetable and fruit intake is not associated with risk for breast cancer [40]. Intake of vegetables may decrease risk in premenopausal women; fruits are weakly associated with a decreased risk [38] • Studies of vitamins A, C, and E, not limited to premenopausal women, are inconclusive in relation to risk. Beta-carotene from food and supplements, lutein/zeaxanthin, and vitamin A from foods were weakly associated with a reduction in risk, but only in premenopausal women who consumed five or more servings per day of fruits and vegetables [39] • No clear association with red meat consumption; however, higher red meat intake may be a risk factor for premenopausal women who develop estrogen and/or progesterone positive breast cancer [41]
Esophagus	• Increased intake of garlic and various types of onions and chives is associated with a reduced risk [24]
Lung	• A reduced risk was observed among those with increased phytoestrogen consumption from food sources, both in nonsmokers and current smokers [19] • While inconclusive and inconsistent, the results of studies have linked tea consumption to a reduced risk [33–37] • Possible increase associated with antioxidant supplements (beta-carotene); no effect with vitamin E [2,7,8]
Gastric	• Beta-carotene, vitamin E, selenium showed a significantly reduced incidence in Chinese men and women [6] • Increased intake of raw and cooked garlic and various types of onions and chives is associated with a reduced risk [22,24] • Increased fruit and vegetable intake reduces risk [61,62] • Increased salt and salt-preserved foods increases risk [61,62]
Pancreatic	• Limited evidence that dietary factors such as increased red meat and decreased intake of fruit and vegetables affect the incidence [57,58] • Increased intake of garlic is associated with a reduced risk [25]
Prostate	• High intakes of calcium and dairy products may be associated with an increased risk [11,12] • Increased consumption of dietary soy revealed a reduction in risk [18] • While inconclusive and inconsistent, the results of studies have linked tea consumption to a reduced risk [33–37] • In animal and in vitro studies, n-3 PUFA, lycopene, and selenium may serve as chemopreventive agents [47] • There are limited epidemiologic data, however one trial suggests isoflavones may be beneficial to prostate cancer patients [48] • Intake of tomatoes and tomato products may reduce risk [49–50]
Ovarian	• No recognized nutritional risk factors [55] • May be less frequent in women consuming calcium from dairy products [14] • While inconclusive and inconsistent, the results of studies have linked tea consumption to a reduced risk [33–37]
Endometrial	• Limited evidence that nutritional factors influence the incidence; cohort studies have failed to substantiate the relationship with fruit and vegetable consumption, dietary fiber, red meat, and antioxidant intakes [51–54]
Colorectal	• After accounting for other dietary risk factors, high dietary fiber intake as an independent variable does not appear to be solely responsible for a reduced risk [43]. However, intake of particularly cereal fiber and whole grains was associated with a reduced risk [3,44] • High dietary fat consumption has been linked to an increased incidence [3] • High calcium intake may confer protection [17] • Higher consumption of raw and cooked garlic is associated with a lower risk [22,23] • While inconclusive and inconsistent, the results of studies have linked tea consumption to a reduced risk [33–37] • Red meat appears to be associated with increased risk [42] • Inconsistent results in regards to fish consumption and risk [45]
Overall Cancer Risk	• Very small inverse association between intake of total fruits and vegetables and cancer risk which was restricted to women [5] • Beta-carotene, vitamin E, and selenium showed a significantly reduced incidence in Chinese men and women [6] • No convincing evidence of a benefit of antioxidants [9] • 300–600 mg elemental calcium plus 1000 IU vitamin D supplementation reduced the risk of all cancers combined by approximately 60% in women [10]

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Part IX

Obesity and Weight Management

John P. Foreyt, PhD

41 Epidemiology of Adult Obesity

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CONTENTS

Epidemiology of Adult Obesity 515
Obesity and Adiposity 515
Measurement of Adiposity 516
Hydrodensitometry 516
Dual-Energy X-Ray Absorptiometry 516
Anthropometric Measurements 517
Body Mass Index 517
Waist Circumference 517
Waist-to-Hip Ratio 517
Skinfolds 517
Bioelectrical Impedance 518
Computed Tomography 518
Ultrasound Technique 518
Prevalence of Obesity 518
U.S. Obesity Trends 518
Global Obesity Trends 519
Potential Causes of Obesity 519
Energy Imbalance 520
Genetics and Epigenetics 521
Infections 521
Smoking 522
Sleep 522
Other Factors 522
Health Consequences of Obesity 522
Economic Costs of Obesity in the United States 522
Direct Costs 522
Indirect Costs 523
Presenteeism and Absenteeism 523
Disability and Premature Mortality 523
Summary 524
References 524

EPIDEMIOLOGY OF ADULT OBESITY

Obesity represents one of the most significant public health issues for the world in recent history. Obesity increases the risk for numerous chronic diseases and significantly contributes to worldwide morbidity and mortality. Obesity results in an excess mortality of approximately 300,000 deaths annually in America [1], and the estimated health care costs associated with obesity morbidity are approaching the $100 billion mark. Indeed, obesity is one of the leading preventable causes of death and disease globally.

Obesity and Adiposity

Clinically, obesity is a condition characterized by the accumulation of excess adipose tissue. Therefore, standards to define and classify obesity require the assessment of total body adiposity. However, the quantitative determination of body fat composition remains difficult and costly to obtain. Techniques such as dual-energy x-ray absorptiometry (DEXA) and bioelectrical impedance possess the ability to quantify total body fat. However, these techniques require the use of specialized equipment by qualified technicians. Thus, these methods

remain largely restricted to small-scale research purposes because the high cost and burden of data collection make their use in large-scale research or clinical practice unrealistic. For practical reasons, researchers and clinicians often rely on proxy measurements to approximate adiposity.

MEASUREMENT OF ADIPOSITY

There are numerous accepted adiposity measurement systems used for indirectly measuring total body fat and for screening nutritional and health status. Those measurements include hydrodensitometry, DEXA, anthropometry, bioelectrical impedance analysis (BIA), computed tomography (CT), and ultrasonic technique. Often more than one method of body fat measurement is used to assess body composition in order to address the clinical or research goal appropriate for the individual and population. All methods that estimate body fat are interpreted using the same cut point for obesity (% body fat > 25.0 for men and > 30.0 for women; Table 41.1) [2].

Hydrodensitometry

Hydrodensitometry or underwater weighing (UWW) has long been considered one of the "gold standards" for measuring body composition and estimating body fat [3]. It is one of the classic two-compartment (2-C) models. In the 2-C model, the body is divided into two components, fat mass and fat-free mass (water, protein, and mineral). Therefore, by subtracting fat-free mass from body weight, fat mass can be defined. The UWW applies Archimedes' principle to determine total body volume or body density by measuring the difference of body's weight in water and in air after correction for the volume of air in the respiratory system and in the gastrointestinal tract [4]. In this model, it assumes that fat-free mass contents are fixed for all ages [3,5]. Using Siri's formula [6], fat mass can be determined and percent body fat can be indirectly estimated using Equation 41.1:

$$\%\,\text{Body fat} = \left(\frac{495}{\text{Body density}}\right) - 450 \qquad (41.1)$$

Although UWW has been widely accepted and frequently referred as a gold standard for body density measurement, there are several limitations associated with this method. It is time and labor consuming, requires special training, and often creates individual discomfort [5,7,8]. In addition, the fat-free mass component normally varies by individuals due to gender, ethnicity, age, and/or physical activity [9,10]; hence, estimates must be corrected for variation from these factors. Furthermore, this technique is particularly challenging with heterogeneous populations such as children, pregnant women, and elderly or disabled individuals.

An air-displacement plethysmography was developed to be an alternative to hydrodensitometry. This method determines body volume by measuring the changes of chamber volume caused by placing an individual in a closed air-filled chamber [7]. Adequate corrections for temperature and gas composition as well as lung volume are required before calculating body volume. Several studies reported that the plethysmographic method demonstrated good agreement with the UWW techniques [11,12]. However, since both of these methods are 2-C models neither is more accurate that the other, making conclusions difficult. The absolute differences between the Bod Pod, the commercially available method of air-displacement plethysmography, and UWW were about 1% body fat and were not consistent in any direction [13]. Studies have demonstrated high agreement (0.91–0.94) [13,14] between the Bod Pod and DEXA, which uses a 3-C model for estimating body fat. In one study of 160 men, the mean difference in body fatness (2.2%) between methods was significant and increased as body fat increased [13]. An advantage of the air-displacement plethysmography technique is that it is less stressful for the individual because they are not immersed in water; however, it may be a problem for those who are claustrophobic.

Dual-Energy X-Ray Absorptiometry

DEXA has been developed to assess body composition in order to improve accuracy over the 2-C model. It uses four-compartment (4-C) models examining regional and whole body composition, including body fat, lean soft tissue, water volume, and bone mineral mass [5,15]. This technique requires participants to remove all metal accessories and lay in a supine position on a bed while the collimated low intensity x-ray source passes below the bed synchronized with the movement of a detector array above the body [16]. DEXA is quick and easy to perform on all types of individuals regardless of their disability and often is used as the gold standard reference method for body composition analysis in clinical settings [17]. Limitations include its expense and moderate validity [15,18]. DEXA's accuracy is affected by varying fat distributions, but it is superior to UWW weighing because it lacks sensitivity to a person's residual volume of unexpelled air or hydration status [15,19]. DEXA measures of central adiposity also correlate well with measures of intra-abdominal fat measured by magnetic resonance imaging (MRI) in nonobese women ($r = 0.88$) and men ($r = 0.87$) [20].

TABLE 41.1
Classification of Overweight and Obesity by BMI Levels and Public Health Action Points

WHO Classification	BMI (kg/m²)	Public Health Action Points, BMI (kg/m²)
Underweight	<18.5	—
Normal	18.5–24.9	23.0
Overweight/preobese	25.0–29.9	27.5
Obese Class I	30.0–34.9	32.5
Obese Class II	35.0–39.9	37.5
Obese Class III	≥40.0	—

Sources: World Health Organization, *World Health Organ. Tech. Rep. Ser.*, 894, i–xii, 1–253, 2000; WHO Expert Consultation, *Lancet*, 363(9403), 157, 2004.

Anthropometric Measurements

Body Mass Index

BMI is the most popular and practical indicator for overweight and obesity classification because it is inexpensive, simple to calculate, and easy to gather weight and height via measurements or self-report [21,22]. Equation 41.2 indicates the calculation of BMI:

$$\text{BMI} = \frac{\text{Body weight (kg)}}{\text{Height (m)}^2} \tag{41.2}$$

Although BMI is the most frequently used measure of adiposity, it does not directly assess fat mass; instead, it is a measure of weight controlling for height. BMI correlates with percent body fat for the majority of the population. The use of BMI in adults allows for the categorization of adiposity estimates independent of gender and age. Therefore, agencies such as the World Health Organization (WHO) and International Obesity Task Force (IOTF) recommend the use of BMI to define and classify obesity. International standards to classify BMI consider an individual with a BMI between 25 and 29.9 kg/m^2 overweight and any person with a BMI ≥ 30.0 kg/m^2 obese [22–27] (Table 41.1). These BMI guidelines are based on numerous longitudinal cohort studies showing increased mortality risk as BMI increases beyond 25 kg/m^2. The BMI guidelines are based on the assumption that body fatness is increased as weight increases in relation to height [28], they do not consider fat content, and inadequately distinguish between lean and fat tissues [29,30] nor does BMI provide information on the distribution of fat mass [27]. Thus, BMI may overestimate fat mass in individuals with high levels of lean (muscle) mass (e.g., athletes, some military) [2,31] and underestimate fat mass in individuals with low levels of lean mass such as the elderly.

The correlation between BMI and percent body fat can vary between gender, age, and ethnic groups. For example, non-Hispanic blacks generally have a lower percentage of body fat for a given BMI compared to other ethnic groups [32,33]. Therefore, the health risk corresponding to a given BMI category may differ among gender, age, and ethnic groups [27,34]. An expert consultation by WHO amended the guidance in 2004 and identified potential public health action points (Table 41.1) to further aid countries' identification of individuals at increased risk for obesity-related comorbidities [27].

Waist Circumference

Waist circumference (WC) is used for measuring the fat located in the central region of the body (intra-abdominal fat). WC is more strongly associated with visceral adipose tissue and central adiposity than are BMI and waist-to-hip ratio [35–37]. In addition, WC is highly correlated with cardiovascular and diabetes risk factors and all-cause mortality and is considered to be a stronger predictor of obesity-related risk factors than BMI [2,38,39]. WC is measured with a nonelastic tape at the superior border of iliac crest [2], the mid-abdomen or midpoint between iliac crest and lowest rib [2], umbilicus level [40], or at the narrowest point of the waist [41], to the nearest 0.1 cm. A WC of >102 cm (or >40 in.) in men and >88 cm (or >35 in.) in women is considered as abdominal obesity, while men with a WC 94–102 cm and women with a WC 80–88 cm are classified as overweight (Table 41.2) [42]. The combination of classification of overweight or obese and a large WC is proposed to carry additional risk [2,43]. WC correlates with MRI measures of intra-abdominal fat in nonobese women ranging from r = 0.49 to 0.77 and among men from r = 0.77 to 0.90 [20]. WC is a comparable measure of abdominal fat mass to DEXA for men, but not for women [20].

TABLE 41.2
Classification of Overweight and Obesity by Anthropometric Measures

	Overweight		Obese	
Anthropometric Measure	**Male**	**Female**	**Male**	**Female**
WC [42]	94–102 cm	80–88 cm	102 cm	88 cm
Waist-to-hip ratio [22]	0.9–1.0	0.8–0.85	>1.0	>0.85
Skinfolds (sum of biceps, triceps, subscapular, and suprailiac) [2]	—	—	>25.0	>30.0

Waist-to-Hip Ratio

WHR is an alternative anthropometric measure for abdominal obesity additional to WC. WHR is obtained by dividing the WC by the hip circumference. For hip measuring, the tape is placed at the maximum extension of the buttocks [22]. Classification of obesity is as follows: men with a WHR > 1.00 and women with a WHR > 0.85, and classification of overweight is as follows: men with a WHR = 0.90–1.00 and women with WHR = 0.80–0.85 (Table 41.2) [22]. Because WHR provides additional information related to hip circumference, gluteofemoral muscle mass, and bone structure, it might be a better predictor of risk factors for cardiovascular disease as hip circumference is inversely related to the development of insulin resistance, dyslipidaemia, cardiovascular disease, hypertension, and death [22,44,45]. WHR and DEXA measures of abdominal visceral fat had the same correlation with MRI measures in men (r = 0.80) but WHR was not as good a measure among women as DEXA when using the MRI as the standard measure (r = 0.19) [20].

Skinfolds

Skinfold thickness measurement has been used as a body composition measurement to estimate percentage of body fat (%BF) since the 1970s [46]. It is still considered the most practical method used to estimate body fat and fat-free mass. This technique is simple, quick, inexpensive, but does require training [47]. According to Durnin and Womersley [46], skinfold thickness is measured to the nearest 0.1 mm on the right side of the body, at the biceps, triceps, subscapular, and suprailiac areas, using a Harpenden caliper (British Indicators Ltd., Luton, United Kingdom). The sum of skinfold thickness

at these four sites is used to predict %BF (Table 41.2). The correlation between body fat measures from skinfolds and DEXA was $r = 0.74$ and for fat-free mass was $r = 0.85$ among 50 chronic kidney disease patients [18]. Studies have shown agreement between skinfold measures and DEXA measures of body fat decline as %BF increases and the measures are lower among females than males. Women consistently have a low agreement with the gold standard possibly due to their ratio of subcutaneous and visceral fat and the ability of the skinfold measures to assess these parameters [48].

Bioelectrical Impedance

Compared to anthropometry methods, BIA is a more sophisticated technique to assess body fatness and %BF. It is noninvasive, simple to use, and has reproducible results. BIA is based on the principle that electrical current is more impeded through fat mass than fat-free mass or lean tissue (mostly water and electrolytes), resulting in differences in electrical resistance between fat mass and fat-free mass [49,50]. Two BIA measurements, whole body BIA and segmental BIA, have been developed for body composition assessment. For whole body BIA, surface electrodes are placed on a hand and a foot, or foot-to-foot or hand-to-hand, sending single or multiple frequencies measuring whole body resistance [51–53]. Because whole body BIA measures use multiple body segments, its results are likely to be influenced by a number of factors such as hydration and fat fraction [51]. In addition, as Lukaski and Scheltinga [54] noted, the trunk, which contains a large volume of conductors, only contributes a small amount to whole body resistance, which might be a problem in overweight and obese individuals [55,56]. Therefore, segmental BIA has been developed to minimize this effect. Segmental BIA focuses on body segment measurements of resistance derived by applying either two additional electrodes on the wrist and foot on the opposite side, the wrist, shoulder, upper iliac spine and ankle, or the forearm, lower leg and trunk [57–59]. Fat-free mass, fat mass, and total body water are estimated using predictive equations including impedance or resistance values [51]. BIA in elderly Finnish women has an agreement with DEXA for fat-free mass of $r = 0.7$ and fat mass of $r = 0.93$ as compared to skinfold measures with DEXA, which were $r = 0.62$ and 0.89, respectively [60]. Results by gender indicate BIA estimates of %BF in males had less error (6.8%) than that among females (8.8%) when compared to DEXA estimates of body fat [48]. General consensus suggests the equations used to calculate %BF from BIA can explain some variation between studies [48,60].

Computed Tomography

CT is an imaging technique widely used for body composition measurement. This technique uses x-ray as a source to detect body fat distribution. During CT scanning, the x-ray rotates around the body or body segments covering 360° while the photodetectors send the information regarding visceral and subcutaneous adipose tissue at each degree of rotation to yield CT images [61,62]. The main advantage of CT is that the images can be used to identify and visualize body adipose tissue mass, providing highly accurate body fat estimation [63,64]. Limitations of CT scanning include high costs and the need for radiation for imaging, which cannot be applied outside clinical or laboratory settings [65].

Ultrasound Technique

Ultrasonography was proposed by Armellini et al. [66] to be an alternative method to CT for visceral adiposity estimation. It is clinically accepted as the best technique for quantifying intra-abdominal fat because it directly measures fat thickness between the muscle and the skin [66,67]. The UT uses an ultrasound wave as a source to determine the thickness of subcutaneous fat [68]. The use of UT in intra-abdominal fat assessment was shown to be strongly correlated with %BF measured by DEXA [68], and CT [65]. UT is considered as a noninvasive and accurate technique of body fat measurement and is cheaper and more convenient to use than CT [69].

PREVALENCE OF OBESITY

BMI remains the most popular proxy measurement for obesity surveillance and monitoring due to its affordability and simplicity. Despite its limitations, BMI allows for the standardized tracking and comparison of obesity within and among populations.

U.S. Obesity Trends

The prevalence of obesity has been increasing for almost 100 years in the United States [70]. Since the 1960s, the National Health and Nutrition Examination Survey (NHANES) has taken an active role in tracking the prevalence of obesity in the United States. The prevalence of obesity remained fairly constant between 1960 and 1980 [71]. However, between 1976–1980 and 1988–1994, the overall prevalence of adult obesity increased by 8% points [72]. Moreover, all age, gender, and ethnic groups experienced a statistically significant increase in obesity prevalence [72]. From 1988–1994 to 1999–2000 the prevalence of adult obesity significantly increased in all age and gender categories except 40- to 59-year-old males [73]. Most recently, the prevalence of obesity increased significantly in men and nonsignificantly in women between 1999–2000 and 2007–2008 [74] (Figures 41.1 and 41.2). Although the recent data suggest obesity trends may be approaching a plateau, the prevalence of adult obesity remains high. The current prevalence of obesity is approximately double that of 1970 with 33.8% of the population considered obese and another 34% considered overweight [24,74].

Significant variations exist in the geographic and demographic distribution of obesity. Geographically, the states of the southeastern and midwestern United States have the highest rates of obesity, although the prevalence has increased in every state over the last 30 years [75]. Demographically, the distribution of obesity varies across gender, age, ethnic and socioeconomic groups. Minority

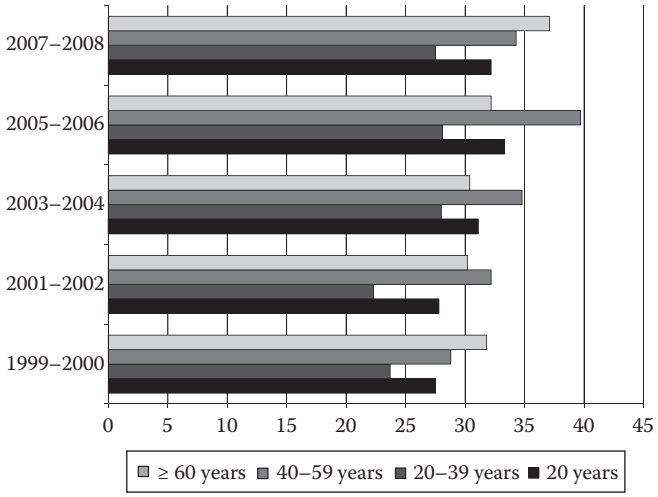


FIGURE 41.1 Trends in male prevalence (%) of obesity (BMI > 30 kg/m^2) by age. (Data from Flegal, K. M., et al. *JAMA* 303, 235–241, 2010.)

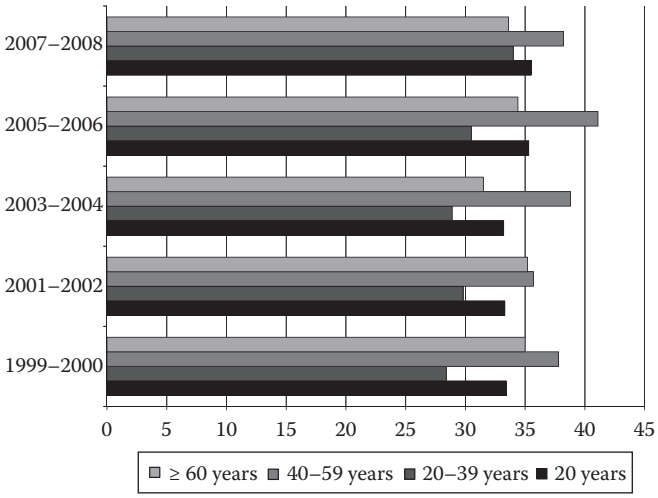


FIGURE 41.2 Trends in female prevalence (%) of obesity (BMI > 30 kg/m^2) by age. (Data from Flegal, K. M., et al. *JAMA* 303, 235–241, 2010.)

populations generally have higher rates of obesity compared to non-Hispanic whites [74]. Additionally, gender differences in the prevalence of obesity often exist within ethnic groups; however, the direction and magnitude of the disparity depends on the population of interest [74]. Finally, the prevalence of obesity is 50% higher among women of low socioeconomic status (SES) compared to women of higher socioeconomic status, whereas the prevalence of obesity is approximately equal among men regardless of socioeconomic status [76].

Every age, sex, race, and smoking status group is experiencing the obesity epidemic; thus distributional changes in these factors cannot fully explain the rapid changes seen in the last three decades. The increasing positive skew of the obesity distribution is worrisome because it indicates the most obese are even more obese than those in previous years [77].

Global Obesity Trends

Obesogenic environments currently exist in almost every country. Meta-analyses of data from 9.1 million participants indicate the mean worldwide BMI increased 0.4 kg/m^2 per decade for men and 0.5 kg/m^2 for women since 1980 [78]. Obesity has indeed reached the pandemic level. It is no longer a crisis only for developed countries as it is increasingly being seen in developing countries [22,78–80]. The onset of a rise in obesity began almost simultaneously in developed countries in the 1970s and 1980s [22,78–80]. While comprehensive data are not available from every country; evidence gathered by the International Association for the Study of Obesity supports the notion that the epidemic has spread globally [80]. Figure 41.3 rank orders a selection of developed and developing countries by the prevalence of obesity among males. Worldwide male prevalence of obesity ranges from 1.3% in India to 55.7% in Nauru. The females in Figure 41.4 are in the male ranked order. Comparison of these two figures clearly indicates the gender discrepancies in prevalence of obesity within countries [80]. The range of obesity prevalence is wider among females than males ranging from 2.8% in India to 70.3% in Tonga. Several large gender differences in the prevalence of obesity among both developed and developing countries are evident in Pakistan, Fiji, Algeria, Barbados, Bahamas, France, Egypt, Wales, Saudi Arabia, Samoa, and Tonga. Obesity is most common in the low socioeconomic status groups and in rural areas in countries with a low gross domestic product, whereas the high socioeconomic groups in urban areas have been the first to have increased obesity prevalence in low- to middle-income countries [79]. Evaluation of women in 37 developing countries suggests lower SES women have had a faster increase in overweight than that among higher SES women [81].

POTENTIAL CAUSES OF OBESITY

Determining the causes of obesity is not a straightforward issue. Many believe it is largely a problem of energy imbalance and the solutions are to reduce energy intake and increase physical activity. Body weight is determined by a combination of metabolic, genetic, environmental, behavioral, cultural, and socioeconomic factors [24]. These factors affect energy balance asymmetrically [79,82]. The proximal role energy imbalance plays in the obesity epidemic is evident [83]. However, the distal factors affecting energy consumption, energy expenditure, and metabolic performance are complicated and their roles are not well understood. The influence of other risk factors for obesity has remained in the shadows of the two big factors: over consumption and inactivity. This section provides a brief overview of energy imbalance issues as well as numerous other risk factors for obesity describing how each could affect weight gain. Future obesity researchers will benefit from a systems approach utilizing all identifiable risk factors to decipher the pandemic etiology.

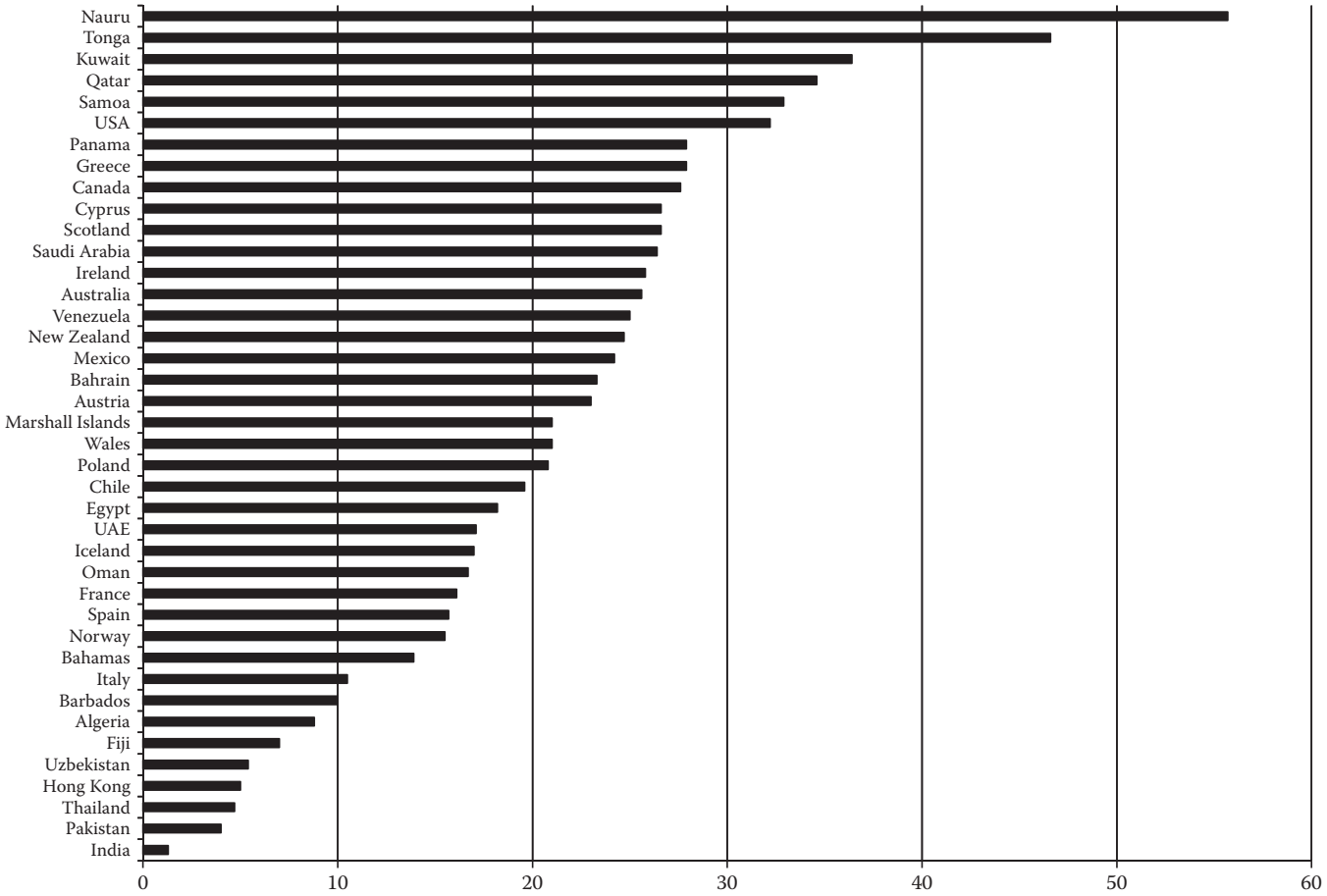


FIGURE 41.3 Adult male prevalence (%) of obesity (BMI > 30 kg/m^2). (Data from International Association for the Study of Obesity. Global prevalence of adult obesity. [database online] 2011.)

Energy Imbalance

Weight change is associated with an imbalance between energy intake and energy expenditure. When energy intake exceeds energy expenditure, the excess is stored as fat, leading to increased adiposity. The effect of energy imbalance on bodyweight has been quantified and models indicate gaining weight is indeed easier to do than losing weight [84,85]. Simply reducing energy intake to tip the balance in favor of weight loss may not result in steady weight loss because of physiologic adaptations of metabolic rate and energy burn from physical activity [2,84,86,87]. This phenomenon is frequently seen in practice and helps explain results from interventions to reduce obesity showing mixed effects and low sustainability [85].

Energy intake changes to support the rise in obesity are attributed to portion size increases [88] and increased availability of inexpensive, energy-dense, nutrient-poor foods and beverages. Portion sizes of many foods did increase from 1977 to 1996 [88]. The portion sizes of salty snacks, desserts, soft drinks, fruit drinks, French fries, hamburgers, cheeseburgers, and Mexican foods increased regardless of whether they were consumed in the home or not. Increased portions resulted in energy increases ranging from 49 to 133 kcal per food [88]. Between 1977 and 2006, changes in portion size accounted for an average 10 kcal/day increase in energy intake [89].

Energy density per eating occasion increased steadily over the last 30 years according to nationally representative data [89]. Inexpensive, convenient, energy-dense food is readily available throughout the day for most people. Much of our food preparation is now done at a mass production level and not by individuals. The available food is inexpensive, highly processed, and contains added sugar (or high-fructose corn syrup), fat, salt, and flavor enhancers enhancing the taste of food and encouraging consumption [79,90]. Overall energy intake in the U.S. population has shifted upward since the 1976–1980 NHANES survey; however, the increase has not been as steep as the rise in obesity [83]. An area of active investigation focuses on the macronutrient mix of the energy component of diet. Weight change can differ by the macronutrient content of the diet even if energy levels remain constant. The energy stored from equal amounts of protein, fat and carbohydrate differs markedly. In addition, the body employs a complex regulation of fuel sources, which varies by macronutrient. And although short-term energy restricted diets of all macronutrient combinations can lead to weight loss, little is known about the long-term efficacy of diets by macronutrient content [84,85,87]. Changes over time in the energy sources of the diet may be an important aspect of understanding the obesity epidemic.

Energy expenditure occurs for metabolism, thermoregulation, and daily physical activity. Metabolism and thermoregulation

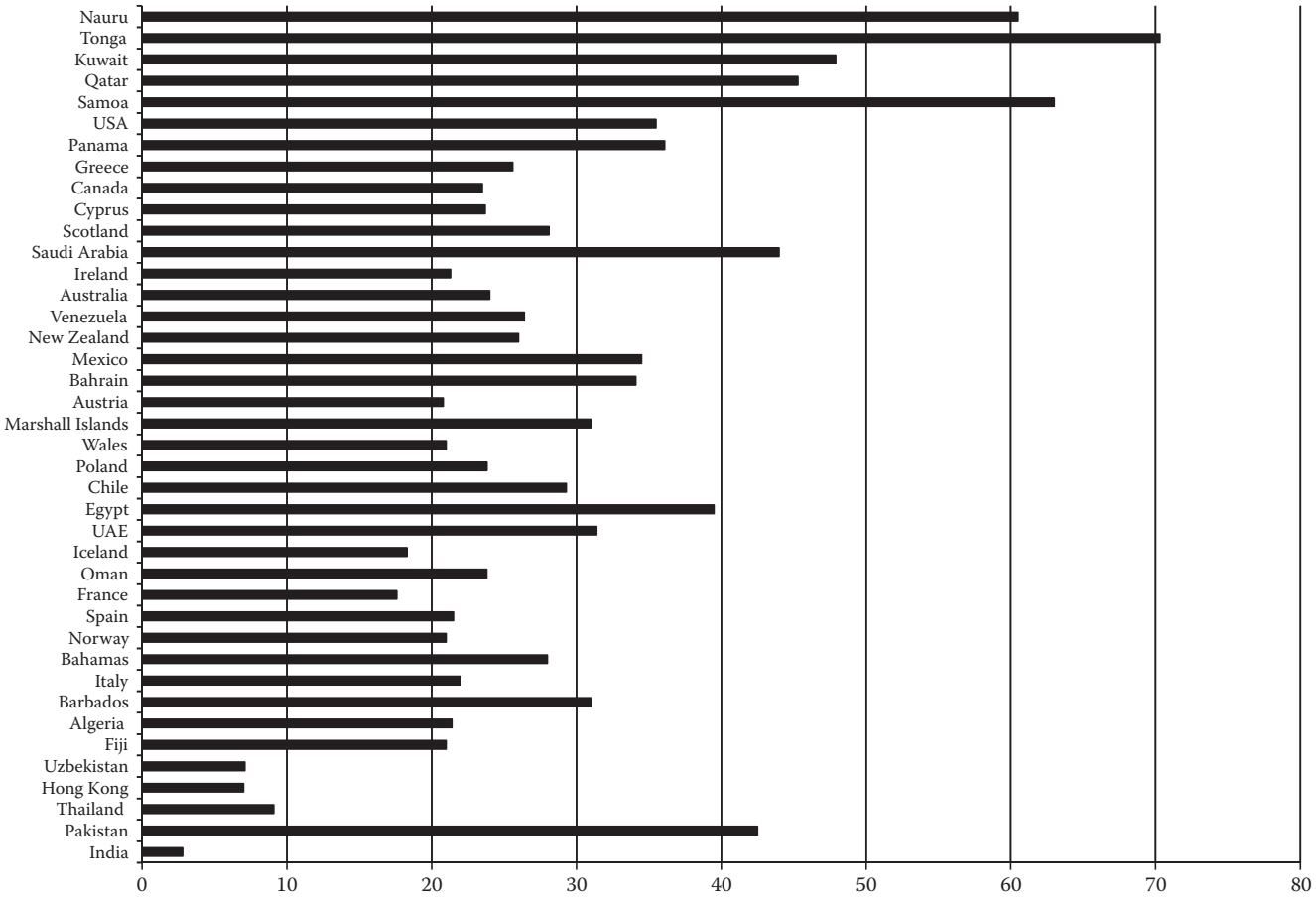


FIGURE 41.4 Adult female prevalence (%) of obesity (BMI > 30 kg/m^2). (Data from International Association for the Study of Obesity. Global prevalence of adult obesity. [database online] 2011.)

account for 60%–70% of energy expenditure and daily physical activity among predominately sedentary individuals about 20%–30% [83]. The energy expenditure concepts thought to influence the rise in obesity include reduced physical activity resulting from the "built environment" and reduced physical activity in schools. Technologic conveniences and labor-saving devices continually make life easier diminishing the energy required for completion of previously labor intensive tasks. Sedentary jobs are prevalent and energy expenditure from transportation decreased. Television, videos, and computers occupy increasingly more of peoples' time. Television viewing has increased steadily from 10.4 h/week in 1965 to 15.1 h in 1985, and 25.2 h/week in 1992–1994 [83]. In 2008, 25.4% of the U.S. population did not engage in any leisure time physical activity [91]. Data to support the impact of reductions in physical activity are scant, thus the impact of changes in these behaviors is difficult to quantify. However, available data suggest this component of energy balance has indeed declined, which could result in increased weight [70,79,84,85,87].

Genetics and Epigenetics

Enormous efforts have provided extensive information about genetic variation associated with obesity summarized in 12 annual reports through 2005 [92]. From this report, 11 different genes with single mutations have been reported from 176 human obesity cases. A total of 50 loci related to Mendelian syndromes commonly associated with obesity have been mapped and candidate genes identified for many of these syndromes. Through 2005, there have been 426 reports of positive associations between DNA sequence variation and obesity with 127 candidate genes [92]. Epigenetic influences include environmental exposures causing alterations or dysregulation of molecular processes leading to weight change. Studies in both animals and humans indicate genes associated with energy balance could be altered by environmental influences influencing susceptibility to obesity [93].

Infections

The etiologic role of infections in the development of obesity is novel. There are possibly interactions between the similar function of the immune system and adipose tissue. There are 10 microbes reported to cause obesity in different experimental models, however Adenovirus-36 (Ad36) is the most studied [93]. Although the adipogenicity action of Ad36 is not well understood, the in vitro and in vivo studies collectively suggest the virus infects preadipocytes and stem cells. Ad36 increases adipogenic commitment in stem cells, preadipocyte replication, adipogenic differentiation,

and lipid accumulation in rodent and human cells [94–96]. Ad36 strongly upregulates glucose uptake by adipocytes and adipose tissue [95,97]. Thus, it appears Ad36 increases not only adipocyte cell number but glucose and lipid uptake by these cells, which may collectively contribute to increased adiposity. Infections can affect metabolism and adipose tissue can impact inflammation, a factor associated with obesity. Ad36, first identified in 1980, coincided with the early recognition of the rising prevalence of obesity.

Smoking

Smokers consistently have been shown to weigh less than nonsmokers. The physiologic response to nicotine includes appetite suppression and alteration in thermogenic responses [77]. Smoking cessation studies provide evidence of weight gain following cessation, but the molecular mechanism for this change is still not well described [98,99]. Smoking prevalence during 1997–2004 was lower than in 1987–1994 for all occupational groups in the National Health Interview Survey [98]. Thus, a lowering prevalence of smokers over time could be associated with the rising prevalence of overweight and obesity.

Sleep

Evidence from animal and human studies supports an inverse relationship between amount of sleep and obesity. Several endocrine changes associated with lack of sleep include decreased glucose tolerance, leptin, and thyroid-stimulating hormone and increased ghrelin levels [77]. Each of these has a role in obesity development stimulating food intake and energy storage [100–109]. As much as 30% of adults and 69% of teens do not get the recommended hours of sleep [110]. Reports suggest hours of sleep have declined in adults and children over the last 20 years [111,112]. Sleep deprivation as a risk factor for obesity should be considered in the systems approach to curbing the obesity epidemic.

Other Factors

Other putative factors are being explored as associated with the rise in obesity such as endocrine disruptors, pharmaceuticals, and ambient temperature control [77,93]. Each of these requires more investigation to establish mechanisms and experimental evidence in animals and humans.

HEALTH CONSEQUENCES OF OBESITY

Obesity is associated with increased overall mortality and is a significant risk factor for developing numerous comorbidities [22,113–116]. Obesity is associated with increased risk of type 2 diabetes, cardiovascular diseases, numerous cancers, asthma, chronic back pain, sleep apnea, gout, osteoarthritis, pulmonary embolism, breathing problems, gallbladder disease, pregnancy complications, menstrual irregularities, stress incontinence, and psychological disorders [24,117–120]. There is a positive trend associated with weight gain and disease risk with even small weight gains of 10–12 lb associated with increased risk [24]. Certain comorbidities have a higher prevalence among different racial groups; however, the increased risks associated with being obese appear to be consistent globally.

ECONOMIC COSTS OF OBESITY IN THE UNITED STATES

The economic costs associated with obesity in the workplace have continued to increase over the last several decades in the United States [74] and worldwide. The economic costs related to obesity have been estimated based on the direct health care costs associated with treating comorbid diseases (e.g., hypertension, diabetes, osteoarthritis) and the indirect costs, which comprised of different indicators of lost productivity and include presenteeism, absenteeism, disability and worker's compensation claims, and premature mortality.

Direct Costs

Obesity direct costs are defined typically as the expenses (both out-of-pocket and insurance covered) related to treatment or services provided by a health care provider (e.g., physician, nurse practitioner) for office-based, outpatient, inpatient hospital, or emergency room care and pharmaceuticals or procedures [121]. However, because obesity as a condition is usually not treated directly, the direct costs of obesity usually are estimated based on the costs associated with treating related comorbid conditions such as hypertension, diabetes, heart and other cardiovascular-related diseases, osteoarthritis, sleep apnea, etc., all conditions for which obesity has been demonstrated to substantially increase risk. Thus, the proportion for each disease condition that can be attributed to obesity and the prevalence of that condition and the medical expenditures associated with each condition are used to estimate the direct costs of obesity with aggregate data [122,123]. If individual data are available, then actual medical expenditures for comorbid conditions can be compared for obese and nonobese individuals [122,123]. A number of studies calculated the direct medical and health care costs attributable to obesity, but their estimates vary based on a number of factors including how many comorbid conditions were included that are linked to obesity [121]. Thus, there is no definitive estimate of health care costs associated with obesity.

The substantial direct costs of obesity in the United States have been estimated in a number of studies [121]. For example, Wolf and Colditz [124] conducted the first study in this area and estimated the direct costs of obesity to be 45.8 billion dollars in 1990 dollars among all Americans. However, more recent studies such as Finkelstein et al. [125] estimated the direct costs attributable to obesity among full-time workers to be 73.1 billion dollars (in 2006 dollars). In addition, they found that individuals with BMI > 35 were culpable for 61% of excess costs. They estimated the per person direct medical expenditures attributable to obesity to be $2568 for men and $6201 for women and found that the costs increased for

each class of obesity, that is, costs per person were higher for workers who were Class III obese when compared to those that were Class II or I obese.

Dor et al. [121] reviewed a large number of studies conducted in the United States over the last 20+ years and adjusted all of their estimates to 2009 dollars. They concluded that the direct costs attributable to obesity have increased substantially over time due to the growing prevalence of obesity. Withrow and Alter [123] also reviewed direct cost estimation studies conducted in a number of mostly industrialized nations including the United States, Canada, Italy, Sweden, France, China, Japan, Australia, New Zealand, and Brazil and concluded the direct costs attributable to obesity accounted for between 0.7% and 2.8% of a country's total health care costs. While the estimates vary based on how the study was conducted and what obesity comorbid conditions were included, it should be clear that obesity results in significant individual and societal direct health care costs diminishing the resources of national economies and employers.

Indirect Costs

Indirect costs are those nondirect medical expenditures representing lost productivity in the workforce. They include presenteeism, absenteeism, disability and worker's compensation claims, and premature mortality [121].

Presenteeism and Absenteeism

Presenteeism is defined as time and productivity lost due to workers who are at work but are unable to perform at their full capacity as a result of obesity-related health problems [121,126]. Absenteeism refers to the loss of productivity associated with missed work days or sick leave [121,126]. A number of studies have examined the relationship between obesity and the primary indicators of lost productivity in the U.S. workplace [126]. For example, Tucker and Friedman [127] found that obese workers were 70% more likely to experience absenteeism categorized as "high level" (i.e., seven or more absences due to illness in the past 6 months) than lean employees. Pronk et al. [128] found that obesity was associated with more work loss days and greater difficulty getting along with coworkers while greater levels of physical activity and cardiorespiratory fitness were associated with better work quality, job performance, and greater work quantity and effort in a diverse sample of workers.

In addition to documenting an association between obesity and losses in work productivity, several studies estimated the economic losses to employers. In a very early study on this topic, Robbins et al. [129] found male military service personnel who exceeded their maximum allowable weights accrued 17,117 lost work days over 12 months totaling to $2.2 million annually, resulting in excess weight attributable costs of approximately $2,809 per male service member. Ricci and Chee [130] conducted a national telephone survey of 7472 adult workers in the United States estimating obesity-attributable costs for both presenteeism and absenteeism combined totaling $42.3 billion (in 2002 dollars).

In a large study of more than 500,000 American workers in a variety of job classifications (e.g., professional, managers, sales, service, office, and equipment and transportation operators), workers who were obese were found to experience a significantly higher probability of missing any work when compared to workers in the normal weight range [131]. In addition, their absences were associated with greater incremental per worker costs when compared to normal weight employees and their aggregated costs to employers were estimated to be nearly $4.3 billion (in 2004 dollars).

Gates et al. [132] evaluated lost productivity in a sample of manufacturing employees and found that workers who were Classes II and III obese reported more work limitations with regard to time needed to complete work tasks and ability to perform physical job demands. They also found that both Class I and Classes II and III obese workers had significantly higher absenteeism than normal weight workers. The resultant loss in overall productivity was estimated to cost the employer $506.00 for presenteeism and $433.00 for absenteeism per each Classes II and III obese worker annually [132].

Poston et al. [133] examined the relationship between obesity and missed work days due to injury in a large group of male, career firefighters in the Midwestern United States. Obese firefighters missed between 2.7 and 5 times (depending on obesity class) the number of days due to injury when compared to normal weight firefighters, even after adjustments for potential confounders. They also computed the economic costs of absenteeism for firefighters who were at increasing levels of overweight and obesity compared to normal weight firefighters. When compared to normal weight firefighters, the additional costs to fire departments because of the greater missed days of work after injury in firefighters who were overweight, Class I obese, and Classes II and III obese combined were estimated to be $74.41, $254.00, and $1682.90 per firefighter, respectively [133].

Finkelstein et al. [125] evaluated the costs associated with presenteeism and absenteeism both at the level of the individual worker and then extrapolated aggregate costs for all workers in a sample of over 32,000 full-time workers. Average incremental annual costs per worker for absenteeism and presenteeism associated with obesity were estimated to be $1960 and $5193 for obese male workers and $1736 and $5393 for obese female workers, respectively. Extrapolated to all workers, obesity was estimated to cost employers 12.8 and 30.0 billion dollars for productivity losses associated with absenteeism and presenteeism [125].

Disability and Premature Mortality

Disability costs, for both short and long term, result from salary continuation benefits, insurance policies, and government programs (e.g., workers' compensation claims) allowing employees time away from work due to illness or injury for periods of time longer than allowed for typical sick leave [121,126]. Premature mortality refers to the lower projected life expectancy experienced by obese workers when compared to nonobese individuals

leading to lost productivity during working years and increased life insurance premiums and payouts [121,126].

Several studies have focused on estimating costs associated with disability and premature mortality. Disability studies usually focus on evaluating costs associated with time away from work that involved disability claims or payments while premature mortality studies estimate the value of years of life lost related to obesity [121,126]. For example, both Dor et al. [121] and Trogdon et al. [126] reviewed several studies and concluded that obesity was consistently a significant predictor of disability, and for studies in the United States, the costs associated with disability for obese individuals were substantial. For example, Soteriades et al. [134] prospectively evaluated risk of any type of short-term or permanent disability in a group of male firefighters over more than 6 years. They found that obesity predicted which firefighters would receive disability; each BMI unit increase was associated with a 5% increase in the likelihood a firefighters would be disabled. Annual costs of short-term disability for a number of studies were computed by Dor et al. [121] and they estimated that when compared to normal weight employees, obese employees' disability costs were $349 per employee.

Other investigators examined the relationship between obesity and Workers' Compensation claims and found that there was significant association between increasing BMI and number of claims [135]. For example, Classes I–III obese individuals had 8.8, 10.8, and 11.7 claims per 100 fulltime equivalents (FTEs) compared to only 5.8 for normal weight workers, respectively. Not surprisingly, this greater number of claims resulted in greater medical and indemnity (i.e., income replacement) claims costs. For example, the total estimated medical and indemnity claims costs for obese workers totaled to $94,125 and $117,107 per 100 FTEs, respectively. The same claims costs for normal weight workers were only $7503 and $5396; thus the excess cost due to obesity was substantial.

Premature mortality, as years of life lost, has been quantified by Fontaine et al. [136] using national data, which were then converted into cost estimates by Dor et al. [121]. For example, they estimated that obesity resulted in a total loss of income of $468,333 and $376,667 for white men and women, respectively, and that the gender difference is partly a function of the fact that obese men have a lower life expectancy than obese women. Other studies estimate the costs of lost earnings in the United States due to obesity to be approximately $30 billion dollars [126].

SUMMARY

The prevalence of obesity is alarmingly high and the trajectory of this epidemic is uncertain. The drivers of the proposed causal factors are complicated; thus, interventions to curb this epidemic are not in place. The economic and health implications of a continued rise in this obesity epidemic are staggering. An immediate global effort is needed with systematic approaches involving governments, businesses, and individuals.

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42 Exercise Management for the Obese Patient

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CONTENTS

Introduction 529
Effect of Physical Activity on Weight Loss 529
Cardiovascular (Aerobic) Activity 529
Resistance Exercise 530
Lifestyle Activity 530
Physical Activity Combined with Reductions in Energy Intake 530
Role of Physical Activity in Surgically Induced Weight Loss 531
Weight Loss Variability in Response to Physical Activity 531
Biological Factors 531
Influence of Physical Activity on Other Components of Energy Expenditure 531
Influence of Physical Activity on Energy Intake 531
Factors Influencing Adherence to Physical Activity 531
Physical Activity, Fitness, and Health Outcomes 532
Effects on Mortality 532
Effects on Risk Factors for Cardiovascular Disease 532
Blood Pressure 532
Lipids 533
Inflammatory Markers 533
Summary 533
References 533

INTRODUCTION

Overweight and obesity are significant public health problems in the United States and other countries throughout the world. Within the United States, the age-adjusted mean body mass index (BMI) was 27.8 kg/m^2 in men and women ≥20 years of age in 2009–2010 based on data from the National Health and Nutrition Examination Survey (NHANES) [1]. Based on the NHANES data [1], the age-adjusted prevalence rates for overweight (BMI ≥ 25.0 kg/m^2) and obesity (BMI ≥ 30.0 kg/m^2) are 68.8% and 35.7%, respectively. Moreover, the age-adjusted percentage of adults with a BMI ≥ 35.0 kg/m^2 or BMI ≥ 40.0 kg/m^2 is 15.4% and 6.3%, respectively. These prevalence rates are of significant public health concern because of the association between many chronic diseases and excess body weight [2]. Thus, interventions are needed to reduce body weight in overweight and obese patients, and the cornerstone of these interventions is behavioral programs that focus on reducing energy intake and/or increasing energy expenditure.

EFFECT OF PHYSICAL ACTIVITY ON WEIGHT LOSS

Cardiovascular (Aerobic) Activity

Physical activity has been recommended as a key behavior within interventions that target overweight and obesity [2]. However, the effects of physical activity on weight loss, when not coupled with a concurrent reduction in energy intake, appears to be modest. For example, average weight loss of 2% at 6 months and 1% at 18 months was reported in a study of overweight adults who were prescribed home-based physical activity without a prescribed reduction in energy intake [3]. Others have reported a similar magnitude of weight loss for interventions lasting 3–6 months that also focused on physical activity without prescribing a reduction in energy intake [4,5]. This is also consistent with the 0.5–3.0 kg weight loss in response to 180–270 min/week of physical activity that was reported in the 2008 Physical Activity Guidelines Advisory Committee Report [6]. However, there may be a dose–response effect, with

the magnitude of weight loss increasing as dose of physical activity increases. For example, a systematic review of the literature conducted for the 2009 Position Stand of the American College of Sports Medicine (ACSM) [7] concluded that there was no significant change in body weight in response to <150 min/week of physical activity, whereas 2.0–3.0 and 5.0–7.5 kg are observed with >150 and 225–420 min/week of physical activity, respectively.

Resistance Exercise

While the majority of research related to the effect of physical activity, in the absence of restrictions in energy intake, has focused on cardiovascular (aerobic) forms of physical activity, there is a body of literature on the effects of resistance exercise on weight loss. It has been proposed that resistance exercise may influence body weight by increasing lean mass that will results in an increase in resting metabolic rate (RMR), increase strength that will result in an increase in free-living physical activity, and increase total daily energy expenditure from performing the resistance exercise [7]. However, numerous systematic reviews have concluded that resistance exercise has a modest influence on weight loss when performed in the absence of reductions in energy intake [7,8]. While it is possible that the resulting increase in lean mass that is proposed to occur with resistance exercise may offset the reductions in fat mass causing absolute weight to remain relatively unchanged [9–12], it should not be expected that energy expenditure from resistance exercise will be sufficient to result in significant reductions in body weight over a period of 3–6 months, with limited data available from longer-term studies to determine if this pattern would change with a longer intervention period [7,8]. Despite the lack of evidence that resistance exercise will result in significant reductions in total body fatness, resistance exercise may reduce subcutaneous abdominal adiposity [13]. Thus, the benefits of resistance exercise in the treatment of obesity may not be in reductions in total body fatness, but rather improvements in lean mass and strength, and the reductions in abdominal adiposity.

Lifestyle Activity

It has been recommended that nonstructured forms of physical activity can also contribute to increases in energy expenditure and should be a component of interventions for obesity. The term nonexercise activity thermogenesis (NEAT) is used to describe energy expenditure that does not result from sleeping, eating, or structured exercise [14]. A common methodology to increase NEAT is through the use of pedometers, with patients recommended to increase the number of steps walked. When this methodology has been used to promote an increase in physical activity, it has been shown that this results in an increase of 2100 steps/day, and this results in a modest decrease in BMI of 0.38 units [7], which is the equivalent of approximately 2.0–3.0 kg of weight loss. However, others have reported that a 12 week pedometer intervention increased steps by 3000/day; however, there was no association between steps walked and change in BMI, but there was an association between steps walked and change in waist circumference [15]. Thus, it may be necessary to combine the increase in energy expenditure resulting from NEAT with the increased energy expenditure resulting from structured forms of activity (exercise) to maximize increases in total energy expenditure, which can contribute to weight loss in overweight and obese adults.

Physical Activity Combined with Reductions in Energy Intake

It is commonly recommended that physical activity be combined with a reduction in energy intake for the treatment of obesity [2]. Examination of the evidence suggests that the addition of physical activity to an energy-restricted diet will result in an additional 2.0–3.0 kg beyond what is achieved with an energy-restricted diet alone. For example, [16,5] reported that the addition of physical activity to an energy-restricted diet increased weight loss at 6 months by 2.7 and 1.2 kg, respectively, above what was achieved with an energy-restricted diet that did not include physical activity. These results are similar to results reported by [4]. While this magnitude of additional weight loss appears to be modest, [17] have suggested that the combination of physical activity and an energy-restricted diet results in 20% greater weight loss than the weight loss achieved with an energy-restricted diet alone.

Physical activity may also be important for enhancing weight loss beyond the initial 6 months of treatment, improving long-term weight loss maintenance, and minimizing weight regain. An important observation is that relatively high levels of physical activity may be necessary to improve long-term weight loss [18–20]. We have contributed to the scientific literature supporting the need for physical activity to improve long-term weight loss. Results of a 24 month intervention in overweight and obese women showed that an increase in physical activity of 1500 kcal/week above baseline levels was associated with weight loss of 14.2 kg (16.8% of initial body weight), whereas significantly less weight loss was observed at 24 months with lower amounts of physical activity [21]. We estimated that the 1500 kcal/week of physical activity above baseline levels was reflective of approximately 275 min/week of brisk walking above what was being performed prior to the start of the 24 month intervention. Additional analysis of the data showed that physical activity was an important behavior in the ability to achieve an initial weight loss of ≥10% and to sustain this magnitude of weight loss at the conclusion of the 24 month intervention period [22]. This magnitude of physical activity is similar to what we have reported in other studies. For example, we

have reported 18 month weight loss of 13.1 kg in women who reported participating in an average of 280–300 min/week of physical activity throughout the entire intervention period, and this weight loss was significantly greater than the weight loss achieved when participating in lower amount of physical activity [23].

Role of Physical Activity in Surgically Induced Weight Loss

Bariatric surgery has become a popular, and effective, method in the treatment of obesity. However, unpublished data from our laboratory have suggested that many patients who have undergone bariatric surgery are not provided information to participate in physical activity, and when provided information related to physical activity, it is not consistent with public health recommendations for physical activity. This is of concern because there is a growing body of literature to support the need for physical activity in patients who have undergone bariatric surgery. For example, greater weight loss has been observed in bariatric surgery patients who participate in ≥150 min/week of physical activity compared to patients participating in <150 min/week [24]. This is consistent with other research showing improvements in weight loss at 6–24 months following bariatric surgery with the inclusion of physical activity [24–26]. Thus, health care professionals are encouraged to include physical activity as a component of a comprehensive treatment plan for patients undergoing bariatric surgery.

WEIGHT LOSS VARIABILITY IN RESPONSE TO PHYSICAL ACTIVITY

As described earlier, on average, modest weight loss on the magnitude of 0.5–3.0 kg is observed with physical activity. However, as reported by [27], there is significant interindividual variability observed in weight loss in response to physical activity. Thus, there is a possibility that physical activity may result in greater weight loss for some individuals than what is commonly reported in the literature. Moreover, it is possible that there will be differences in weight loss between individuals in response to participation in similar doses of physical activity. Bouchard et al. [28] reported that weight loss in response to 4 months of highly controlled exercise resulted in a range of weight loss equivalent to approximately 3.0–12.0 kg. Thus, it is important to consider factors that may contribute to this variability in weight in response to physical activity.

Biological Factors

Bouchard et al. [29] have suggested that there may be biological factors that contribute to the weight loss observed in response to physical activity. These investigators studied seven pairs of identical male twins examined over a period of 93 days in which energy intake was held constant and physical activity performed twice daily. Subjects were also monitored 24 h/day to minimize any variability in energy intake or physical activity. The results from this study showed that weight loss was similar within each pair of twins; however, weight loss was highly variable between pairs of twins. Thus, the variability in weight loss observed between individuals may have biological underpinnings.

Influence of Physical Activity on Other Components of Energy Expenditure

A state of negative energy balance in which energy expenditure exceeds energy intake is necessary to induce weight loss. It has been stated that physical activity is the most variable component of total energy expenditure, and therefore this component of energy expenditure may have the greatest influence on the ability to create this state of negative energy balance [30]. However, it has been suggested that physical activity may also influence other components of energy expenditure, namely RMR, which can further affect total energy expenditure. There appears to be an acute increase in RMR in response to physical activity, and chronic physical activity participation may be associated with a higher RMR [31]. This may be of importance for overweight and obese individuals because RMR tends to decrease in the presence of weight loss, which can decrease total energy expenditure and possibly affect weight loss and weight loss maintenance. However, even when physical activity is included as a component of the intervention, RMR has been shown to decline in response to significant weight loss [32]. Thus, health care and health-fitness professionals should refrain from promoting that physical activity will increase or at least prevent the decline observed in RMR with weight loss.

Influence of Physical Activity on Energy Intake

There is evidence of interindividual variability in energy intake in response to physical activity, and this may provide some evidence of why physical activity results in greater weight loss in some individuals compared to others. For example, in response to 50 min of physical activity, Finlayson et al. [33] reported a positive increase in energy balance in 50% of study participants. This is very similar to the findings of a study conducted in our laboratory in which 58% of participants consumed more calories following a 35–45 min period of activity compared to following a seated rest period [34]. This may suggest that for some overweight and obese adults, physical activity increases hunger and appetite, whereas in others physical activity may enhance satiety, which can influence energy intake.

Factors Influencing Adherence to Physical Activity

The variability in weight loss observed in response to free-living physical activity may also be a reflection of one's ability

to adopt and adhere to an adequate dose of physical activity to promote weight loss. It has been suggested that there may be genetic factors that contribute to physical activity participation [35–37]. However, there is also evidence of more traditional behavioral factors contributing to physical activity participation in overweight and obese adults. For example, we have previously reported that higher levels of physical activity self-efficacy are associated with higher levels of physical activity in response to a 6 month behavioral weight loss intervention [38], and recent unpublished data support the continued association between long-term physical activity participation and physical activity self-efficacy. Moreover, identifying and overcoming barriers to physical activity contribute to physical activity participation in overweight and obese adults [38,39]. This appears to suggest that overweight and obese adults need to engage in interventions to increase self-efficacy and to reduce barriers for physical activity. Thus, simply instructing overweight and obese adults to engage in physical activity without addressing the behavioral factors that are associated with physical activity may not be effective. This may require that health care and health-fitness professionals receive additional training in these areas of behavior change when treating overweight and obese adults and recommending physical activity as a component of the intervention plan.

PHYSICAL ACTIVITY, FITNESS, AND HEALTH OUTCOMES

In addition to the potential benefits of physical activity on weight loss, overweight and obese adults also realize significant improvements in cardiorespiratory fitness in response to engaging in sufficient amounts of physical activity. Numerous studies have shown that cardiorespiratory fitness improves only when physical activity is included as a component of the intervention program, and these improvements are present regardless of whether or not the intervention results in weight loss [40]. However, fitness does not improve significantly when weight loss is induced by energy restriction alone [40,41]. Thus, physical activity is an important component of interventions for overweight and obese adults that results in improved cardiorespiratory fitness. However, the magnitude of improvement in fitness depends on the dose of physical activity performed. For example, a dose–response relationship has been reported between the improvement in cardiorespiratory fitness and prescribed dose of physical activity in overweight adults across an 18 month intervention [3]. Church et al. [42] reported similar findings in response to 6 months of supervised physical activity in overweight and obese postmenopausal women [42]. Thus, these data support the need for clinicians to recommend physical activity to overweight and obese adults.

Effects on Mortality

An interesting observation is that the association between higher levels of cardiorespiratory fitness and reduced risk of mortality is present even when data are adjusted for level of adiposity. The findings reported by Blair et al. [43] showed an association between fitness and mortality, and this association remained even after controlling for level of BMI. Additional findings from the Aerobics Center Longitudinal Study have consistently supported the finding that a higher level of fitness remains an important factor in reducing the risk of mortality, and this effect appears to be independent of the influence of BMI [44–47] or body fatness [48,49].

Despite these findings, not all data support the contention that fitness will completely ameliorate the risk of a higher level of BMI or body fatness on these outcomes. A prospective examination of data from older men in the Veterans Exercise Testing Study found that both higher levels of cardiorespiratory fitness and a higher BMI were protective of all-cause mortality [50]. Data from the Lipid Research Clinics Study also suggest that both fitness and fatness contribute to risk of mortality [51]. These findings appear to suggest that interventions for overweight and obese adults should focus on both weight loss and improving fitness to elicit reduced risk of all-cause and cardiovascular disease mortality.

Effects on Risk Factors for Cardiovascular Disease

Cardiovascular disease is a leading cause of death, and results in significant health care costs, in the United States. As described earlier, cardiorespiratory fitness appears to at least partially contribute to reduction in cardiovascular disease mortality in overweight and obese adults. This may be a result of the influence of cardiorespiratory fitness on risk factors known to be associated with cardiovascular disease such as blood pressure, lipids, inflammatory biomarkers, and diabetes. However, as described in detail later, fitness may not completely eliminate the association between adiposity and these risk factors for cardiovascular disease.

Blood Pressure

It is commonly accepted that hypertension is a primary risk factor for cardiovascular disease. However, the combined influence of fitness and fatness on blood pressure appears to have mixed findings. For example, Rankinen et al. [52] have reported a significant association between BMI and risk of developing hypertension; however, this association was attenuated with cardiorespiratory fitness. Conversely, Chen et al. [53] reported that both BMI and cardiorespiratory fitness are associated with systolic blood pressure, yet when both variables were considered concurrently, BMI but not fitness continued to be associated with systolic blood pressure. Wing et al. [54] reported that both BMI and cardiorespiratory fitness were significantly associated with systolic blood pressure in women regardless of whether medication was being taken for blood pressure control. However, in men not taking medication for blood pressure control, BMI but not fitness was associated with systolic blood pressure. Thus, these findings appear to suggest that both BMI and fitness may be important for blood pressure control in overweight and obese adults, and both should be targets of clinical interventions.

Lipids

An abnormal blood lipid profile is considered a primary risk for cardiovascular disease. Because of the association between obesity and blood lipids [2] interventions that target obesity may also have a favorable influence on blood lipids. However, physical activity appears to have a modest influence on blood lipids in overweight and obese adults. For example, the results of a meta-analysis of studies that included overweight and obese adults concluded that total cholesterol was reduced by 3.4 mg/dL, LDL was reduced by 3.0 mg/dL, and HDL was increased by 1.6 mg/dL in response to physical activity interventions that did not include dietary restriction or result in significant weight loss [55]. This same meta-analysis reported that physical activity interventions significantly reduced triglycerides by 16.1 mg/dL in overweight and obese adults [55]. Church et al. [56] reported no influence of 4 months of exercise without concurrent caloric restriction on blood lipid parameters compared to a control condition.

When combined with caloric restriction, there are mixed results for the effect of physical activity on blood lipids. For example, Goodpaster et al. [16] reported that the addition of physical activity to an energy-restricted diet did not improve blood lipids when compared to the improvements observed with an energy-restricted diet without exercise in severely obese adults (BMI $\geq$ 35.0 kg/m^2) [16]. However, results from the CALERIE Study showed that when physical activity was added to calorie restriction, there were significant reductions in both total cholesterol and LDL-C, and these improvements were not observed with calorie restriction that did not include physical activity as part of the intervention [57].

Inflammatory Markers

It has been suggested that biomarkers of inflammation such as C-reactive protein (CRP), interleukin-6 (IL-6), tissue necrosis factor-α (TNFα), and the anti-inflammatory molecule adiponectin contribute to the prothrombotic processes of atherosclerosis [58]. Because of the impact of physical activity and cardiorespiratory fitness on other cardiovascular disease risk factors, one could hypothesize that physical activity and cardiorespiratory fitness would also have an influence on inflammatory markers that may contribute to cardiovascular disease. However, both Church et al. [56] and Nicklas et al. [59] have reported that physical activity does not improve the markers of inflammation. Moreover, Hamer and Steptoe [60] reported no association between cardiorespiratory fitness and measures of inflammation. Thus, physical activity may not be the optimal therapy for improving measures of inflammation that can reduce cardiovascular disease risk in overweight and obese adults.

SUMMARY

Physical activity is recommended as a component of comprehensive interventions for weight loss in overweight and obese adults. Physical activity can contribute to modest short-term weight loss of approximately 0.5–3.0 kg and can also enhance weight loss when combined with a reduction in energy intake. Moreover, physical activity appears to be important for enhancing long-term weight loss and prevention of weight regain following initial weight loss. Of interest, physical activity also appears to be an important intervention component for individuals who have undergone bariatric surgery. Physical activity has also been shown to improve health outcomes beyond the effect that it has on weight loss, which further supports the need to promote physical activity in overweight and obese adults. However, there is significant interindividual response to physical activity with regard to weight loss that may be influenced by biological factors, the effects on other component of energy expenditure, the effects on energy intake, and factors that influence the adoption and adherence to a physically active lifestyle. Thus, health care and health-fitness professionals need to consider these factors when developing weight loss interventions and when recommending the physical activity for overweight and obese adults.

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43 Dietary Management of the Overweight and Obese Patient

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CONTENTS

Traditional Diets: Definitions 537
Medical Assessment for Weight Loss Treatment 538
Nutrition and Diet Assessments for Weight Loss Treatment 539
Dietary Intervention 540
Diet Composition 542
Evidence Related to Diet and Body Weight 542
Beyond Diet 543
The Future of Dietary Treatment 543
References 544

The dietary management of overweight (BMI of 25–29.9) and obese (BMI > 30) individuals is one of the greatest health care challenges today. During the past 20 years, there has been a dramatic increase in the rates of obesity with no state in America having a prevalence rate of obesity <20% [1]. Health consequences of obesity and medical costs associated with obesity continue to rise and have a significant economic impact on health care [2,3]. The growing global epidemic of obesity calls attention to its serious nature and treatment limitations as a continuing worldwide public health threat [4]. Obesity is now well-recognized as a disease that is rarely, if ever, cured [5,6]. Weight reductions of as little as 5%–10% of initial body weight produce significant benefits to health and are recognized as successful outcome measures [5].

There remains no doubt that weight management and maintenance of overall health are both related to the quantity and quality of food intake. The role of the diet in producing successful outcomes for the treatment and prevention of obesity are to: (1) provide essential nutrients to achieve and maintain optimal nutritional status; (2) produce an energy deficit to yield a reasonable weight loss or to provide sufficient energy to prevent further weight gain; and (3) provide enjoyment of eating while supporting healthy and sustainable eating patterns. Dietary management is essential for any treatment for obesity to succeed.

The most current treatment guidelines from the National Heart, Lung, and Blood Institute (NHLBI) categorize treatment strategies based on body mass index (BMI) and comorbidities [5]. For a BMI of 25–29.9 with comorbidities, weight loss is best achieved through diet, physical activity, and behavior change. Pharmacotherapy can be considered for BMI $\geq$ 30 kg/m^2 or with a lower BMI $\geq$ 27 kg/m^2 with a comorbidity. Bariatric surgery can be considered at a BMI $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with a comorbidity. Surgical interventions are reserved for patients who have failed less invasive interventions and are at high risk for obesity-related morbidity and mortality.

TRADITIONAL DIETS: DEFINITIONS

The major classification of diets for weight management has been based on the total level of energy in kilocalories (kcal) per day provided. Low-calorie diets (LCDs) are those which provide a caloric deficit of 500–1000 kcal/day aimed at achieving a weight loss of 1–2 lb/week and produce an average weight loss of 8%–10% of body weight over a period of 3–12 months. Balanced deficit diets (BDDs) have been defined as LCDs generally above 1200 kcal/day and are nutritionally adequate; they provide the essential nutrients by using a variety of well-chosen foods [5]. LCDs above 1200 kcal/day are generally safe. LCDs less than 1200 kcal/day may have different nutrient composition and should be used with caution since they may not provide the essential nutrients needed. It should be recognized that the majority of dieting individuals will embark on weight reduction regimens without professional advice and will engage in self-help forms of treatment, including books and/or organized commercial groups. Generally, these are safe for individuals without medical complications over the short-term and involve using a variety of individual approaches and diet fads currently in vogue.

Very low-calorie diets (VLCDs) are those that usually provide approximately 800 kcal/day (or 6–10 kcal/kg) and are considered to induce a modified fast [5]. Regular foods are replaced with specially formulated foods and/or drinks and supplements. Emphasis is placed on the provision of 40–100 g (or 0.8–1.5 g/kg of ideal body weight) of high biological value protein to meet minimum protein requirements. Up to 100 g of carbohydrates and 100% of the daily value of essential vitamins and minerals are also provided. Weight loss averages 20 kg over 12 weeks or approximately 3 lb/week [3,4]. Although initial weight loss is greater on VLCDs, overall long-term weight loss (>1 year) is not different from LCDs. In 1998, the NHLBI expert panel recommended against the use of the VLCD based on studies showing no differences in long-term success and greater weight regain. VLCDs are sometimes prescribed before bariatric surgery to reduce overall surgical risk due to higher compliance and results over the short-term. There may be other circumstances where VLCDs are recommended, but the duration of treatment is usually limited to 12–16 weeks and patients are carefully monitored. Recognizing LCDs as the dietary treatment of choice, this chapter will primarily focus on dietary intervention utilizing an LCD.

MEDICAL ASSESSMENT FOR WEIGHT LOSS TREATMENT

Before interventions are implemented, a medical history and examination along with a nutrition assessment should be performed. First, the patient should be categorized as overweight or obese and then matched with the treatment recommended for that level of BMI category, as shown in Table 43.1 [5]. It is important to note that diet, physical activity, and behavior change are recommended for all levels of BMI > 25. The medical history should query conditions associated with obesity such as symptoms of diabetes, cardiovascular disease, sleep apnea, and gallstones, in particular. Gathering family and social history is important to identify the patient's support networks and to identify other members of the household who are overweight and might also be targeted for intervention and/or support or assessed for behaviors that might be detrimental to success. Further, social pressures, environmental conditions, and situational factors that may impact the ability for the patient to lose weight should be identified and discussed with regard to how they might be barriers to success.

Acquiring medication history is also helpful because certain drugs can cause weight gain and should be identified. Medications for diabetes such as insulin, sulfonylureas, and thiazolidinediones can cause weight gain. Additionally, several psychiatric medications can also cause weight gain such as the antidepressants paroxetine (Paxil), fluoxetine (Prozac), and atypical antipsychotics such as clozapine (Clozaril), olanzapine (Zyprexa), and risperidone (Resperdal) [7]. Alternatively, the antidepressant bupropion (Wellbutrin) can cause weight loss [8].

It is critical to offer an appropriate office environment to accommodate overweight and obese patients. Some simple but important measures are to have larger chairs or chairs without arms, step stools near examination tables, large sized examination gowns, and larger sized blood pressure cuffs. The physical examination should be performed with attention paid to findings that are conditions associated with obesity. During the examination, the patient should be warned that rapid weight loss can increase the incidence of symptomatic gallstones and the area of the gallbladder should be pointed out to the patient. He or she should be warned to notify the physician if pain occurs in that area during the weight management treatment. Also, sensitivity to possible causes of weight gain (such as water retention) should be explained to the patient and assessed with them so that temporary incidents of weight gain will not be discouraging.

Medical causes for obesity should be carefully ruled out. If a patient has fatigue, weight gain, constipation, and cold intolerance, a TSH and Free T4 can be measured to rule out hypothyroidism. Cushing's disease is rare and is suggested by the physical examination findings of moon face or buffalo

TABLE 43.1
Guide for Selecting Treatment

	BMI Category				
Treatment	**25–26.9**	**27–29.9**	**30–34.9**	**35–39.9**	**≥40**
Diet, physical activity, and behavior change	With comorbidities	With comorbidities	+	+	+
Pharmacotherapy		With comorbidities	+	+	+
Surgery				With comorbidities	+

Source: National Heart, Lung, and Blood Institute (NHLBI) and North American Association for the Study of Obesity (NAASO). The practical guide to the identification, evaluation, and treatment of overweight and obesity in adults, National Institutes of Health, Bethesda, MD, Publication No. 00-4084, 2000.

hump. This can be assessed with a 24 h urine cortisol test, if suspected. In addition, a routine CBC to screen for anemia should be done. Importantly, for women, pregnancy should be ruled out before recommending a weight management regimen. For women who are pregnant, the Institute of Medicine has set guidelines for total and rate of weight gain during pregnancy by prepregnancy BMI. Any recommendations for weight gain during pregnancy should be individualized based on prepregnancy BMI to improve pregnancy outcome, avoid excessive maternal postpartum weight retention, and reduce risk of the child acquiring chronic disease later in life [9].

Other medical, psychological and/or physical conditions that may impair success for weight loss (i.e., terminal illness, severe psychiatric disorders, orthopedic problems, etc.) should be evaluated and documented and patient motivation should be considered. It is also helpful to establish the patient's readiness for current recommendations by assessing past dieting history, current physical activity limitations, and weight gain, particularly in the past 3, 6, and 12 months. Drastic changes from current lifestyle patterns without patient education and realistic commitment are typically unsuccessful. It may also be advantageous to assess the patient's weight history; in particular, highest adult body weight (HABW), lowest adult body weight (LABW), usual body weight (UBW) (within the last 6 months) and, finally preferred body weight (PBW). This information can help determine individualized goals for weight loss over time.

Nutrition and Diet Assessments for Weight Loss Treatment

The nutrition assessment begins with a measurement of BMI and waist circumference. First, height should be assessed using a wall-mounted stadiometer to obtain an accurate measurement. Next, weight should be assessed on a balance beam scale or a medical grade electronic scale with the patient wearing light clothing or a gown and without shoes. BMI is calculated as weight (kg)/height $(m)^2$ or if pounds and inches are used [weight(pounds)/height$(inches)^2$] × 703 or through the use of a BMI Calculator. For waist circumference, use a nonstretchable tape (7–12 mm wide) and measure the waist at the top of the iliac crest while the patient is standing with the tape placed in a horizontal plane around the abdomen parallel to the floor [10].

A personalized, patient-centered nutrition assessment also includes determining the appropriate energy level for maintenance of current weight. To calculate the patient's baseline total energy intake (TEI) or kcal/day needed to maintain their current weight, the total energy expenditure (TEE) for that individual must be estimated.

$$\text{TEI} = \text{TEE}$$

The TEE consists of three components including: basal energy expenditure (BEE), thermic effect of food (TEF) and an adjustment factor for the physical activity level (PAL).

$$\text{TEI} = \text{TEE} \quad \text{or}$$

$$\text{TEI} = (\text{BEE} + \text{TEF} + \text{PAL})$$

In practice, the resting energy expenditure (REE) is used in lieu of the BEE because it is impractical to measure energy expended in the basal state. The REE is considered to be ~10% above the basal state and is substituted for the more difficult to measure TEF, which is also approximately 10% of TEE.

$$\text{TEI} = \text{TEE} \quad \text{or}$$

$$\text{TEI} = (\text{REF} + \text{PAL})$$

To complete an estimation of TEE, the PAL must be estimated. Assess the patient's current activity level and apply the appropriate activity factor of REE × 1.2 (sedentary), × 1.4 (low active to moderate), and × 1.6 (active) (or 20%, 40%, and 60% above REE, respectively). Subsequent adjustments for intentional activity or exercise (such as walking, biking, dancing, or exercise routines, etc.) are added as individuals engage in these activities and can be adjusted per day or averaged per week. Evidence-based medicine (EBM) guidelines recommended by the Academy of Nutrition and Dietetics (AND) prioritize the estimation of energy needs based on resting metabolic rate or RMR (same as REE). It is recommended that RMR should be measured (e.g., indirect calorimetry) [11] whenever possible. New hand-held, medical devices for practical measurement of RMR/REE in the primary care setting have become available at reasonable cost. These devices measure inspired and expired airflow and use the Weir formula to estimate RMR/REE mainly from the oxygen consumed over time under standard pretest conditions at rest. These new devices have been demonstrated to correlate well ($r = 0.91$) with the more sophisticated, expensive instruments such as the standard Douglas Bag technique [12]. However, if measurement is not possible, RMR should be estimated using the most accurate formula found to predict RMR within ±10% of measured in most individuals, the Mifflin-St. Jeor Equation (MSJE) [11,13,14].

$$\text{Females}: 10\,\text{Wt (Kg)} + 6.25\,\text{Ht (cm)} - 5\,\text{age (years)} - 161$$

$$\text{Males}: 10\,\text{Wt (Kg)} + 6.25\,\text{Ht (cm)} - 5\,\text{age (years)} + 5.$$

The MSJE has been made available in computerized handheld devices for convenient access along with other tools including charts and wheels, which facilitate practical and user-friendly applications in the office setting (Table 43.2) [15].

Because TEI from food and beverages is difficult to assess in the office setting, patients can be instructed to bring in a food diary (1–7 days or a typical day) and TEI can be estimated with a quick review and focused

TABLE 43.2
Predicted Resting Energy Expenditure from Body Mass Index

	Age Range					
BMI	**18–29**	**30–39**	**40–49**	**50–59**	**60–69**	**70**
Women: Predicted REE (kcal/24 h) = (BMI × 28.15) − (Age × 6.44) + 905						
18	1260	1190	1125	1061	996	932
19	1289	1218	1153	1089	1024	960
20	1317	1246	1181	1117	1053	988
21	1345	1274	1210	1145	1081	1016
22	1373	1302	1238	1173	1109	1045
23	1401	1330	1266	1201	1137	1073
24	1429	1358	1294	1230	1165	1101
25	1457	1387	1322	1258	1193	1129
26	1486	1415	1350	1286	1222	1157
27	1514	1443	1378	1314	1250	1185
28	1542	1471	1407	1342	1278	1213
29	1570	1499	1435	1370	1306	1242
30	1598	1527	1463	1399	1334	1270
31	1626	1555	1491	1427	1362	1298
32	1654	1584	1519	1455	1390	1326
33	1683	1612	1547	1483	1419	1354
34	1711	1640	1576	1511	1447	1382
35	1739	1668	1604	1539	1475	1410
36	1767	1696	1632	1567	1503	1439
Men: Predicted REE (kcal/24 h) = (BMI × 28.15) − (Age × 6.41) + 1290						
18	1645	1575	1510	1446	1381	1317
19	1674	1603	1538	1474	1409	1345
20	1702	1631	1566	1502	1438	1373
21	1730	1659	1595	1530	1466	1401
22	1758	1687	1623	1558	1494	1430
23	1786	1715	1651	1586	1522	1458
24	1814	1743	1679	1615	1550	1486
25	1842	1772	1707	1643	1578	1514
26	1871	1800	1735	1671	1607	1542
27	1899	1828	1763	1699	1635	1570
28	1927	1856	1792	1727	1663	1598
29	1955	1884	1820	1755	1691	1627
30	1983	1912	1848	1784	1719	1655
31	2011	1940	1876	1812	1747	1683
32	2039	1969	1904	1840	1775	1711
33	2068	1997	1932	1868	1804	1739
34	2096	2025	1961	1896	1832	1767
35	2124	2053	1989	1924	1860	1795
36	2152	2081	2017	1952	1888	1824

Source: Harrington, M.E. et al., *Obes. Res.* 1997;5:17s. With permission.

discussion [16]. It has been determined that a 7 day food record is a representative of intake over 28 days ($r = 0.89$) [6] and can be combined with an activity record to serve as a baseline assessment on which to measure changes. Many obese individuals underestimate their intake and do not adequately describe their consumption on a recall basis. Thus, a 7 day prospective food record is recommended to be kept by all patients in as much detail as possible. This record should reflect the patient's "usual" diet prior to intervention and should also be sensitive to the pattern of eating (time, place, and occasion), portion size, and method of preparation. Patients should be instructed in detail how to keep the food record and counseled with regard to why it is important to establish a true baseline before any interventions. The 7 day food record should then reflect a good pattern on which to base any dietary interventions or recommendations for change.

Because food and nutrient intake are generally compromised in dieting individuals, a well-formulated multivitamin to provide 100% of the recommended daily allowance (RDA) should be considered, especially for those individuals at the lower intake levels (≤1200 kcal/day).

Access to food, food selection, and functional capacities for food preparation are key considerations to assess before outlining a treatment plan. Observing a patient's verbal and nonverbal cues is also important to assess as they may provide clues to confidence and self-efficacy in making changes. Furthermore, weight maintenance (±5 lb between any two points in time or ~3% of body weight) [31] should be considered when patients are resistant to weight loss and calorie deficit diets.

DIETARY INTERVENTION

Close collaboration with the patient will help to create a realistic diet plan that takes into consideration weight loss and adequate nutrition. The total energy intake is of central importance; however, reductions in intake are too often accompanied by a decline in essential nutrients and overall quality of the diet. A major outcome of dietary treatment should be a notable improvement in diet as evidenced by adherence to the dietary guidelines the majority of the time (or at least 4 days of the week) [17]. The adequacy of low-calorie diets that are not carefully selected poses particular concern for intakes of calcium, folic acid, and vitamin B-12. In addition, even overweight Americans not dieting have diets inadequate in calcium, potassium, vitamin D, and fiber [18].

The dietary intervention should begin with the patient's usual pattern in mind. The first goal is either to achieve caloric balance to maintain weight or to achieve a caloric deficit to accomplish a desired weight loss. The diet plan should build on the strengths of the patient's current diet and incorporate modifications necessary to manage comorbid conditions. An intervention plan can be made using the plate method (choosemyplate.gov), as outlined in Figure 43.1 or by examples of the 1200- and 1600-cal meal plans found in the Clinical Guidelines document [5]. Foods eaten that are out of proportion to the recommendations from the plate are then targeted for evaluation jointly with the patient. It is important to be realistic about what can be achieved and what weight loss can be expected. Thus, the usual food pattern derived from the 7 day food record can be used to begin recommendations for

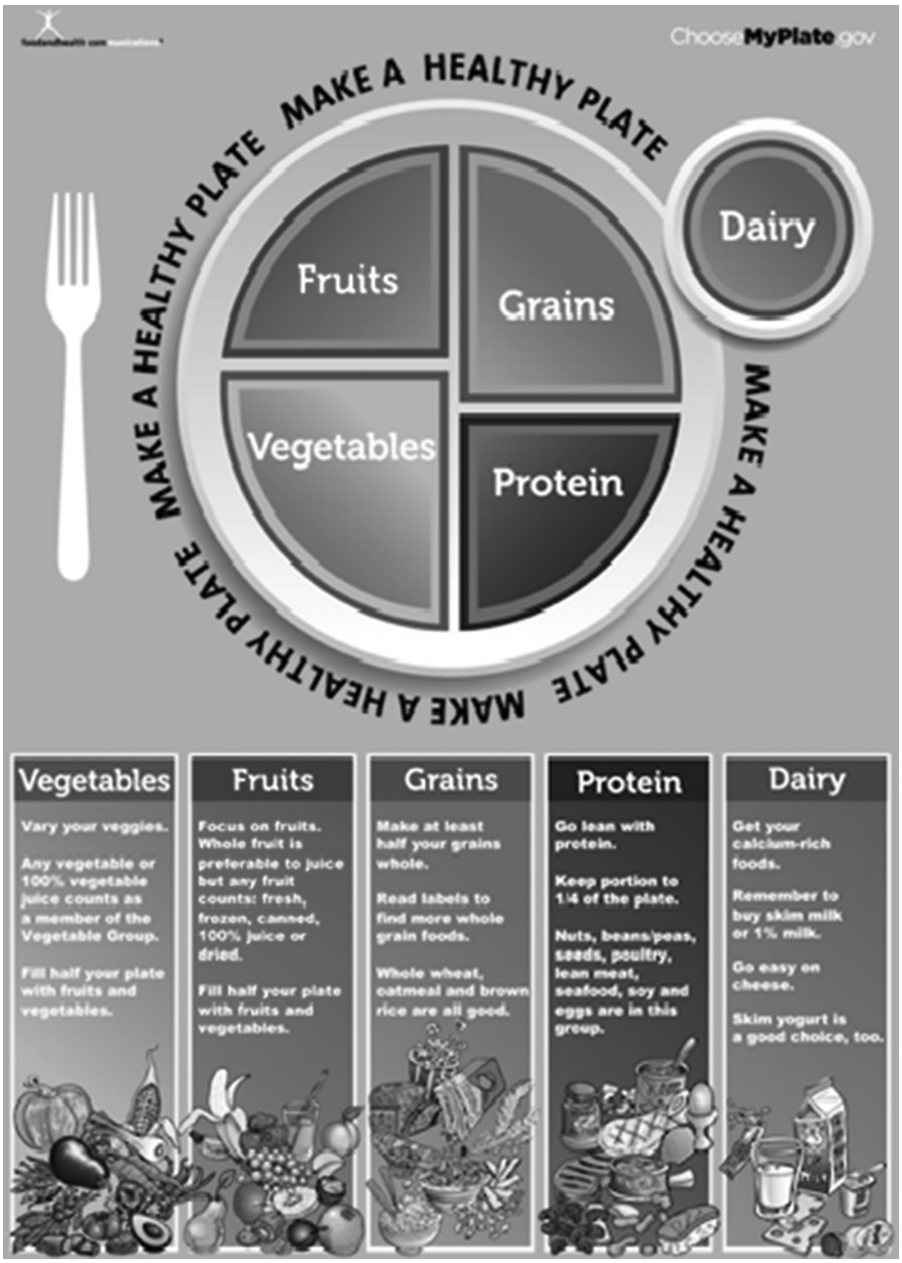


FIGURE 43.1 Foods and portions making up a healthy diet.

change (increasing or decreasing food groups, assessing portion sizes, changing or substituting foods especially of high caloric and/or high fat value, and changing eating patterns where feasible) in order to impose a practical deficit (250–1000 kcal/day in general) to attain a 0.5–2 lb weight loss/week using the approximation of −500 kcal/day = −1 lb/week.

In the past, it has been difficult for patients to monitor their daily caloric intake and diet composition. However, the ease and availability of online programs that can be used with smart telephones to record both caloric intake and nutrition composition may be very useful in achieving weight loss. These web-based programs allow the user to monitor progress toward goals for weight, food intake, and physical activity. Self-monitoring can also be achieved through traditional paper monitoring. Self-monitoring with these tools can be used to reinforce behavioral changes and to encourage adherence to prescribed dietary and activity changes. By simply asking a patient to record daily food and beverage intake or weekly weights or weight changes, simple changes can be encouraged, monitored, and assessed. The goal is to encourage small, incremental changes in behaviors toward a prescribed balanced deficit diet with increases in physical activity monitored by activity type and time or by counting steps through the use of a pedometer.

Food Record

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Breakfast							
Snacks							
Lunch							
Snacks							
Supper							
Snacks							

FIGURE 43.2 Sample food record.

DIET COMPOSITION

Although consensus was seemingly established around the efficacy of prescribing diets low in fat, the increasing incidence of obesity despite lower fat intakes in the United States has raised many questions regarding associated trends in low-fat diets and has shifted attention to total caloric intake [18]. In actuality, the ideal composition of the diet for weight loss and weight maintenance has not been established. Additionally, the advantages of different diets such as the Mediterranean diet, Asian diets, European diets, and American diets are currently being compared and published, leaving many health professionals confused regarding the diet composition to recommend. During weight reduction, it appears that the greatest impact of diet is from its total energy deficit, and the diet composition has little effect on the rate or magnitude of weight loss over the short-term [19].

The effect of diet composition on total energy balance through increased intake and/or increases in energy expenditure through the TEI need further study. Further, the role of fat intake on fat stores through selective oxidative processes and the genetic predisposition to gain fat and deposit fat centrally are important issues still to be addressed. Behavioral, psychological, and environmental factors also affect eating patterns and food intake, thus ultimately affecting diet composition. Additionally, physiologic stimulators as well as genetic factors may predispose the selection of foods higher in carbohydrates and/or fat. Thus, dietary patterns are highly individual and highly variable, resulting in unpredictable outcomes. Importantly, long-term compliance to dietary interventions is affected by how well the diet composition meets the most important of these established needs.

Studies have demonstrated the efficacy of meal replacements (liquids, bars, frozen entrees) in improving compliance with low-calorie diets and enhancing long-term successful weight management [20,21]. Meal replacements, which are generally formulated products such as shakes or portion controlled entrees, have value because they provide a regulated amount of calories per serving, are usually fortified with essential nutrients and fiber, and are economical, safe, and convenient to use. They also provide a departure from normal eating patterns and can serve as a venue for reeducation about and/or reformulation of what foods can be substituted or reintroduced.

EVIDENCE RELATED TO DIET AND BODY WEIGHT

Although not conclusive, the USDA Nutrition Evidence Library along with the Academy of Nutrition and Dietetics Evidence Analysis Library provide many clues to successful outcomes in the management of obesity [20,22]. In addition, the National Weight Control Registry (NWCR) provides insights on indicators of weight management success [23]. Current recommendations supporting successful weight loss outcomes include the following.

1. Meal replacements can be an effective tool because they are portion controlled, lower in calories, convenient and include foods of lower energy density.
2. Eating breakfast can be effective in controlling appetite, lowering the chances of overeating later in

the day. Breakfast eating is a key strategy for people who are able to maintain weight loss.
3. Three to four servings of low-fat dairy foods should be included to meet nutritional needs.
4. Total caloric intake should be distributed throughout the day, with the consumption of four to five meals, including breakfast.
5. Portion control should be included as part of a comprehensive weight management program.
6. Limited television screen time should be encouraged along with recommendations to increase physical activity overall.
7. Self-monitoring of intake, physical activity, and weight should be encouraged as an important part of a weight management program.

BEYOND DIET

Fat and sugar substitutes have a role in the dietary management of overweight and obese individuals primarily because they can potentially lower fat and caloric intake overall. However, it is important that they are used in the context of a regular diet, used in moderation and balance with other foods, are appreciated for total energy and nutrient value, and do not replace other nutritious foods [24,25]. Dietary supplements should be considered when eating patterns are compromised, erratic, limited in choices, or <1200 kcal/day [6]. Vitamin and mineral supplements should never be used in lieu of a healthy diet, and their use should be evaluated on a case-by-case basis. Meal patterns and food portion sizes are also deemed important in regulating dietary intake overall and should be evaluated as part of the dietary history and 7 day food records. Interventions should be focused on the total diet, eating patterns rather than specific foods, and obtaining nutrient adequacy through a variety of foods. Finally, the enjoyment of eating should not be overlooked, and flexibility in a meal plan must be included to maximize the potential for long-term adherence rather than short-term compliance.

THE FUTURE OF DIETARY TREATMENT

Diet fads come and go. There will always be a popular diet or dietary strategy that will seemingly monopolize the current marketplace. Education of consumers toward realistic goals, maintenance of a diet that complies with the dietary guidelines, and the rationale that there is no one food, nutrient, or strategy that will be uniquely successful will always be a major challenge. Fad diets usually emphasize: (1) large weight losses in short amounts of time; (2) the best or ideal macronutrient composition of the diet (fat, carbohydrate, or protein); (3) special attributes of a ingredient, food, or substance; (4) a rationale for a specific mechanism of a food or food combination that is preferred: (5) featured and/or structured meal plans and recipes; (6) foods or food combinations with special actions; and/or (7) a focus on why other diets do not work. Diet recommendations should be seriously evaluated with regard to efficacy, safety, and long-term effects. Although there can usually be some "half-truth" imbedded in any claims, the best way to evaluate a diet fad is by asking the following questions (all of which should be answered affirmatively) [26].

1. Is the diet well-balanced and does it include a variety of foods? Are all the major food groups included?
2. Does the diet impose a consistent caloric deficit or balance? Are the weight loss expectations reasonable? Is a safe weight: loss (0.5–3 lb/week) consistent?
3. Is a minimum of 50 g protein provided daily?
4. Is a minimum of l00 g of carbohydrate provided daily?
5. Are the meal plans practical, flexible, and individualized? Does the plan allow for special foods and preferences?
6. Is increased energy expenditure or physical activity emphasized without compensation by foods?
7. Are total kilocalories emphasized along with other aspect of the diet (fat, carbohydrate, protein, alcohol) in a totally integrated lifestyle change approach?
8. Are reasonable dietary goals established?
9. Is nutrition education provided?
10. Is positive behavior change for both diet and activity incorporated into the program?

Practical approaches that emphasize normalized eating patterns and a variety of foods as part of a long-term, integrated lifestyle should form the foundation of a solid dietary approach. Special efforts to maximize individual treatment considerations should be given when the dietary management includes attention to adjunctive therapies, such as pharmacotherapy or pre- or postsurgical interventions for weight loss and/or special dietary needs for the management of obesity-related conditions, such as diabetes, hypertension, and cardiovascular diseases. Caution should be taken to ensure adequate intake because some patients may compromise their intake because of increased motivation to new treatments, such as pharmacotherapy, and lose weight more rapidly than anticipated.

Weight loss of 5%–10% of body weight is significant and yet low-calorie diets are not appropriate for everyone. Pregnant and lactating women, those with eating disorders, and patients who have illnesses that can be negatively impacted by a caloric reduction require further evaluation before undertaking weight loss. In addition, caution and expertise is needed when reducing caloric intake of children. Implications for the treatment of obesity for people over the age of 65 is controversial and requires careful assessment and follow-up for protein adequacy and changes in body composition to prevent muscle loss and its consequences [27].

The future of dietary treatment for obesity includes innovation to meet these new challenges and emphasis on

maintenance of weight lost or the prevention of weight gain/regain. A seven-step process is recommended before initiating any dietary treatment for obesity [28].

1. Establish and assess BMI and related risks (waist measurements for men >40 in. and women >35 in.)
2. Assess weight-related comorbidities (diabetes, hypertension, cardiovascular diseases), medications, readiness to diet, and any contraindication to a low-calorie diet (pregnancy, cancerous cachexia, and other debilitating diseases) or Asian male >35 in. and women >31 in.
3. Calculate and evaluate REE from BMI
4. Estimate level of activity and usual activity
5. Estimate dietary intake and/or establish a dietary intake pattern
6. Project energy balance and prescribe a level of energy deficit and other dietary parameters
7. Develop long-term, practical dietary strategies, and individual goals with individuals to prevent weight gain or regain utilizing ±5 lb (or 3% of BW) as an indicator of significant change [29,30].

Thus, as we begin to better assess the needs and future directions for the dietary management of the obese, as well as overweight individuals, we can project important successful outcomes that take time and effort. Short-lived, unhealthy diet fads should be avoided, and emphasis should be placed on practical interventions that support health and the enjoyment of eating.

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44 Pharmacological Management of the Obese Patient

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CONTENTS

Introduction 548
Obesity: A Serious Condition 548
Obesity Treatment 548
Mechanisms of Action and Categories for Obesity Drugs 549
Reduction of Energy Intake 549
Centrally Active Serotonergic Agents 549
Centrally Active Adrenergic Agents 549
Enzyme Inhibitors 549
Increase in Energy Expenditure 549
Altering the Set Point/Settling Point 550
Food and Drug Administration-Approved Obesity Drugs 550
Orlistat (Xenical) 550
Drugs Approved for Short-Time Use 551
Phentermine 551
Diethylpropion 551
Mazindol 551
Drug Combinations 551
Off-Label Drug Use 552
Antidepressants 552
Fluoxetine 552
Bupropion (Wellbutrin) 552
Antiseizure Drugs 553
Topiramate (Topamax) 553
Zonisamide (Zonegran) 553
Atomoxetine 553
Antidiabetic Drugs 553
Metformin 553
Acarbose 554
Exenatide 554
Amylin 554
Pramlintide 554
Ephedrine with Caffeine and/or Aspirin 554
Nonprescription Medications for Obesity Treatment 555
Food and Drug Administration Approved 555
Ephedra 555
Laxatives 555
Phenylpropanolamine 555
Dietary Supplements 555
Fat Substitutes for Weight Loss 556
Drugs Awaiting FDA Approval 556
Lorcaserin 556
Contrave 556
Qnexa 556

Candidates for Developing Obesity Drugs 557
Cannabinoid Antagonists 557
Ciliary Neurotrophic Factor 557
Leptin 558
Neuropeptide Y 558
Human Growth Hormone 558
Dehydroepiandrosterone 559
Testosterone/Dehydrotestosterone 559
Gastrointestinal Pathway Drugs 560
Cholecystokinins 560
Glucagon-Like Peptide 560
Liraglutide 560
Ghrelin 560
Peptide Y Y 561
Who Should Receive Pharmacotherapy for Obesity? 561
Which Drug to Choose 562
Clinical Considerations for FDA-Approved Obesity Drugs 562
How to Use Phentermine and Orlistat: An Opinion 562
Weight Regain and Pharmacotherapy 563
Obesity Drugs Use: Various Approaches 563
Obesity Drug Needs and the FDA: An Uneasy Relationship 564
Summary and Conclusions 564
References 565

INTRODUCTION

Obesity: A Serious Condition

The prevalence of obesity continues to rise globally. Based on the body mass index (BMI) calculated from measured heights and weights, the 2007–2008 National Health and Nutrition Examination Survey (NHANES) noted a high prevalence of overweight (BMI 25.0–29.9 kg/m^2), obesity (BMI 30.0 kg/m^2 or greater), and extreme obesity (BMI 40.0 kg/m^2 or greater) to be 34.0%, 33.8%, and 5.7%, respectively [1].* Previous NHANES surveys were conducted about every 4 years with at least 1 year between survey periods. Beginning in 1999, NHANES became a continuous survey. There is an increase in obesity between the late 1980s and today, with an estimated age-adjusted prevalence moving from a previous level of 23% in NHANES III (1988–1994) to approximately 34% in 2007–2008. The World Health Organization (WHO) estimates that over one billion people are overweight globally, and that if current trends continue, that number will increase to 1.5 billion by 2015.† It is estimated that there are more than 475 million obese people worldwide.‡

Obesity promotes numerous medically significant comorbidities such as diabetes mellitus, hypertension, dyslipidemia, sleep apnea, several cancers, and gall bladder disease, all of which contribute to the increase in morbidity and mortality, particularly in younger individuals [2–5]. It has been estimated that more than 300,000 people die each year from obesity-related diseases in the United States [6,7]. Therefore, measures to prevent and treat obesity are urgently needed.

Obesity Treatment

Historically, clinical treatment of obesity has focused on calories and macronutrient intake, and lifestyle modification, but has recently evolved to include drug therapy and bariatric surgery. Although each component claims efficacy, a successful treatment of obesity often needs more than just a single approach. Combinations of some of these components are recommended for maximum weight loss and successful maintenance.

Physicians have often been reluctant to prescribe antiobesity drugs. In the past, this was due to the addictive potential of amphetamines (which are no longer used as obesity drugs) and the belief that obesity drugs do not work in the long term. Currently available obesity drugs approved for short-time use can be effective, and drugs approved for long-term weight loss usage usually produce less impressive, but medically effective, weight loss in the long run. Some people, including some physicians and health care professionals, seem to believe that obese people have little or no personal control over their eating and behavior patterns and attitudes about their weight control. This leads to a misconception that a simple change in patient's attitude and behavior is all that is necessary to achieve medically needed weight loss. Furthermore, since obesity is perceived to be a self-imposed issue, drug side effects of any degree are considered unacceptable for treating this "behavioral" condition. It is hard to achieve successful weight management for the majority of the obese population if the option of drug therapy is underutilized due to misconceptions.

* National Health and Nutrition Examination Survey 2007–2008. http://www.cdc.gov/nchs/nhanes.htm
† http://www.who.int/mediacentre/news/releases/2005/pr44/en/
‡ International Obesity Task Force, http://www.iaso.org/iotf/obesity/obesitytheglobalepidemic.

This environment has created reluctance on the part of some physicians to use obesity drugs. Research from past several decades has revealed that lifestyle modification alone as a treatment for obesity may help some individuals, but is inadequate to bring about the changes at the community level or to stop the global obesity epidemic. Concerted efforts are required from various angles to prevent or treat obesity and this includes the use of pharmacological agents to supplement the weight loss efforts of individuals. New discoveries on the genetic and chemical basis for obesity [8–12] have led to a rapid expansion of research on obesity drugs. Obesity experts and primary care physicians have a renewed and intensified interest in the drug industry, together with the support of the Food and Drug Administration (FDA), to develop new and more effective obesity medications for the acute and long-term management of obesity and weight maintenance. Many obese adults will have tried several self-help approaches available through advertisements, social media, and on the advice of friends and family before consulting with their physicians for advice about their unhealthy weight. Some patients feel that their doctors are both too busy, and lack the expertise and perhaps the compassion to help them [13]. The public awareness is increasing about the medical and lifestyle consequences of being an obese individual. There is no obvious cure in sight. The medical profession needs to be at the forefront to treat patients with obesity. This chapter will discuss mechanisms of action of obesity drugs, theories of altered body defense of body weight, FDA-approved drugs, off-label use, over-the-counter (OTC) medications and diet supplements, fat substitutes, drugs awaiting FDA approval, compounds under development, drug combinations, approaches to the drug management, and the role of the FDA.

MECHANISMS OF ACTION AND CATEGORIES FOR OBESITY DRUGS

In obesity, body stores excess energy in the form of fat. A period of negative energy balance is required to reduce this excess body fat. This can be accomplished either by a reduction of food intake or an increase in energy expenditure (EE). Pharmacologic agents act by various mechanisms on this energy balance equation but mainly focus on reducing energy intake. Maintenance of energy balance is so critical to survival that there are many redundant mechanisms that influence food intake and EE [14]. Numerous areas of the brain, participate in the regulation of energy balance and they respond to different neurotransmitters. Most of the drugs currently approved for the treatment of obesity in the United States act on two of the more important neurotransmitters systems to regulate energy balance: the centrally acting serotonergic and adrenergic systems. Some other drugs reduce energy intake by reducing the digestibility and absorption of macronutrients.

Reduction of Energy Intake

Energy intake may be reduced in several ways. All currently FDA-approved obesity drugs except orlistat are thought to reduce appetite or hunger, increase satiety, and modify food-seeking behavior [15–17]. There is some evidence that obesity drugs may alter dietary preference for fat or carbohydrates but this evidence is limited. By using obesity drugs selectively, patients may be better equipped to regain control over eating behaviors and possibly more compliant with behavior and lifestyle changes that are needed for a long-term change in body weight.

Centrally Active Serotonergic Agents

Centrally active serotonergic agents are DEA class IV drugs that prevent the reuptake of serotonin in the neural clefts. Studies suggested [18] that serotonin may reduce cravings for carbohydrates. Sibutramine (Meridia) is a serotonin agonist drug that was FDA approved in 1997 and withdrawn in 2010 after an FDA review. Currently there are no drugs available in this class that are FDA approved for obesity. There are however, serotonin reuptake inhibitors approved by the FDA as antidepressants (fluoxetine [Prozac] and sertraline [Zoloft]), which have some potential to produce weight loss [19]. These drugs are not FDA approved for obesity management.

Centrally Active Adrenergic Agents

Centrally active adrenergic agents are DEA schedule class IV drugs that includes phentermine, diethylpropion, and mazindol. The schedule IV obesity drugs have minimal addiction or abuse potential and are the most prescribed adrenergic drugs for obesity in America [20]. These adrenergic agents either stimulate the secretion of norepinephrine from the central nerve terminals (phentermine and diethylpropion) or inhibit its uptake (mazindol), thus leading to actions on food intake and EE.

Schedule III drugs include benzphetamine, chlorphentermine, clortermine, and phendimetrazine. They are rarely used by most physicians to treat obesity, since their abuse potential is higher than the more favored and low-risk schedule IV drugs. Schedule II drugs are only used in extremely rare circumstances due to their significant abuse potential. They do not produce more weight loss than the schedule III or IV agents and should be used only with extreme caution. These drugs include dexamphetamine, methamphetamine, and phenmetrazine.

Enzyme Inhibitors

As a class they act by reducing the intestinal absorption of nutrients. Prescription orlistat (Xenical) and OTC orlistat (Alli) are the only FDA-approved drugs for obesity management in this class.

Increase in Energy Expenditure

Animal and human studies suggest some obesity drugs may act by increasing energy consumption, by increasing the resting metabolic rate (RMR), or through increased thermogenesis

induced by diet, cold, or exercise. Another mechanism is to stimulate physical activity through tremors or spontaneous physical activity but this literature is controversial [16,21]. Anecdotally, patients on obesity drugs report an increase in willingness to exercise and are comfortable when active but there have been no studies to clearly document this phenomenon or to attribute it to drug action. The FDA-approved drugs phentermine, diethylpropion, and mazindol fall in this category. The drug combination of ephedrine and caffeine with or without aspirin increases RMR probably by stimulating β-adrenergic receptors [22,23].

Most clinical trials that use obesity drugs also include behavioral therapy including a focus on increasing activity. The independent contribution of medications on increasing EE is difficult to determine in these trials.

Altering the Set Point/Settling Point

Since the 1980s, researchers have theorized that obesity drugs may reduce the level at which body weight is defended. This has raised the question of a "set point" theory. The set point theory holds that the body has a complicated homeostatic feedback system for controlling body fat stores [24–26]. There is also the concept of a "settling point," a defense of body weight, which is a confluence of many factors that have an effect body weight [27]. Weight loss lowers the metabolic rate [26]. Weight regain appears to be caused by additional factors besides variations in metabolic rate [28]. It has been argued that treatment with obesity drugs reduces body weight and this reduction is maintained despite the lower metabolic rate [16].

FOOD AND DRUG ADMINISTRATION-APPROVED OBESITY DRUGS

The majority of obesity drugs currently on the market are centrally active adrenergic drugs and were FDA approved when the FDA only required short study periods for approvals. Reviews in 1976 and in 1992 of over 200 studies of antiobesity drugs concluded that all of the antiobesity agents produced similar results [17,29]. The average weight lost in these reviews was about one-half pound per week greater than placebo [17,29]. The centrally acting serotonergic drug sibutramine was approved in 1997 as a long-acting antiobesity treatment but was removed from market by the manufacturer after FDA review in 2010. In 2001, the FDA approved the enzyme inhibitor orlistat for long-term use and was approved for OTC use at a lower dose in 2007. This was the last time the FDA has granted approval for a new drug for the pharmacological management of obesity.

Orlistat (Xenical)

Orlistat (Xenical) is a gastrointestinal (GI) lipase inhibitor acting through inactivating intestinal enzymes and partially inhibiting the digestion of fat. This action results in a decrease in fat absorption and energy intake, and the promotion of malabsorption [30–33]. Fat absorption can be reduced by approximately a third, in subjects eating a meal containing 30% fat. Less than 1% of this peripherally acting drug is absorbed. GI side effects can occur in up to 40% of patients. Malabsorption can result in diarrhea, fecal incontinence, or urgency, oily stool, anal leakage, bloating abdominal pain, and gas. There may be the need for fat-soluble vitamin replacement. Higher dietary fat content increases the likeliness of GI adverse events [34]. In a 2 year Orlistat study, drug-treated subjects lost nearly 10% body weight in the first year compared to 5%–6% weight loss in the placebo group [34]. Study dose of orlistat was 120 mg three times a day (TID). There was about a 4 lb weight regain during the second year in the treatment group versus 8 lb in the placebo group. This signified a sustained weight reduction in study year 2. Orlistat also partially inhibits the digestion of triglycerides. During the study fasting low-density lipoprotein cholesterol and insulin levels improved. Some lipid values improved more than can be explained with weight reduction alone. Lipid-soluble vitamins A, D, and E and β-carotene concentrations may be slightly reduced after treatment orlistat. Some nutrients and some medications might have decreased absorption. The antihypertensive agents, warfarin, and oral contraceptives concentrations are not affected by orlistat [34–36].

In studies of obese subjects with or without type 2 diabetes, orlistat demonstrated an improvement in glucose metabolism and a reduction in high blood pressure [37,38]. In a 3 year orlistat weight maintenance study, there was no change in eating behavior, except in a subgroup that selectively decreased their intake of fatty foods. The subgroup had an enhanced weight maintenance, which the study authors ascribed to a change in fat consumption behavior [39]. Education on lowering dietary fat consumption is needed for maximizing weight loss with the help of orlistat.

A 3 year Orlistat study involved 383 adults who had abdominal obesity and metabolic risk factors, including dyslipidemia, impaired fasting glucose, and diet-treated type 2 diabetes. The study aim was to investigate the effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet (VLED). Subjects who lost at least 5% of their body weight (309 of 383 subjects) were then randomized to receive lifestyle counseling together with a placebo or orlistat 120 mg TID for 3 years. Study results identified that compared to the placebo group, orlistat plus lifestyle intervention resulted in an additional 2.4 kg weight loss after VLED and a reduced occurrence of type 2 diabetes for up to 3 years. The study authors concluded that orlistat may be a useful adjunct to conventional dietary and lifestyle treatment of high-risk obese subjects [40].

Another study examined the effect of orlistat on eating behavior in a 3 year weight maintenance trial. Three hundred and six obese women and men (19–45 years old), were a part of the Scandinavian Multicenter study of obese subjects with the metabolic syndrome. Subjects were treated with orlistat after a VLED-induced weight loss and followed for the next 3 years in a maintenance program. Results

showed that dietary restraint increased and disinhibition, hunger, and binge eating decreased in orlistat and placebo groups in a similar fashion. The authors pointed out that these changes in eating behaviors are needed for successful weight maintenance [39].

In 2007, FDA approved orlistat as an OTC obesity drug for adults. The commercial name is Alli. The dose is 60 mg TID and should be taken in conjunction with a reduced calorie and low-fat diet. Exercise and a multivitamin are also recommended. Side effects of the OTC orlistat are similar to prescription orlistat. See OTC obesity drug section for further details. The FDA has received reports of rare cases of severe liver injury in the use of orlistat by prescription or the OTC use. In response, the FDA has added a drug label.*

Drugs Approved for Short-Time Use

Phentermine

Phentermine is the most commonly prescribed obesity drug in the United States. The FDA approved phentermine for short-term treatment of obesity in 1959. It is a centrally active adrenergic drug, a sympathomimetic amine that stimulates norepinephrine release in synaptic terminals. With phentermine usage, patients can experience increased satiety and less of hunger, craving, binging, and nighttime eating. There are no recent studies with phentermine, but earlier studies show effectiveness and safety [41,42] including studies in combination with fenfluramine [43–46].

The popularity of phentermine over the other schedule IV drugs is most likely due to the long-term medical research and the subsequent clinical experience gathered with the drug combination of phentermine and fenfluramine [43–45]. Also, phentermine is associated with a rapid onset of appetite control and the improvement in patient attitude and weight management program adherence [43–45].

The most common side effects of phentermine include decreased appetite, dry mouth, headache, insomnia, irritability, nervousness, euphoria, palpitations, tachycardia, and an elevated blood pressure. Phentermine should be avoided in patients with active cardiovascular disease, moderate to severe hypertension, hyperthyroidism, agitated states, glaucoma, and a history of drug abuse. Drug abuse potential and addiction is reported as minimal [47]. There have been a few case reports of primary pulmonary hypertension in patients taking phentermine alone [48].

Phentermine is available as a 37.5 mg scored tablet and a 30 mg nonscored tablet or capsule form. These are also the maximum approved doses. Due to a possible association with valvular heart disease, fenfluramine was removed from the market by the FDA in 1997. Phentermine was not shown to contribute to valvular heart disease and was not withdrawn.

Diethylpropion

Diethylpropion is a centrally active adrenergic sympathomimetic agent with an action similar to phentermine. Diethylpropion is structurally similar to the FDA-approved antidepressant drug bupropion. Bupropion has been studied for its weight loss effect but is not FDA approved for weight loss and will be discussed in a later section [49]. Short-term studies [50] have compared diethylpropion to placebo in a 6 month trial where the diethylpropion-treated group lost 12.3% of initial body weight compared to 2.8% loss in the placebo group. In a 24 week study comparing continuous diethylpropion daily or every other month, the continuous therapy group was the most successful. Blood pressure reduction occurred in proportion to the weight lost [42]. Adverse effects included dry mouth, euphoria, asthenia, nervousness, decreased appetite, insomnia, and sleeplessness with frequent awakening. There was a delay of rapid eye movement (REM) sleep and increased time in stage 1 sleep [42]. In this study, the dropout rate was a high 82%. Diethylpropion is not recommended for patients with heart disease, high blood pressure, hyperthyroidism, or glaucoma. The recommended dose is 75 mg/day.

Mazindol

Mazindol is an FDA-approved drug for weight loss. It is a norepinephrine and serotonin reuptake inhibitor that has been withdrawn by the manufacturer from the U.S. market. There are no long-term double-blind placebo-controlled studies using mazindol but open-labeled long-term studies show significantly greater weight loss with mazindol, compared to the placebo group [51]. Side effects are similar to that of phentermine.

Drug Combinations

Currently, there are no FDA-approved combination drugs for obesity treatment. The FDA has disallowed three new drug requests for drug approval between November 2009 and January 2011, two of which are drug combinations. Historically, the only successful drug combination for obesity treatment was the combination of phentermine with the now-withdrawn drug fenfluramine. Fenfluramine, a serotonin agonist, and phentermine, an adrenergic agonist, were first reported in combination for obesity management in 1984, and then in 1992, a 4 year study was published [43,45]. Treatment in these studies included behavior modification, nutrition education, and exercise. Weight loss plateaued at 6 months with a 15.8 kg weight loss at the end of study year 1 [45]. After 3.5 years of treatment, the phentermine and fenfluramine (phen-fen) combination was discontinued, and at a 6 month follow-up, body weight returned to near-baseline levels, demonstrating the requirement of these drugs in maintaining weight loss. Side effects included dry mouth, fatigue, sweating, and insomnia. There were few dropouts due to side effects. A large phen-fen combination study included over 1300 subjects treated up to 2 years [43]. Weight losses of about 16 kg persisted for 2 years in subjects who continued on drugs.

Fenfluramine and dexfenfluramine were removed from the market by the FDA in 1997 due to a suspected association

* NIH Publication No. 07-4191 November 2004, Updated December 2010.

with fibrosis of the mitral and/or aortic heart valves resulting in regurgitation. It was initially suggested that the mechanism responsible was an increased level of circulating serotonin.

However, fenfluramine was not shown to increase the circulating serotonin and the exact mechanism responsible for the heart valve problems is unclear. No clear cases of heart valve problems due to phentermine alone have been reported and phentermine remains an FDA-approved drug, without valvular heart implications, for the short-time treatment of obesity.

When prescribing antiobesity medication, an echocardiogram may be indicated if a heart murmur or symptoms of dyspnea on exertion, easy fatigue, fainting, or chest pain are present, especially if a patient has previously been on the combination of phentermine and fenfluramine.

OFF-LABEL DRUG USE

The off-label and the investigational use of marketed drugs is defined by the FDA as follows; "Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner *when the intent is the "practice of medicine"* does not require the submission of an Investigational New Drug (IND) Application, Investigational Device Exemption (IDE), or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.*

The FDA also regulates how an approved medication can be promoted and advertised. There is no FDA restriction on physicians relying on their clinical experience in using an FDA-approved medicine for a condition, or a dose or duration that is different than that approved by the FDA. The National Institutes of Health document entitled "Prescription Medications for the Treatment of Obesity" reminds prescriber that for off-label determinations, there need to be a balance between a drug's known and unknown side effects and the potential added benefit of off-label use.† The medical needs of a patient in conjunction with a physician's knowledge of the complexity of obesity, should guide the decision for an off-label drug use. It is recommended that a careful and detailed review of the rationale for an off-label drug use should be documented in patient records. Each patient should be informed and educated as to why this drug is being prescribed and the patient's agreement to the treatment should be documented. It is recommended that such a document be signed and maintained in the patient's record.

Clinical evidence for the off-label use for obesity treatment is reported for the following medications.

Antidepressants

Fluoxetine

Fluoxetine (Prozac) is a highly selective serotonin reuptake inhibitor (SSRI) approved by the FDA as an antidepressant. It has been investigated for its weight loss effect. Weight loss has not been consistent in all clinical trials and patients who lost weight in the initial 6 months of the trial tend to regain weight despite the ongoing fluoxetine therapy [19,52,53]. In trials that contained a behavior modification component, significant weight loss at 1 year was reported [52,53]. The weight loss mechanism for fluoxetine is not well understood. The most common side effects of fluoxetine include anxiety nervousness, weakness, asthenia, decreased sexual desire or ability, loss of appetite, nausea, diarrhea, dizziness, drowsiness, dry mouth, flu-like symptoms, increased sweating, or trouble sleeping. Fluoxetine dosage for obesity treatment varied from 20 to 80 mg in clinical trials [19,52–54]. A 1 year study of fluoxetine for depression showed that weight loss occurs early in the fluoxetine group (20 mg) compared to no weight loss in the placebo group. Later in the study, both groups increased their weight, but the weight gain in the fluoxetine treated group was slower [55].

Interestingly, the study authors concluded that after depressive symptoms went into remission, weight gain in patients taking fluoxetine for long periods is not different from the placebo group and is most likely related to recovery from depression. A 6 month weight loss trial of obese subjects prescribed with fluoxetine (20–60 mg/day) and phentermine hydrochloride (from 18.75 to 37.5 mg/day) produced significant weight loss [56]. A phen-flu combination had been proposed as an alternative obesity treatment for the phen-fen combination. A retrospective chart review study compared the use of phen-flu in 97 subjects with those treated with phen-fen. They were all compared to obese subjects never treated with drug therapy. This was a 6 month open-label trial and all patients were seen at a university nutrition clinic. Results showed that the phen-flu group lost 9% weight loss, compared to 12.6% in the phen-fen-treated group. Echocardiograph assessments identified eight of 38 phen-fen subjects with cardiac valve lesions and none in the 15 phen-flu subjects or in the 25 non-drug-treated control subjects [57]. These results suggested that a fluoxetine combination therapy may be an alternative for phen-fen combination for obesity management.

Bupropion (Wellbutrin)

Bupropion (Wellbutrin) is FDA approved and indicated for the treatment of depression and smoking cessation. Bupropion is not related to the tricyclic antidepressants and is not an SSRI

* "Off-label" and investigational use of marketed drugs, biologics, and medical devices—Information sheet guidance for institutional review boards and clinical investigators: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm

† Prescription medications for the treatment of obesity. NIDDK. Weight Control Information Network. U.S. Department of Health and Human Services. National Institutes of Health NIH Publication No. 07-4191. November 2004. Updated December 2010.

but a norepinephrine, serotonin, and dopamine uptake inhibitor. It is effective in promoting weight loss in patients with or without depression [58,59]. Like fluoxetine, bupropion-treated subjects had varied weight loss results and the weight lost was maintained for as long as 1 year [58,59]. Bupropion dosage in clinical trials varied from 300 to 400 mg/day for a period of 26–48 weeks [58,59]. Side effects were reported as minimal. Most common side effects include agitation, weight loss, dry mouth, nausea, headache, constipation, dizziness, tremors, and tachycardia.

Antiseizure Drugs

Topiramate (Topamax)

Topiramate (Topamax) is an antiepilepsy drug that blocks sodium channels and enhances the neuroinhibition of γ-aminobutyric acid (GABA). Common side effects of topiramate include fatigue, sedation, concentration and focus issues, slow thinking, memory problems, psychomotor slowing, diplopia, nystagmus, dizziness, ataxia, paresthesia, anorexia, headache, and speech problems [60].

There have been observational reports of weight loss associated with topiramate treatment of bipolar disorders. A retrospective study reviewed the treatment of five patients with bipolar disease and schizoaffective disorders treated with topiramate that was gradually titrated to a maximum dose of 125 mg in the morning and 150 mg at bedtime. Treatment produced good psychiatric response. Weight was monitored up to 3 months and all patients lost an average of 22 lbs with a range of 8–56 lb [60].

In a 6 month clinical trial for weight loss, the topiramate groups lost significantly more weight than placebo patients at all doses of topiramate [61]. The dropout rate was greater for the drug group (21%), compared with that for the placebo patients (11%), which was attributed to the side effects of cognitive dysfunction and paresthesia.

Another clinical trial of obese subjects evaluated weight loss maintenance [62]. Subjects were first treated for 8 weeks with a low-calorie diet followed by topiramate or placebo therapy for weight maintenance for 44 weeks. Study dose varied from a placebo to 96–192 mg/day of topiramate. The weight loss phase resulted in clinically significant reduction in body weight and visceral fat. During the 44 week maintenance period, weight loss was maintained and an additional 6% weight loss occurred for the topiramate group [62]. Topiramate was generally well tolerated.

A 2 year study of 1289 healthy obese adults explored the long-term efficacy and safety of topiramate at various doses [63]. All study subjects received behavior modification training, and were randomized to doses of topiramate that were titrated to the following final doses: 0 (placebo), 96, 192, or 256 mg/day. The study sponsor elected to discontinue the study at the end of the first treatment year in order to commence development of a new controlled-release drug formulation. At 60 weeks, subjects in the placebo group lost 1.7% of their baseline body weight. In the topiramate groups, weight loss was 7.0%, 9.1%, and 9.7%. There were improvements in glucose tolerance and in blood pressure. Side effects mostly occurred during upward drug titration and included difficulty with concentration/attention, depression, difficulty with memory and concentration, language problems, nervousness, and psychomotor slowing and paresthesia.

Zonisamide (Zonegran)

Zonisamide (Zonegran) was approved by the FDA in 2000 for the treatment of partial focal seizures in adults with epilepsy. Zonisamide also has serotonergic and dopaminergic actions and weight loss was identified during clinical trials for epilepsy. It has since been studied for weight loss [64]. In a 16 week study with an additional 16 week extension that included a 500 kcal deficit diet, zonisamide-treated subjects lost considerably more weight compared with placebo. The study doses of zonisamide were gradually increased from 100 to 400 mg/day. In subjects who had lost less than 5% body weight at 12 weeks of therapy, the dose was titrated to 600 mg/day. Zonisamide-treated subjects had a mean weight loss of 9.2 kg at 32 weeks compared to 1.5 kg for the placebo group. Waist circumference and systolic and diastolic blood pressure reduced significantly in the treatment group. There was also an associated improvement in mobility, occupational functioning, and activities of daily living. Fatigue was the only drug-related side effect reported. However, in clinical trials of zonisamide as an antiepileptic drug, cognitive impairment, dizziness, and somnolence were frequently noted. Zonisamide is a sulfonamide and there is a potential for hypersensitivity reactions.

A combination of zonisamide and bupropion was compared to zonisamide alone in a 12 week weight loss study of 18 obese women. The initial zonisamide dose was 100 mg/day, with a gradual increase to 400 mg/day in both groups and given as a nighttime dose. Bupropion was titrated up from 100 to 200 mg/day and given as a morning dose [65]. The combination produced more weight loss (8.1 kg) than zonisamide alone (3.0 kg).

Atomoxetine

Atomoxetine is FDA approved for treating attention deficit/hyperactive disorder (ADHD). It is a central norepinephrine uptake inhibitor. A 12 week study of atomoxetine for weight loss included 30 healthy but obese women. The study dose of atomoxetine was titrated from 25 to 100 mg/day. Modest weight loss (5% of body weight) was recorded with 3 of the 12 completers compared to placebo in this preliminary study [66]. The most common side effect reported was a decrease in appetite.

Antidiabetic Drugs

Metformin

Metformin (Glucophage) is an FDA-approved antidiabetic drug. Studies with metformin have shown it to be either weight neutral or promoting weight loss compared to sulfonylureas, thiazolidinediones, and insulin, which are more associated with weight gain. In a clinical trial to assess weight

changes associated with antihyperglycemic agents in type 2 diabetes mellitus, the study authors concluded that a case can be made for the early use of metformin as a treatment of choice in the management of type 2 diabetes to prevent weight gain or to promote weight loss [67,68]. In some metformin obesity trials, hunger and calorie intake were reduced [69,70]. Metformin for weight loss has also been studied in obese children [71].

A 1 year study of 100 severely obese children aged 6–12 years was designed to determine whether metformin promoted weight loss and improved obesity-related comorbidities in obese insulin-resistant children. The metformin dose was titrated from 500 mg twice daily to a maximum dose of 1000 mg twice daily over a 3 week period. Results demonstrated modest weight loss and improved measures of body fatness. Body circumference and skinfold thickness measurements decreased in the treatment group. There were no significant liver function abnormalities. Side effects included nausea and loose stools, and fatigue [72].

Acarbose

Acarbose (Precose) is FDA approved for the treatment of diabetes. It is an alpha-glucosidase inhibitor, which blocks the digestion of complex carbohydrates [73,74]. Studies of acarbose for obesity treatment in diabetic patients and in polycystic ovary syndrome patients have demonstrated only small changes in body weight [74–77].

Side effects of acarbose are due to undigested complex carbohydrates in the colon and include increased intestinal gas, flatulence, diarrhea, and abdominal pain. In an NIH publication, it was reported that there is not sufficient efficacy or safety evidence to consider prescribing acarbose in nondiabetics as an off-label treatment for obesity.*

Exenatide

Exenatide is FDA approved for type 2 diabetes. It is part of the incretin family of type 2 diabetes drugs, a glucagon-like peptide-1 (GLP-1) receptor agonist. It suppresses appetite and promotes weight loss in obese diabetic patients [78]. Studies to investigate exenatide as a weight loss drug for nondiabetics are ongoing and are discussed further in this section.

Amylin

Amylin is a peptide hormone that is secreted from pancreatic β cells in response to eating a meal and is part of a complex neurohormonal feedback system. It slows gastric emptying and stimulates satiety after a meal [79]. It acts within the brain to reduce food intake and body weight [80].

Pramlintide

Pramlintide is a subcutaneous injectable synthetic analog of human amylin. It is FDA approved for type 1 diabetes and used for patients with type 1 or type 2 diabetes who are taking insulin and need diabetes control. In studies of obese type 2 diabetic adults, pramlintide has produced sustained reductions in food intake, body weight, and total daily insulin usage [81]. The addition of pramlintide to preexisting insulin treatment of type 2 diabetes results in reductions in HbA1c and body weight [82]. Pramlintide appears to have a therapeutic role in type 2 diabetics with obesity. It also produces weight loss in nonobese diabetics [83]. A 24 week human weight loss study using a combination of pramlintide and metreleptin (leptin) resulted in about 13% weight loss. This weight loss was significantly greater than pramlintide or metreleptin treatment alone [84]. The study authors suggested that while previous trials using metreleptin as single therapy failed to show significant weight loss with doses up to twice as much as those used in this study, amylin and leptin together may have therapeutic use as a neurohormonal combination treatment for obesity. In a study, 204 obese men and women (30–70 years old), with or without type 2 diabetes, were treated with pramlintide. Almost 90% of treated subjects were able to escalate to the highest dose of 240 μg TID. Weight loss in pramlintide-treated subject was accompanied by a reduction in waist circumference [85,86]. In a 20 week study of 139 nondiabetic obese subjects, pramlintide (360 μg b.i.d.) was compared to pramlintide/metreleptin (360 μg/5 mg b.i.d.) and metreleptin group (5 mg b.i.d.). Subjects treated with the pramlintide/metreleptin combination had a significantly greater weight loss (13% vs. about 8% in subjects receiving either pramlintide or metreleptin). This weight loss was continuous through the study time frame while weight plateaued at approximately week 12 in the metreleptin and pramlintide monotherapy groups. Nausea was the main side effect in this study [87]. In a 12 month study, 411 obese subjects were treated to assess weight loss, efficacy, and safety of various doses of pramlintide. Subjects were randomized to one of six subcutaneous (sc) dosage arms, from 120, 240, or 360 μg sc injected either BID or TID versus placebo. Clinically significant weight loss (greater than 5%) was reached in the treated groups and maintained in 44%–47% of drug-treated versus 28% of the placebo-treated groups, over the course of the study year. Nausea was the main side effect [85].

Ephedrine with Caffeine and/or Aspirin

The FDA has banned ephedrine from OTC products. Clinical trials with ephedrine in combination with caffeine and aspirin have demonstrated an increase in lean body mass and a decrease in fat mass with mild and transient side effects [22,23,88–90]. The combination possesses anorectic and thermogenic properties, resulting in a prolonged norepinephrine activity. Ephedrine increases the synaptic release of norepinephrine, modulating food intake and the heart rate and blood pressure. It enhances thermogenesis through its sympathomimetic effect. Caffeine appears to potentiate the effect of ephedrine through delaying the degradation of norepinephrine and inhibiting phosphodiesterase in the postsynaptic neurons. Aspirin inhibits the activity of prostaglandins that degrade norepinephrine in the neural cleft [22,23,88,89].

* Diabetes prescription medications for the treatment of obesity. NIDDK. Weight Control Information Network. U.S. Department of Health and Human Services, National Institutes of Health NIH Publication No. 07-4191. November 2004. Updated December 2010.

A placebo-controlled 50 week study evaluated the combination of ephedrine and caffeine without aspirin in 180 subjects taking doses of ephedrine 20 mg TID and caffeine 200 mg TID, or ephedrine alone 20 mg TID, or caffeine alone at 200 mg TID, versus the placebo. A weight loss of about 16 kg was demonstrated in the ephedrine and caffeine group [89]. Another study assessed the safety and efficacy of the combination of ephedrine, caffeine, and aspirin. Study doses were as follows: ephedrine 75–150 mg TID, caffeine 150 mg TID, and aspirin 330 mg TID as premeal doses. Calories were not restricted. Weight loss at 5 months for the treatment group was 5.2 kg compared to a slight weight gain for the placebo group. From months 7 to 26, there was weight regain in the treatment group, but overall modest weight loss from the beginning of the study was maintained [88]. Similar results were also reported by Greenway et al. [91]. Adverse effects from the use of an ephedrine/caffeine combination in these studies were minimal and included tremor, insomnia and dizziness, and increased heart rate and blood pressure. If occurring, symptoms happened early in treatment and resolved within 1–2 months. Elevated serum insulin levels and occasional worsening of glucose intolerance or diabetic control were observed [22,23].

NONPRESCRIPTION MEDICATIONS FOR OBESITY TREATMENT

Food and Drug Administration Approved

Alli was introduced as an OTC drug in 2007 as a low-dose version of the FDA-approved obesity drug orlistat. This GI lipase inhibitor that partially blocks the absorption of dietary fat is the only FDA-approved OTC product for weight loss. A 16 week study of 391 mild to moderately overweight individuals assessed the efficacy and safety of a low dose of orlistat (60 mg TID) in subjects on a lifestyle management plan [92]. After the initial 2 weeks of treatment, the orlistat-treated subjects lost significantly more weight than placebo-treated subjects (3.05 vs. 1.90 kg). GI events were more common in the orlistat-treated group [92].

In a 2 year orlistat obesity trial involving 1187 subjects, orlistat dosage in the first year was 120 mg TID [34]. The second year focused on preventing weight regain and the orlistat dosage was decreased to 60 mg TID (equivalent to the OTC dose) or placebo. In the orlistat group, body weight was maintained within two-thirds of the maximum loss in year 1. Study subjects who were initially taking orlistat but then switched to placebo in year 2 regained most of the lost weight [34]. A 3 month-long pharmacy-based OTC study tested how consumers would use the dosing of orlistat in a nonsupervised environment. A total of 237 patients purchased and used orlistat and completed at least one post-use interview. About 80% successfully used the educational materials and lost approximately 5% body weight. Most took 2–3 capsules per day with meals throughout the study. GI side effects were noted, but there were no dropouts as a result of side effects [93].

Ephedra

In 2004, the FDA banned Ephedra from all OTC products. Ephedra was commonly used in dietary supplements, OTC sinus and cold preparations, and stimulants. The FDA ban was due to reports of palpitations, hypertension, strokes, and deaths.*

Laxatives

Laxatives have been included in selective OTC weight loss products. There are no data to support their use in weight management.

Phenylpropanolamine

The FDA has removed phenylpropanolamine (PPA) from OTC weight loss and cold and sinus preparations. In some states, nonprescription products containing PPA can be purchased with a personal ID card directly from the pharmacist.

Dietary Supplements

The U.S. Congress defined the term "dietary supplement" in the Dietary Supplement Health and Education Act (DSHEA) of 1994 as follows: "A dietary supplement is a product taken by mouth that contains a 'dietary ingredient' intended to supplement the diet. The 'dietary ingredients' in these products may include: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. They can also be in other forms, such as a bar, but if they are, information on their label must not represent the product as a conventional food or a sole item of a meal or diet. Whatever their form may be, DSHEA places dietary supplements in a special category under the general umbrella of 'foods,' not drugs, and requires that every supplement be labeled a dietary supplement."†

The FDA does not analyze dietary supplements before they are sold to consumers. It is the manufacturer's and not FDA's responsibility for ensuring that a dietary supplement or ingredient is safe before it is placed on the market. Manufacturers and their distributors do not need FDA approval to sell dietary supplements. It is only after a dietary supplement is on the market that the FDA becomes responsible for taking action against any reported unsafe dietary supplement. The reporting of all serious adverse events to the FDA falls upon the party whose name appears on the label. Except for the dietary ingredients, manufactures are not obligated to document to the FDA or to consumers any data on product safety or what claims they are making about their product. The FDA's Center for Food Safety and

* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108379.htm

† http://www.cfsan.fda.gov

Applied Nutrition (CFSAN) is responsible for the agency's oversight of these products.*

Many of the popular dietary supplements used for weight loss contain some of the following ingredients: chromium picolinate, guar gum, chitosan, *Citrus aurantium*, *Camellia sinensis*, conjugated linoleic acid, and calcium [94]. Dietary supplement use by the overweight population is common. It has been estimated that as many as 20.6% of women and 9.7% of men have at one time used a weight-loss supplement and many of these patients do not share their use of supplements with their doctor [95].

Most of the weight-loss supplements contain stimulants and the majority of users have no idea that the safety and efficacy of the product they are about to purchase, lacks FDA regulation [96]. Some physicians also misunderstand the dietary supplement regulations [97].

Intake of supplements for weight loss should be asked of all patients and charted. It should be the responsibility of treating physicians to dispel common misconceptions about weight-loss supplements, as needed. The evidence against their use, if any, should be presented in a nonjudgmental fashion. Issues surrounding safety and efficacy of some dietary supplement warrant caution in recommending dietary supplements as part of a weight-loss program [95].

Fat Substitutes for Weight Loss

Fat substitutes are nonprescription food additives. They were developed by the commercial food industry to provide, amongst other benefits, a more pleasing taste, while providing a lower fat content for prepackaged grocery store foods.

Olestra (Olean) is a long fatty acid chained sucrose polyester that is too big a molecule to be digested or absorbed. It is a food additive, fat substitute developed to replace the fat content of prepackaged foods such as potato chips and crackers [51]. An early study used a sucrose polymer as a substitute for dietary fat (30 g/day) in a hypocaloric diet and demonstrated a 3.7 kg mean weight loss and a 23% reduction in low-density lipoprotein cholesterol (LDLC) in the familial hypercholesterolemia population of five subjects [98]. Side effects of olestra-containing products are similar to orlistat and include flatulence, diarrhea or loose stools, bloating, and anal leakage. Manufacturers are required to include vitamins A, D, and E in the food product containing olestra substitutes [99].

DRUGS AWAITING FDA APPROVAL

Lorcaserin

Lorcaserin is a selective serotonin receptor agonist influencing hunger [100]. A 12 week weight loss study used different doses of lorcaserin versus placebo in 469 adults. Compared to the placebo group, there was more weight loss in the lorcaserin groups proportionate to the dose. Side effects included headache, dizziness, and nausea [101]. In a 1 year lorcaserin study, 4008 obese and overweight adults received either lorcaserin 10 mg once or twice daily. All subjects received a lifestyle intervention program. Weight loss (in the 5%–10% range) was statistically significant in the lorcaserin groups than in the placebo group and was dose dependent. No increase in valvulopathy was seen in serial echocardiograms [102].

A 2 year clinical trial involved 3182 obese or overweight adults, who received placebo or lorcaserin 10 mg twice a day plus counseling. The treatment group showed significant weight loss at 1 year and maintenance of weight loss at 2 years. First year weight loss in the lorcaserin-treated group averaged 5.8 kg compared to 2.2 kg in the placebo group. Weight loss was maintained in year 2 in almost 70% of the lorcaserin group compared to 50% for those on placebo. The most common side effects were headache, nausea, and dizziness. There were no increased cardiac valvulopathy findings [100]. In a December 2010, an FDA review of lorcaserin did not receive approval. The manufacturer has agreed to work closely with the FDA to address the various concerns and will present new data about its use in type 2 diabetics.

Contrave

Contrave is an off-label combination of drugs bupropion and naltrexone. Both drugs have been approved by the FDA for almost 25 years. Bupropion is a dopamine and norepinephrine reuptake inhibitor approved for depression and smoking cessation. Naltrexone is an opioid receptor antagonist approved for alcohol and opioid dependence. The drug combination appears to suppress appetite. A 56 week study involving 1742 patients studied the drug combination for weight loss [103]. The two study doses included sustained-release bupropion 360 mg/day plus either sustained-release naltrexone 16 or 32 mg. The third group received placebo. Weight losses were 6.1% and 5.0% at the higher and lower doses of drugs, respectively. The placebo group lost 1.3% of body weight. Side effects included a transient rise in systolic and diastolic blood pressure of 1.5 mmHg, followed by a 1 mmHg reduction below baseline. There was no increase in depression or suicidal events compared with placebo, whereas headache, constipation, dizziness, vomiting, and dry mouth were experienced more frequently in the drug groups.

In December 2010, the FDA Advisory Committee approved Contrave but on January 30, 2011, the FDA turned down their approval recommendation, stating that the side effect of hypertension was worrisome enough to the FDA to refuse approval. A new 2 year study for Contrave is planned to further assess effectiveness and cardiac side effects.

Qnexa

This drug is a combination of the appetite suppressant phentermine together with the anticonvulsant topiramate. This drug combination was initially rejected by the FDA in December 2010 but will be reconsidered. The FDA has requested the

* http://www.cfsan.fda.gov

assessment of potential teratogenic risk and cardiovascular risk and a review of additional long-term data.*

A 56 week phase 3 study of phentermine plus topiramate assessed the efficacy and safety of the drug combination on body weight and comorbidities in 2487 overweight and obese adults, who had two or more of the following comorbidities: hypertension, dyslipidemia, type 2 diabetes, prediabetes, or abdominal obesity [104]. The drug doses were a once-daily phentermine 7.5 mg plus topiramate 46.0 mg or phentermine 15.0 mg plus topiramate 92.0 mg. All subjects received counseling for lifestyle management. The change in body weight was minimal in the placebo group (−1.4 kg) but significant and dose dependent in the drug groups (−8.1 kg and −10.2 kg, respectively). The most common side effects in the treatment groups were also dose related. At the higher dose, they included dry mouth and paresthesia (21%); constipation (17%); insomnia, dizziness, and dysgeusia (10%); anxiety-related adverse events (8%); and depression-related adverse events (7%).

CANDIDATES FOR DEVELOPING OBESITY DRUGS

Cannabinoid Antagonists

The endocannabinoid system, through its CB-1 receptors, has its effects on energy homeostasis through both central and peripheral effects on food intake and body weight. CB-1 receptor blockers decrease both central and peripheral effects of the endocannabinoid system and increase satiety and promote weight loss [105]. Rimonabant is a selective CB-1 receptor. It is a ciliary neurotrophic factor (CNTF) described in the next section. The original 12 week study of 173 obese human adults treated with a recombinant human variant ciliary neurotrophic factor (rhvCNTF) demonstrated greater weight loss in the treatment group compared to that in the placebo group [106].

A series of studies called RIO-Europe, RIO-North America, RIO-Lipid, and RIO-Diabetic used similar formats—all subjects received diet, behavior modification, and rimonabant at 5 or 20 mg/day or placebo. The RIO-Europe study showed that rimonabant 20 mg dose produced greater reduction in body weight, waist circumference, and triglycerides levels, and an increase in HDL-cholesterol, and improved plasma glucose–insulin homeostasis compared with the 5 mg dose. Both drug doses were significantly better than placebo. The 20 mg dose resulted in 6.6 kg weight loss versus 1.8 kg in the placebo group [107].

In the RIO-Lipid study, body weight and waist circumference reductions were similar to that in the RIO-Europe study. A focus of this study was on improvement in metabolic risk factors in overweight dyslipidemic patients. Improvement was documented in LDL particle size, adiponectin levels, glucose tolerance, fasting and post-challenge insulin levels, and plasma C-reactive protein levels. Side effects were also similar to that of the RIO-Europe study. The most frequent adverse events resulting in discontinuation of study drug were depression, anxiety, or nausea [108].

RIO-North America was a 2 year study to test the effect of rimonabant on weight and cardiometabolic risk factors in 3045 overweight or obese subjects [109]. After 1 year of rimonabant treatment (5 or 20 mg/day), subjects were re-randomized to receive placebo or continued to receive the same rimonabant dose in the second year. The placebo group continued to receive placebo during year 2. Compared to the placebo weight loss of 2.3 kg, the subjects who received 20 mg drug for two uninterrupted years had a mean weight loss of 7.4 kg and the weight loss was well maintained during the second year. There were improved waist circumference measures and risk factors. Patients treated with 5 or 20 mg of rimonabant at year 1 and re-randomized to placebo in year 2 regained a substantial amount of the weight lost. Final body weight in this group was slightly lower than that in the placebo group at 2 years.

RIO-Diabetes was a 1 year study of 692 obese subjects who had uncontrolled diabetes despite metformin or a sulfonylurea as single drug antidiabetes therapy [110]. Weight loss was greater in both rimonabant groups (−2.3 and −5.3 kg) in contrast to the placebo group (−1.4 kg). The HbA1c levels decreased by −0.6% in the 20 mg drug dose group, but increased by 0.1% in the placebo group. A trial of drug-naïve type 2 diabetic subjects studied the effects of 20 mg rimonabant on body weight, glycemic control, and lipid profile [111]. The baseline HbA1c (7.0%–10.0%) was reduced by −0.8% and −0.3% in the rimonabant and the placebo groups, respectively. Hemoglobin A1C was less than 7.0% at the end of the study in 51% of the drug-treated group and in 35% of the placebo group. Rimonabant also improved fasting blood glucose. Weight loss was 6.7 kg for the drug group versus 2.8 kg with placebo. Adverse events that led to discontinuation of study drug were mainly due to depressed mood disorders, nausea, and dizziness. The study authors felt that the data indicated that Rimonabant, in combination with diet and exercise, may produce a clinically meaningful weight loss and improve HbA1c in overweight or obese patients with type 2 diabetes inadequately controlled by metformin or sulfonylureas.

The FDA denied approval for rimonabant at the end of 2010. Further studies were discontinued because of disappointing weight loss results. This class of drugs may still have the potential to produce an antiobesity drug.

Ciliary Neurotrophic Factor

CNTF is a member of a cytokine family related in structure and action to a number of other metabolically active proteins and peptides including leukemia inhibitory factor (LIF), interleukin-6 (IL6), interleukin-1 (IL-1), and oncostatin M (OSM) that play some role in the regulation of EE [112]. In a study of amyotrophic lateral sclerosis (ALS), recombinant human CNTF (rHCNTF) was used as treatment. rHCNTF was not effective in altering ALS progression, but a marked

* http://ir.vivus.com/releasedetail.cfm?ReleaseID=524576

weight loss occurred in these nonobese study subjects. Side effects of anorexia, weight loss, and cough seemed to be dose related [113]. In mice, CNTF suppressed food intake without triggering hunger signals, and when CNTF treatment was stopped, the expected overeating and immediate rebound weight gain did not occur [114].

Leptin

It was shown in the 1990s in a mouse model that the regulation of energy balance could be controlled through the interactions of an obesity gene (ob gene) and that a defect in this gene causes massive obesity in these mice [12]. This gene product called leptin helped to strengthen claims for a genetic basis for obesity. Leptin is secreted by adipocytes, circulates in the blood and acts in the brain to regulate food intake and EE. Leptin functions as part of a signaling pathway from adipose tissue to the brain and plays a pivotal role in long-term body weight regulation [8,10–12]. To date, attempts to use recombinant leptin (metreleptin) for the treatment of obesity have not been very successful [84]. A leptin receptor (OB-Rb) is active in the parts of the brain associated with food intake and EE [8,10,11]. Researchers have been assessing the role leptin plays in homeostasis after either weight loss or weight gain. With a loss of body fat, leptin levels fall, appetite increases, and EE decreases. With an increase in body fat, leptin levels rise, appetite is suppressed until body fat mass is restored [115–118]. The role that leptin plays as a central regulator of homeostasis of body fat mass in human is under investigation [119].

Globally, there are only a few known cases of congenital leptin-deficient individuals. In a 19 week study of three genetically leptin-deficient patients, fat oxidation and EE were studied in response to weight loss, and the results were compared to values attained by typical obese adults after weight loss [120]. The three leptin-deficient patients received subcutaneous daily doses of recombinant methionyl human leptin and easily lost weight. Control obese individuals lost a similar amount of weight. However, after weight loss, the obese control subjects, but not the genetic leptin-deficient individuals, had EE lower than that expected for their new body weight. Also, the fat oxidation, which was similar at baseline for both groups, increased significantly upon weight loss for the genetic leptin-deficient individuals [120]. This study further confirmed what other studies have also shown: that leptin-deficient subjects who have undergone leptin replacement lose weight but do not manifest a reduction in EE and increased fat oxidation. The authors reported that their data suggest that leptin may have a thermogenic effect in humans [120].

A study testing recombinant leptin for weight loss in obese and lean adults included 54 lean and 73 obese adults. Leptin was given by a daily morning subcutaneous injection in varying doses. Lean subjects were treated for only 4 weeks and only obese subjects were allowed to continue for an additional 20 weeks. Lean subjects were on a eucaloric diet to maintain body weight and obese subjects on a calorie reduction of 500 kcal/day. Weight loss increased with the dose of leptin in both, lean and obese adults. In the highest dose of leptin, more than 95% of the weight loss was due to fat loss. There was considerable variability in the amount of weight lost by individuals. Baseline serum leptin concentrations were not related to weight lost. No significant side effects were reported during the study [121].

A study of five males and five females was designed to assess the role of leptin in the maintenance of weight loss. Leptin administration was continued in the post-weight loss phase in doses to restore circulating leptin concentrations to baseline levels present prior to weight loss. Results showed a reversal of the suspected decline in EE and the changes in skeletal muscle energetics that usually accompany weight loss [122], which may help in weight maintenance.

Neuropeptide Y

Neuropeptide Y (NPY) is a neuropeptide neuromodulator found in the brain and whose receptor may be involved in the regulation of food intake and body weight in humans [123]. The NPY stimulatory effect is primarily on carbohydrate intake [124,125]. In mice with diet-induced obesity, an NPY antagonist decreased body weight and body fat [126]. Human clinical trials have not yet shown NPY antagonists to have a significant effect on body weight or food intake [127].

Human Growth Hormone

Early studies suggested that growth hormone (GH) treatment in subjects who were obese and deficient in GH, would mobilize fat, reduce body fat stimulate oxygen consumption, and decrease protein loss [128]. A 6 month study recruited adult female patients who had laparoscopic-adjustable silicone gastric banding (LASGB) bariatric surgery in the past and had a functional severe GH deficiency. The subjects received either a placebo or recombinant human GH daily for 6 months [129]. Results demonstrated a decrease in fat mass (8.8%) and a reduction in visceral adiposity and lean body mass in the GH group. Insulin resistance increased during the GH therapy. The effects of GH on weight, fat mass, visceral adiposity, and lean body mass disappeared shortly after GH withdrawal.

A 12 month study of 40 postmenopausal women with abdominal obesity evaluated the effect of GH on visceral fat. The women received GH (0.67 mg) in a randomized, double-blind, placebo-controlled fashion. The GH treatment group reduced abdominal visceral fat, increased thigh muscle area and improved insulin sensitivity and lipid values. The improvement in insulin sensitivity was associated with reduced hepatic fat content [130]. In another 12 month study, 30 men with visceral obesity who did not have GH deficiency were tested for the effects of GH treatment on reducing visceral adiposity [131]. Subjects received GH or placebo in a double-blind fashion for the first 6 months followed by a 6 month washout period. After 6 months, the GH group had an increase in body weight and in lean body mass

(2.5 kg), yet an 8.8% reduction in visceral adiposity compared to placebo. Resting EE was increased, as was fasting insulin, glucose, and insulin resistance. Shortly after drug discontinuation, there was an increase in body fatness and visceral adiposity and a decrease in lean body mass. Total body weight remained the same after drug withdrawal. Waist circumference did not change during GH therapy, and at the 1 year assessment, the waist circumference was greater in the GH-treated subjects. The study authors concluded that although there was a small but statistically significant decrease in visceral adiposity, due to an increase in lean body mass and body weight and the worsening of metabolic parameters, the supra physiological dose of GH used was not an effective treatment approach.

Dehydroepiandrosterone

The role of the hormone DHEA in the treatment of human obesity remains unclear. In a 20 week randomized double-blind crossover study involving 14 subjects, there was significantly more loss of weight and body fat during treatment with etiocholanedione (ED), an oral steroid derivative of DHEA. During ED administration, the mean weight loss was 2.8 kg and a 5% loss in body fat, whereas, no weight change during the placebo phase. Three of the obese subjects had fat losses of 18%, 19%, and 25%. No significant side effects were reported [132]. A 10 week study involving 13 morbidly obese adolescents measured the effect of DHEA administration on body weight, body composition, lipids, and insulin resistance. DHEA was given as a 40 mg sublingual dose. Results documented an increase in DHEA and testosterone concentrations but there were no effects on body weight, sense of well-being, or any other measured variables [133].

DHEA has been used as a performance enhancing drug for athletes due to the supposition that it decreases central fat deposit and increases lean body mass. A 28 day study of the acute effects DHEA on body composition and serum steroids hormones was performed on 20 young competitive soccer players ages 19–22 years. DHEA dose was 100 mg daily or placebo. The drug group increased DHEA and testosterone levels but no significant change in body fat, total muscle mass or BMI, or waist-to-hip ratio was noted [134].

Many of the actions of DHEA in humans are thought to be mediated through its conversion to sex hormones, which are modulators of adiposity, muscularity, and insulin sensitivity. A 12 month study determined the effect of restoring DHEA level in 120 older men and women aged 60–88 years. DHEA 50 mg/day or placebo was given as an oral dose. Abdominal fat, thigh muscle, and fat were measured by computed tomography and trunk mass by DXA measurement. DHEA serum levels were restored to normal during the study. By the end of the study, central adiposity was not reduced nor was insulin action improved. Triglycerides were decreased but HDL-cholesterol was also decreased. Study authors concluded that restoring of DHEA serum levels to that of a young adult does not appear to reduce central adiposity or improve insulin action in older adults [135].

DHEA can be purchased OTC in drug stores or health food stores and online as a dietary supplement and can be labeled DHEA. DHEA component of a dietary supplement can be an extracted plant sterol derived from wild yams. It is called diosgenin (*Dioscorea villosa*). As an extract, it could even be labeled and sold as a "natural" DHEA without FDA approval. DHEA and testosterone are widely promoted as antiaging supplements, but the potential harm or long-term benefits are unknown. To test this, another 2 year study of 144 elderly men and women was conducted to restore low levels of DHEA or testosterone. Replacement therapy showed increases in plasma levels of both DHEA and testosterone. No significant effect on body composition of DHEA in men and women was documented. Fat-free mass was slightly increased in men who received testosterone, and men and women had an increase in bone density. Measured outcomes of physical performance, and quality of life showed no improvement. No major side effects were reported [136].

Testosterone/Dehydrotestosterone

Testosterone is the principal androgen product of the testis and is responsible for body masculinization. Testosterone is converted peripherally to DHT. Serum testosterone concentrations are associated with the severity of prostate cancer, metabolic syndrome, and type 2 diabetes. The well-recognized regional fat deposition pattern of men and women is considered a secondary sex characteristic involving sex steroids including testosterone [137,138]. Changes in fat deposition from puberty are an ongoing process [139,140]. Testosterone studies in humans have been mostly in older men and women and have documented that low testosterone is associated with increased body fat and fat distribution and increased waist circumference. As the level of obesity increases, testosterone levels drops [141]. Effects of low testosterone have been investigated during clinical trials of metastatic prostate cancer therapy where the mainstay treatment is androgen deprivation [142]. One such study showed that that when serum gonadal steroid concentrations were lowered to castration levels there was an increase in subcutaneous abdominal fat area without significantly changing the intra-abdominal fat [142].

An 18 month study involved 36 adult men aged 22–69 years with acquired hypogonadism [143]. Prestudy values showed that percent body fat in these men with low testosterone was significantly greater compared to normal controls. In this study testosterone treatment was initiated at a dose of 100 mg/week and resulted in a decrease in subcutaneous fat and an increase in lean muscle mass. Serum testosterone concentrations correlated directly with muscle mass and negatively with fat mass. Testosterone treatment also reduced bone remodeling and increased trabecular bone density [143]. A study of six healthy lean young men (mean age 23.2 years) evaluated changes in muscle strength and adiposity before and after gonadal suppression [144]. Testosterone suppression lasted 10 weeks. All subjects showed a decrease

in fat-free mass, an increase in fat mass, a decreased lean body mass, and increased adiposity. Leg muscle strength also decreased as did EE. The rates of lipid oxidation and whole body protein synthesis also decreased [144].

Overall, an increase in lean body mass, but not a particularly significant impact of testosterone on body fat is reported in young or older subjects [144–147]. The findings by Bhasin et al. [147] suggested that a short-term administration of androgens may have beneficial effects in patients who are immobilized; those with cancer or human immunodeficiency virus-related cachexia, or other chronic wasting disorders; or in space travel. The authors, however, acknowledged that anabolic steroids are used and abused by some athletes, recreational body builders, and others wishing to increase muscle mass and/or to lose weight and further emphasized that their results "in no way justify the use of anabolic–androgenic steroids in sports because with extended use such drugs have potentially serious adverse effects on the cardiovascular system, prostate, lipid metabolism, and insulin sensitivity" [147].

Gastrointestinal Pathway Drugs

The GI pathway is among the most active of endocrine organs. Food intake may be influenced by neural and hormonal actions of the GI tract. These peptides appear to have a function on eating behavior and the regulation of energy balance and body fat accumulation [148]. Meal anticipation and the presence of food in the upper GI tract stimulate the release of gut hormones and neurotransmitters that are then relayed to the central nervous system [149]. The mechanisms involved in sustaining weight loss following bariatric surgery are being investigated. Since gut hormones are thought to play a role in the sustained weight loss following the gastric bypass surgery, there may be a potential role for selective GI hormones as a direct treatment for obesity [149].

Cholecystokinins

CCK is a GI peptide produced in the stomach, gallbladder, and pancreas. It is secreted postprandially into the circulation and effects energy balance by decreasing food intake. Plasma CCK levels rise within 15 min after meals [149]. In response to a dietary fat load, CCK action results in a slowing of gastric emptying and satiety [150].

Glucagon-Like Peptide

Glucagon-like peptide (GLP-1) is a hormone produced in the distal ileum and colon. It inhibits glucagon secretion, stimulates insulin secretion following carbohydrate ingestion, delays gastric emptying, and increases satiety [149,151–153]. It improves blood glucose levels in diabetic subjects. In obese individuals, GLP-1 secretion is likely to be decreased and may contribute to the development of obesity [154]. GLP-1 is significantly elevated post-intestinal bypass surgery and may be a factor in influencing weight loss after bypass surgery by reducing appetite and food intake.

Liraglutide

Liraglutide is a human GLP-1 analog approved by the FDA in 2010 for the treatment of adults type 2 diabetes. It is prescribed together with diet and exercise in diabetic patients who have not responded to initial diabetes therapy. A 2 year clinical trial with liraglutide involved 564 individuals aged 18–65 years [155]. The trial evaluated the safety, tolerability, and sustained weight loss using liraglutide treatment for obesity for over 2 years. A report of the initial 20 weeks of the trial compared subcutaneous liraglutide treatment with orlistat and a placebo arm [156]. Liraglutide was initially given once daily subcutaneously at doses from 1.2 to 3.0 mg. The other treatment groups received orlistat 120 mg TID or placebo. The liraglutide patients treated at the 3.0 mg during the initial 20 weeks lost more weight than the other study groups and body fat decreased by 15.4% and lean tissue by 2.0%. All liraglutide groups lost more weight than the other two groups. There was an 84%–96% reduction in the prevalence of prediabetes in the 1.8–3.0 mg dose range and a reduction of blood pressure at all liraglutide doses. Side effects included nausea and vomiting that rarely lead to study discontinuation. In the report on the 84 week extension of the study, the liraglutide group maintained a 7.8 kg weight loss, which was also much greater than the other groups [155]. The study authors also reported that the 2 year prevalence of prediabetes and metabolic syndrome decreased by 52% and 59%. There were improvements in blood pressure and lipid values. The most frequent drug-related side effects were mild to moderate, transient nausea and vomiting.

Ghrelin

Ghrelin is a peptide hormone discovered in 1999. It is produced in the stomach and secreted into the circulation. It stimulates food intake and it is elevated in the fasting state and is suppressed in the postprandial state [157]. Obese subjects however exhibit a less marked drop in plasma ghrelin after a meal [149]. A study investigated the effects of intravenous ghrelin or saline infusion on appetite and food intake in nine nonobese adults [158]. Calorie consumption at a single free-choice buffet meal increased by 28% in ghrelin-treated subjects. Study authors suggested that a drug that inhibits ghrelin action may potentially be a target for obesity treatment [158]. A study measured ghrelin levels after Roux-en-Y gastric bypass surgery (RYGB) [159]. This study included nonobese subjects and obese subjects who were either postsurgery or who had lost weight with diet treatment. In subjects with diet-induced weight loss, ghrelin levels were higher than those for nonobese subjects. In the postsurgery subjects, plasma ghrelin levels were markedly lower than those of the lean and obese controls, and the surgery group did not have pre- and postprandial variations of ghrelin. The authors raise the possibility that suppression of ghrelin is one mechanism by which the gastric bypass surgery reduces body weight.

A study investigated the effects of a low- or high-dose intravenous ghrelin on food intake in 12 lean and 12 obese adults [160]. The low-dose ghrelin administration increased

energy intake (36.6%) only in the obese group, measured at a single buffet meal. High-dose ghrelin infusion increased energy intake in lean (20.1%) and obese (70.1%) groups. The authors concluded that inhibiting circulating ghrelin may be a useful therapeutic target in the treatment of obesity. Other GI peptides can affect the stimulatory action of ghrelin on food intake. New treatments for obesity drugs may result from such a research focus [161].

Peptide Y Y

Peptide Y Y (PYY) is a GI tract hormone that is secreted postprandially and appears to result in a decrease in postprandial hunger and calorie intake in both obese and nonobese individuals. PYY inhibits GI motility [162]. A greater release of PYY is observed with the ingestion of fat, compared to that of a carbohydrate or protein meal of similar calories. PYY may regulate EE, delay gastric emptying, and reduce acid secretion [149]. An 8 week weight loss study evaluated the effects of low-fat or low-carbohydrate energy-restricted diets on serum PYY levels. Results demonstrated that greater weight loss was associated with lower PYY levels, regardless of the diet plan. Study authors concluded that reduced PYY levels after weight loss likely represent a compensatory response to maintain energy homeostasis and that PYY contributes to the difficulty patients have losing weight while on a calorie-restricted diet [163].

A study compared the effects of medical or surgical weight loss of similar magnitude on PYY levels. RYGB and sleeve gastrectomy (SG) patients had increased PYY levels, increased satiety, and a decrease in appetite. In the medically treated group PYY levels did not decrease and appetite was unchanged [162,164,165]. The study authors suggest that the weight loss effects of RYGB and SG are enhanced by an increase in PYY and satiety.

WHO SHOULD RECEIVE PHARMACOTHERAPY FOR OBESITY?

BMI guidelines for identifying overweight and obesity, evaluation, and treatment are developed for physicians and health care professionals by the National Heart, Lung, and Blood Institute (NHLBI), in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases.* However, the pharmacological treatment of obesity has no established and proven algorithm, although this has been attempted on a limited scale [166]. The ideal obesity pharmacotherapy has yet to be developed. There is no proven and assured course of action to prevent obesity. The following sections provide one view about how pharmacotherapy of obesity may be managed. Several considerations are offered based on clinical experience. Clearly, other meritorious approaches are also possible.

Obesity experts emphasize the importance of early identification of overweight and obesity as an important first step for both, prevention and treatment. Primary care physicians see 11.3% of the U.S. population monthly and obese patients represent a high proportion of those visits [167,168]. In the most recent National Ambulatory Medical Care Survey (2005 and 2006 data) in medical practices where BMI was routinely captured, 27% of the patients seen in a doctor's office had a normal BMI, 31% were overweight, and 37% were obese. Only 30% of the obese patient visits included a recorded diagnosis of obesity [167]. Physician awareness and use of an electronic medical record may help in the documentation of obesity [169]. Primary care practices do not carry the entire burden of early detection of overweight and obesity. There is a wider spectrum of medical subspecialists and surgeons who see these patients for their comorbidities associated with obesity. These referral doctors could be educated to discuss and guide patients about their obesity risks. The prescribing of antiobesity drugs however should be the responsibility of physicians who have specific knowledge of the pharmacology of obesity medication, their side effects, and safety profile and access to health care professionals that can provide the important behavior modification and dietary components of overweight and obesity management to their patients.

When weight management options including pharmacotherapy should be discussed with patients is not well defined. Physicians who have an expertise and comfort level in their ability to treat obesity are more likely to have an early discussion with overweight or obese patients. For the majority of physicians, therefore, the trigger points to initiate a medical conversation about body weight are quite broad. Some clinicians wait until a patient requests help; others use the BMI or associated comorbidity as their triggers. There are variations amongst primary care physicians as to their specific BMI threshold for initiating the dialogue. Physicians match their medical expertise with the needs of individual patients in choosing a course of action and pharmacotherapy options [170]. A decision not to discuss obesity or not to treat obesity may be based on a patient's readiness to commit to a weight management program. For a patient to get maximum benefit from pharmacotherapy, a physician needs to gauge patient's compliance, ability, and willingness to follow medical directions. This information significantly improves a physician's ability to pick the right time to initiate successful pharmacotherapy. There are screening questionnaires that could provide such information [171].

If weight loss is medically necessary, patients may be self-motivated to follow a weight management plan but health is usually not a compelling motivator from a patient's standpoint and if used as the only argument by a physician, it may be unsuccessful. Patients who claim cosmetic reasons for wanting to lose weight and who qualify for obesity pharmacotherapy should not be turned away. Vanity can be a motivating force for success and is not a reason to deny drug treatment if the patient fulfills the medical criteria. A patient's request for pharmacotherapy during initial obesity consultations is

* National Heart, Lung, and Blood Institute, National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The evidence report. Bethesda, MD: National Institutes of Health; September 1998 NIH publication No. 98-4083.

not unusual and is not necessarily a sign of a patient looking for a "short cut." A patient who insists on a pill to lose weight, could likely be one of your least successful patients, now seeking a different approach. Failed previous weight loss attempts or even yo-yo dieting are not contraindications to drug treatment.

Decisions to use FDA-approved drugs to treat conditions beyond the recommended guidelines are up to the physician. This is considered "off-label" use of the FDA-approved drugs. A decision to use pharmacotherapy beyond FDA guidelines is not prohibited by the FDA. The comorbidities of obesity can severely limit lifestyle and may shorten life. More progressive or chronic obesity, presence of comorbidities, and impaired quality of life contribute to the decision to initiate pharmacotherapy for weight loss. It is not uncommon that an obesity management program includes pharmacotherapy sooner rather than later. This may mean including drug therapy at the onset of a comprehensive program [172].

Guidelines suggest that pharmacotherapy for adults with obesity may be appropriate for those with BMI 27–29.9 kg/m^2 if comorbidities are present or for those with a BMI $\geq$ 30 kg/m^2 with or without comorbidities. It is also suggested that pharmacotherapy be considered after a patient has tried behavior therapy including diet, exercise, and lifestyle change and has had limited or no response. In reality, most patients have had some exposure to nonpharmacological approaches before seeking medical help for weight loss, since various establishments and online programs offer a variety of nonmedically supervised diet and exercise programs.

As with any pharmacological agent, the risk and benefit possibilities must be weighed before prescribing an obesity drug. Treating obesity in patients older than 65 years should be done with caution [43]. It is important to recognize that at present, obesity can be controlled, but cannot be cured. Therefore, a relapse is possible if an obesity drug is discontinued. If a patient loses and/or maintains weight loss on an obesity drug and no serious side effects have been identified, the drug may be continued and the drug efficacy and safety should be monitored for the duration of its use [173].

WHICH DRUG TO CHOOSE

In addition to the merits, limitations, adverse effects, and the mechanism of action of various drugs, selection of an obesity drug should be personalized to accommodate considerations for a patient's past medical and social history, current medical and mental health issues, and current medications including OTC drugs.

Clinical Considerations for FDA-Approved Obesity Drugs

Many obesity researchers and clinicians believe that long-term and possibly lifelong use of obesity drugs may be necessary for significantly obese individuals [174]. Studies suggest that a pharmacological agent that produces a weight loss of less than 4 lb in first month is unlikely to promote clinically effective weight loss in the long term. Initial weight loss, obtained during the first 2–4 weeks of treatment, is reported as predictive of subsequent weight loss response [175]. Before deciding to discontinue an obesity drug for inadequate effect, the dosage may be reassessed. If the current dose is below the recommended maximum dose then a dose increase may be appropriate. Patient compliance with the medication should also be considered.

Perhaps, changing the time of drug administration may be needed to promote better compliance. The possibility should be considered that other prescription or nonprescription drugs may interfere with drug effectiveness or may cause side effects that the patient may wrongly attribute to an obesity drug. Another consideration is the patient's compliance with dietary changes and physical activity. As the daily need of energy decreases with decreasing weight, consider if the calorie goals need to be redefined for continued weight loss. Is the rate and amount of weight loss appropriate for the patient's medical needs? Should the drug be now used to maintain the weight lost? As far as possible, the class of drug chosen should consider the eating behaviors of each patient. Information about hunger, cravings, eating between meals, binging, and nighttime eating issues should be obtained by using validated questionnaires or through questioning of all patients by physician or staff. With the exception of orlistat, all drugs currently on the market are centrally acting adrenergic antiobesity drugs and may control many of the eating-related issues. A written questionnaire detailing eating habits may help patients better focus on their eating issues, if any. Food preferences and types of foods frequently overeaten may influence the type and timing of obesity drug administration.

How to Use Phentermine and Orlistat: An Opinion

Phentermine is supplied by generic manufactures as phentermine–HCl in a 37.5 mg scored dose. It can be prescribed under the brand name *Ionamin* in a 15 or 30 mg capsule, as *Fastin* in a 30 mg capsule, and as *Adipex*, which is available either as a scored 37.5 mg tablet or capsule. Because this sympathomimetic drug is associated with side effects early in treatment, a stepped dose approach is an option, but not a requirement [7,176]. Starting with a half dose of phentermine (½ of a 37.5 mg tablet or a 15 mg capsule) and increasing it as needed may be quite effective at the onset of treatment. This approach can prolong the active weight-loss period [43]. The onset of action of phentermine is within a few days to a week, allowing a physician to increase the dose depending on patient response at each office visit. It can be given as a single daily dose or a split between morning and before dinner, depending on which helps the most with hunger control, with minimal side effects. Phentermine has also been shown to be effective even on an alternate day and even on an intermittent schedule [41,177]. A dose higher than 37.5 mg for tablets and 30 mg for the capsule is not approved nor is shown to be more effective. Side effects can be dose related, but are usually short lived and resolve with dose

lowering or drug discontinuation. If the occurrence of side effects is related to a specific time of the day, such as at bed time, it may be blunted or eliminated by taking that dose earlier. Insomnia and nighttime agitation may be an issue with an evening dose. If phentermine had been discontinued for reasons other than side effects, it could be reintroduced and may again be effective. If an alternative antiobesity medication is chosen, it could be started within a week of stopping phentermine. A patient who had been on phentermine and switches medications should be instructed that unlike phentermine, the onset of action of noncentrally acting weight loss drugs is slower and the almost immediate effectiveness experienced with phentermine will not occur with other currently approved medications. If not so instructed, patients may wrongly assume that the new medication is ineffective

After about 6 months, lost weight usually reaches a plateau [41,43,177]. There are no long-term studies of phentermine, and future studies are unlikely, since it is a generic drug. However, a study of long-term management of eight adults on continuous phentermine treatment for more than 10 years for weight loss and maintenance is reported [178] (see the section "How Are Drugs Being Used Differently in Various Clinical Settings").

Orlistat decreases dietary fat digestion and absorption. To maximize weight loss with orlistat, reduction in dietary fat intake should be encouraged. A high-fat intake may accentuate side effects of orlistat and may force patients to discontinue the drug. To preempt this, the negative effects of orlistat should be described to patients. However, the GI side effects must be presented in a manner so as not to prejudice a patient away from taking the drug. The conversation should be focused on minimizing the side effects, and an emphasis on their transient nature. The drug works best if taken with every meal. However, the drug may be skipped when a particularly low- or no-fat meal is taken. If a patient is unsure of dietary fat content, the drug should be taken. If a meal is skipped, orlistat could be skipped. A patient can monitor their fat intake by observing their stool texture and the presence of undigested floating fat in the commode. Physicians could use this information as a dietary teaching tool. The occasional GI event should be used as a teaching tool for food selection advice for future meals. Patients should be discouraged from abusing orlistat to counter intentional high fat consumption, which may not only lead to a significant GI event but may also undermine long-term weight loss efforts.

Weight Regain and Pharmacotherapy

Obese patients will regain some if not all of their lost weight, but the degree of weight loss and weight regain will vary. If a patient returns for care after some weight regain, mention the possibilities that in addition to behavioral factors, weight regain can also occur due to hitherto unclear reasons, outside of the patient's control. Weight regain may be due in part to self-regulatory mechanisms of energy balance, attempting to restore the body weight to a steady state [179]. Any situational life events that may contribute to recidivism should be identified and addressed. Some of these factors may be modifiable. Until the biochemical factors of weight gain or regain are better understood, counseling should be provided to prevent a lapse from progressing to relapse and eventually to collapse of the entire treatment for the individual. A decision needs to be made about restarting the original weight management plan including drug therapy. A variation of that plan may be more appropriate, or a completely different approach including bariatric surgery should be considered, if the criteria are met. Current guidelines to qualify for bariatric surgeries in the United States and Canada are a minimum BMI of 40, or a BMI of 35 with one or more severe comorbidities. The minimum BMI for a laparoscopic insertion of a Lap-Band device is a 35, or 30 with one or more severe comorbidities [180].

OBESITY DRUGS USE: VARIOUS APPROACHES

Between 2002 and 2005, 86,804 patient records of a large health care insurance company were reviewed to evaluate trends and patterns of obesity drug treatment. The results showed that a decreasing number of obese patients were prescribed obesity drugs during this time frame [170]. In this medical record review, orlistat was the most commonly used medications (39.4%), followed by phentermine (39.1%) and sibutramine (32.2%, but no longer available). Other older sympathomimetic medications were little used (8%). The trend was toward a decrease in orlistat and sibutramine use, while the use of phentermine remained stable. The study authors suggested that, the increased use of bariatric surgery, the hesitancy of both physicians and patients to use obesity medications due to their efficacy and safety concerns were among the reasons for the decrease in obesity drug use. High cost of the newer medications was also an issue [170]. Along with the obesity medications, 57% patients were also taking narcotics and 38% were taking antidepressants. An additional 8% of subjects were taking more than one obesity medication at the same time. These findings highlight the importance of physician awareness, preparedness, and experience when prescribing medications. Physicians need to be familiar with the concomitant medications taken by their patients. The authors pointed out that prescribers should be aware of FDA-approved drug durations of treatment and potential contraindications. Screening for depression and substance abuse should occur before starting obesity treatment, and asking about prescription and nonprescription medications is necessary.

Physician specialists may have a prescribing approach that is different from nonspecialists. In 2009 a report described the obesity drug prescribing approach of some physician members of a professional bariatric society [181]. Two hundred sixty-six physicians (35% of the membership) anonymously responded to a questionnaire about their approach to prescribing obesity drugs. All responders prescribed antiobesity drugs. Results identified varied approaches to drug management of obesity that included choice of drug, drug dosage, duration of treatment, and the use of drug

combinations. Phentermine was prescribed by 97% of these physicians and for various lengths of time beyond the FDA-approved 3 months of therapy. Of these, 56% prescribed phentermine for as long as they and their patients felt it was helpful in achieving weight loss or weight maintenance goals. Diethylpropion (48%) and phendimetrazine (29%) were other sympathomimetics used long term by these physicians. Sibutramine (no longer available) and orlistat approved by the FDA for long-term use were used less often by these physicians (32% and 33%, respectively). The study authors commented that, with the generic drugs being considerably less expensive, cost of the medications may have played a factor in their choice. The prescribing of more than one FDA-approved obesity drugs was practiced frequently or occasionally, by 83% of those surveyed. About 65% prescribed combinations of medications that are not approved for obesity treatment by the FDA, but are reported in medical literature to induce weight loss. About 14% used the combination of orlistat with sibutramine while another 1.4% prescribed the combination of caffeine with ephedrine. There were an additional 20% of physicians who used some drug combinations that had no scientific reports recorded in the medical literature.

A report from a single medical practice was published in 2004 [178]. It was an extensive review of the records of eight patients who received comprehensive obesity management that included 19 years of continuous antiobesity drug treatment. Six of the eight patients used phentermine as the primary therapeutic agent. A seventh initially used diethylpropion or mazindol and was ultimately prescribed phentermine. Occasionally other FDA-approved obesity drugs were prescribed to assess their effectiveness and tolerability, but all of the patients returned to the one medication that they have found to be most helpful. Only one patient used diethylpropion exclusively. No drug tolerance, or adverse events, addiction, or misuse related to phentermine occurred. Weight lost during the active weight-loss phase was maintained within 1 kg. The author emphasized that this was a small patient population, and that the experience of these eight individuals may not be generalizable. It did suggest that there are some patients who respond well to obesity medications and that consideration should be given to the chronic use of medications for the continuing management of obesity. The author recommended that efforts should be made to identify such responders so that a long-term pharmacological treatment of obesity could be pursued.

These studies are described here to demonstrate the variety of approaches in drug selection, length of treatment, and the variation in the prescribing habits of physicians. No single approach presented in this section is an endorsement by the authors of this chapter.

OBESITY DRUG NEEDS AND THE FDA: AN UNEASY RELATIONSHIP

Obesity is the second leading cause of preventable deaths in the United States. The U.S. Senate Committee on Appropriations at their September 8, 2011, meeting highlighted obesity as "a disease linked to cancer, high blood pressure, heart disease, diabetes, and stroke." The committee expressed a concern with the "absence of novel medicines to treat obesity" and called the lack of obesity drugs "a significant unmet medical need." This was recorded in a report accompanying a year 2012 appropriations bill for agriculture and rural development.* The committee noted that obesity treatment options include diet, exercise, and obesity surgery, but there is a lack of obesity pharmacotherapy options. The committee report included a section entitled "Obesity Therapeutics." In this section of the report, the FDA was instructed to provide steps it will take to support the development of new treatments for obesity. The FDA report is due March 30, 2012. The FDA was to use its "Risk Evaluation and Mitigation Strategy" to help especially with issues of drug safety. Drug safety has been a major reason for the FDA's nonapproval of all new drugs they have evaluated since the approval of orlistat in 1999.

The disapproval rate of all new antiobesity medications since 1999 has had an impact on physicians and their patients involved in obesity management. Why FDA disapproval has seemingly occurred so frequently in pharmacotherapy for obesity compared to that for other diseases has been questioned. Some experts however disagree on whether the FDA is too tough or on weight-loss medications.

Sibutramine had been an FDA-approved drug for the treatment of obesity since its introduction in 1998 and was a mainstay treatment of obesity management until October 2010 when it was voluntarily withdrawn by the manufacturer at the request of the FDA following a review. The antiobesity drugs lorcaserin, Qnexa (phentermine and topiramate), and Contrave (bupropion and naltrexone) failed to receive FDA approval. In March 2011, a meeting was held between the FDA officials and the obesity experts representing the Obesity Society, the Obesity Action Coalition, the American Society for Metabolic and Bariatric Surgery, and the American Dietetic Association. The meeting was with the director of the FDA's Center for Drug Evaluation and Research (CDER) and members of her staff. The goal was to help clarify the direction and future approaches to meaningful drug approval endpoints. Approval of obesity drugs by the FDA is vital to provide encouragement to research and commercial development of newer obesity drugs. It is hard to expect a continuous stream of obesity drug development, if the FDA is not likely to grant approvals. On the other hand, it is the responsibility of the FDA to ensure safety and efficacy of drugs and to approve only the meritorious drugs.

SUMMARY AND CONCLUSIONS

Obesity is a chronic disease that requires lifelong treatment. There is currently no cure for obesity. Experience with long-term use of obesity drugs is limited. However, current evidence suggests that pharmacotherapy in conjunction with lifestyle changes, improves the outcome and patient outlook.

* http://appropriations.senate.gov/sc-agriculture.cfm

There is insufficient data to assume that obesity drugs are totally safe, but the literature does seem to reinforce the benefits. Weight loss usually is modest with obesity drugs, but there are significant improvements in comorbidities of obesity. Obesity drugs must be used with caution and only in patients with medically significant obesity. Careful selection of a drug, its dose, and duration; follow-up and continuous assessment of efficacy; and due diligence on recognizing side effects are mandatory. For treating obesity, physicians should have the knowledge and expertise to successfully use FDA-approved obesity drugs. Also, they should familiarize themselves with the off-label use of other FDA-approved medication for managing obesity.

Few patients treated for their obesity will reach their goal weight and almost no one reaches the "ideal" weight with or without drug therapy. This, however, is not a reason to withhold pharmacotherapy. Obesity *drugs are not substitutes, but supplements, to other lifestyle interventions for weight loss*. Obesity drugs are expected to empower a person to adhere to a reduced calorie intake, in some cases provide better control over aberrant eating behaviors, increase compliance, and consequentially, increase weight loss and maintenance, and may also alleviate comorbidities of obesity. Obesity is a serious medical condition and not a moral failure or a character flaw. Behavioral treatment of obesity has marginal success, and pharmacotherapy should be given a serious consideration as an adjunct to lifestyle management.

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45 Surgery for Severe Obesity

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CONTENTS

Introduction 571
Bariatric Surgical Procedures 572
Importance of Lifestyle Intervention 574
Preparing the Patient for Surgery 574
Weight-Loss Outcomes and Improvement in Obesity-Related Medical Conditions 574
Lifestyle Interventions in the Postoperative Care of Bariatric Surgical Patients 574
Nutritional Care 574
  Dietary Changes after Bariatric Surgery 574
  Recommended Dietary Patterns and Eating Behaviors 575
  Prevention of Micronutrient Deficiencies after Bariatric Surgery 575
Physical Activity 575
  Physical Activity Levels after Bariatric Surgery 575
  Benefits of Physical Activity in Postoperative Bariatric Surgery Patients 576
  Barriers to Physical Activity after Bariatric Surgery 577
  Recommendations for Physical Activity after Bariatric Surgery 577
Behavioral/Psychological Care 577
  Mood Disorders 577
  Disordered Eating 577
  Alcohol Misuse 577
  Psychological Counseling and Peer Support in the Postoperative Period 578
Comprehensive Lifestyle Interventions after Bariatric Surgery 578
Weight Regain Following Bariatric Surgery 579
Conclusion 579
References 579

INTRODUCTION

Various expert panels have endorsed bariatric surgery as an acceptable weight-loss option for patients with a BMI of $\geq$40 kg/m^2 or those with a BMI of $\geq$35 kg/m^2 who have comorbid conditions [1–7]. An international survey of 36 nations or national groups estimated that over 344,000 bariatric surgery operations were performed in 2008; 220,000 of these operations were performed in the United States or Canada [8]. The exponential growth in procedures is due to several factors including improved surgical techniques, reduction in the postoperative mortality rate, significant improvement in obesity-related comorbid conditions [9], increased media attention, and profitability. The upsurge in surgical procedures also reflects the increasing prevalence of severe obesity in the United States. Between 1986 and 2000, the prevalence of severe obesity (BMI $\geq$ 40 kg/m^2) quadrupled from about 1 in 200 adult Americans to 1 in 50; the prevalence of a BMI of $\geq$ 50 increased by a factor of 5, from about 1 in 2000 to 1 in 400 [10]. Nearly 6% of adult Americans are considered severely obese with prevalence figures reaching 14% for African-American women [11]. It is therefore likely that health care professionals from all disciplines will encounter patients who have undergone a bariatric surgical procedure. Similarly, primary care physicians will be expected to monitor and manage their patients on a long-term basis. Many of the weight-loss surgeries, most notably the combined restrictive–malabsorptive surgical procedure—Roux-en-Y gastric bypass (RYGB)—and the malabsorptive biliopancreatic diversion (BPD) and biliopancreatic diversion with duodenal switch (BPDDS), place patients at high risk for development of both macro- and micronutrient deficiencies unless they are properly counseled and supplemented. Since most of the deficiencies can be identified early at a preclinical stage, early treatment will prevent or reduce symptoms and deficiency syndromes. Although bariatric surgery does not cure obesity, it is considered a significant tool for weight loss and maintenance of weight loss. As such, patients are at risk to experience weight regain several years following surgery. This chapter will review the most commonly performed weight-loss procedures, the importance of preoperative and postoperative management, identification and management of nutritional deficiencies that may occur following bariatric surgery, and factors associated with weight regain.

BARIATRIC SURGICAL PROCEDURES

Weight-loss surgeries fall into one of three categories—restrictive, restrictive malabsorptive, and malabsorptive (Figure 45.1). Restrictive surgeries limit the amount of food the stomach can hold and slow the rate of gastric emptying. The vertical banded gastroplasty (VBG) is the prototype of this category but is no longer performed due to limited effectiveness in long-term trials. Laparoscopic adjustable gastric banding (LAGB) has replaced the VBG as the most commonly performed restrictive operation. The first banding device, the LAP-BAND™, was approved for use in the United States in 2001. A second device, the REALIZE™ band, was approved in the United States in 2007. In contrast to previous devices, the diameter of these bands is adjustable by way of its connection to a reservoir that is implanted under the skin. Injection or removal of saline into the reservoir tightens or loosens the band's internal diameter, respectively, thus changing the size of the gastric opening. Since there is no rerouting of the intestine with LAGB, the risk for developing nutritional deficiencies is entirely dependent on the patient's diet and eating habits. The third and most recently described restrictive procedure is the laparoscopic sleeve gastrectomy (LSG). In this procedure, the stomach is restricted by stapling and dividing it vertically and removing approximately 80% of the greater curvature, leaving a slim "banana shaped" remnant stomach along the lesser curvature.

The restrictive–malabsorptive bypass procedure combines the elements of gastric restriction and selective malabsorption. The RYGB is the most commonly performed procedure. It involves formation of a 10–30 mL proximal gastric pouch by either surgically separating or stapling the stomach across the fundus. Outflow from the pouch is created by performing a narrow (10 mm) gastrojejunostomy. The distal end of jejunum is then anastomosed 50–150 cm below the gastrojejunostomy. "Roux-en-Y" refers to the Y-shaped section of small intestine created by the surgery; the Y is created at the point where the pancreo-biliary conduit (afferent limb) and the roux (efferent) limb are connected. "Bypass" refers to the exclusion or bypassing of the distal stomach, duodenum, and proximal jejunum. RYGB may be performed with an open incision or laparoscopically.

There are two malabsorptive procedures. In the BPD a subtotal gastrectomy is performed, leaving a much larger gastric pouch compared with the RYGB. The small bowel is divided 250 cm proximal to the ileocecal valve and connected directly to the gastric pouch, producing a gastroileostomy. The remaining proximal limb (bilio-pancreatic conduit) is then anastomosed to the side of the distal ileum 50 cm proximal to the ileocecal valve. In this procedure, the distal stomach, duodenum, and entire jejunum are bypassed, leaving only a 50 cm

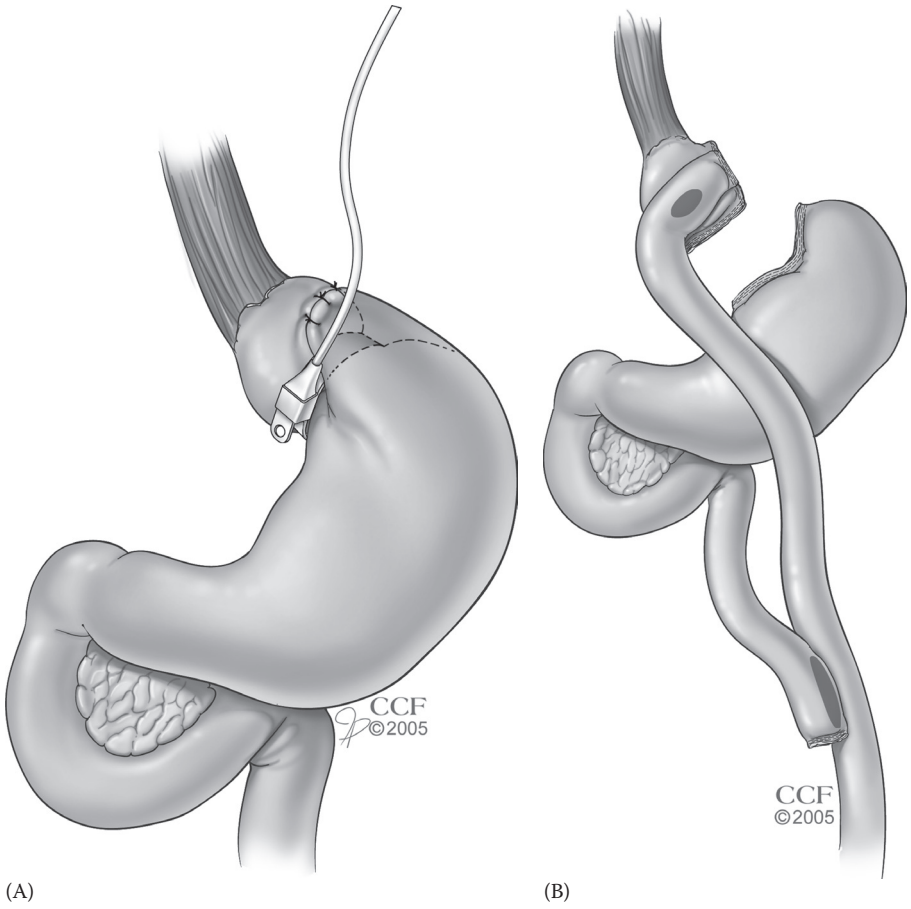


FIGURE 45.1 (A) Laparoscopic adjustable gastric banding. (B) Laparoscopic sleeve gastrectomy.

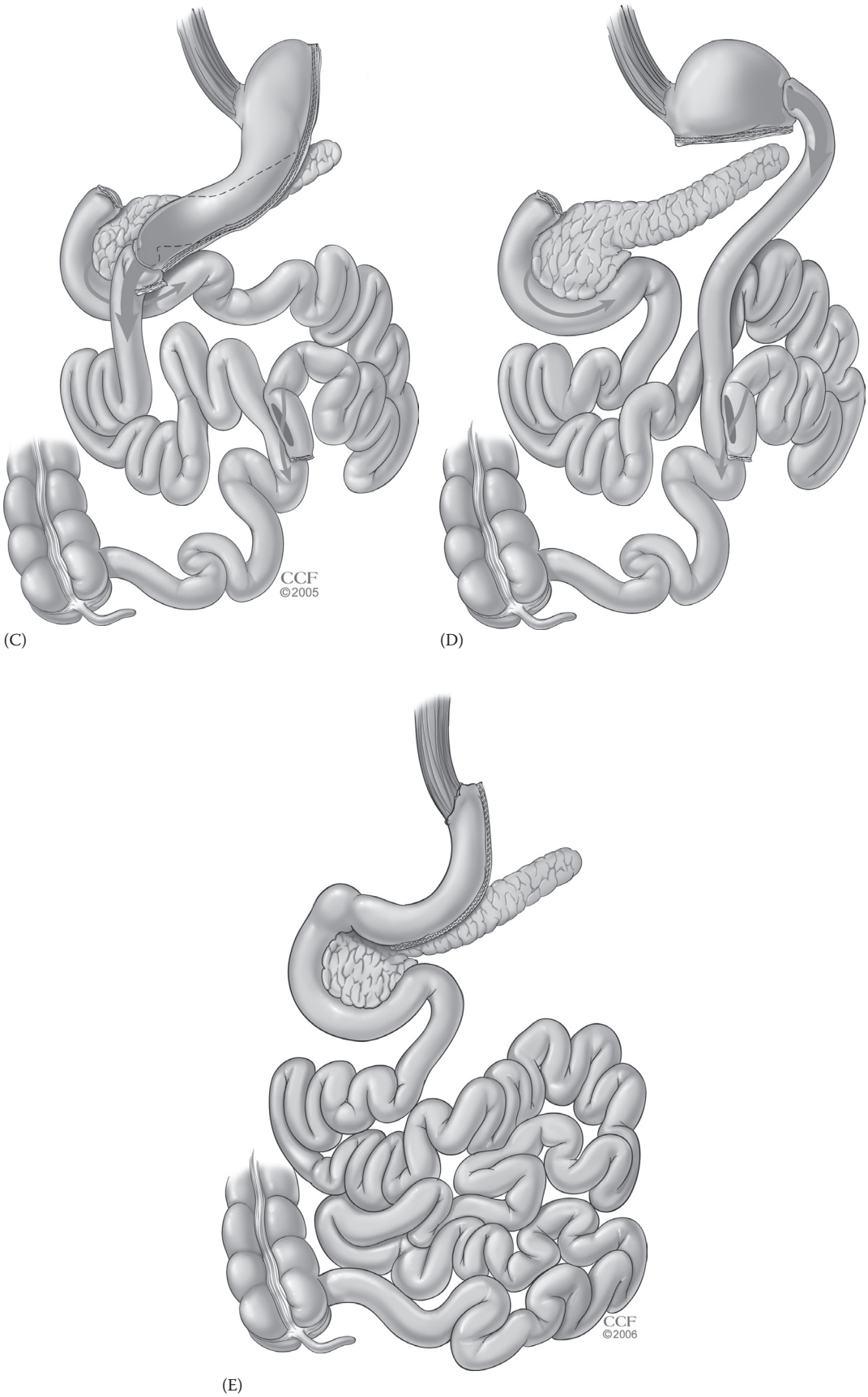


FIGURE 45.1 (continued) (C) Roux-en-Y gastric bypass. (D) Biliopancreatic diversion. (E) Biliopancreatic diversion with duodenal switch.

distal ileum common channel for nutrients to mix with pancreatic and biliary secretions. The BPDDS is a variation of the BPD, which preserves the first portion of the duodenum. In this procedure, a vertical subtotal gastrectomy is performed and the duodenum is divided just beyond the pylorus. The distal small bowel is connected to the short stump of the duodenum, producing a 75–100 cm ileal–duodenal "common channel" for absorption of nutrients. The other end of the duodenum is closed, and the remaining small bowel connected onto the enteral limb at about 75–100 cm from the ileocecal valve.

IMPORTANCE OF LIFESTYLE INTERVENTION

Since obesity is fundamentally a disorder of energy balance, all treatments must include attention to caloric intake (energy in) and physical activity (energy out). By altering gastrointestinal anatomy and physiology, weight-loss surgery is a powerful tool to reduce caloric intake. Nonetheless, patients need counseling on diet and nutrition that is consistent with the specific surgical procedure (restrictive versus malabsorptive) and with optimal health. They also need guidance on implementing dietary changes within the structure of their daily life. Similarly, patients benefit from education and advice about increasing daily physical activity and implementing an exercise routine.

PREPARING THE PATIENT FOR SURGERY

All patients who are considering weight-loss surgery should undergo a comprehensive assessment by a multidisciplinary team of health care providers that includes a physician, registered dietitian, and mental health care professional [1,5]. Preparation for surgery commonly spans 3–12 months depending on the patient's medical condition and criteria for insurance approval. During the preoperative process, patients are typically instructed on healthy eating and physical activity patterns, behavioral strategies to implement the lifestyle changes, and the importance of stress reduction and social support for long-term success. Specific dietary and nutritional recommendations pertinent to the surgical procedures include use of protein supplements, consumption of multiple meals and snacks, and slowing the rate of eating. Patients are seen either individually or in small groups. Many centers offer panel discussions between candidate patients and patients who have already undergone a procedure to provide a peer-to-peer discussion of risks, benefits, and challenges of life after bariatric surgery.

Although it is reasonable to encourage weight loss prior to surgery, the literature is conflicting regarding the benefit of mandating preoperative weight loss as a criterion to undergo surgery. The primary rationale for requiring routine preoperative weight loss is to decrease the short-term operative morbidity and mortality. Furthermore, the patient's motivation for and ability to adhere to the dietary restrictions considered essential for a successful surgical outcome can be assessed. While 5%–10% preoperative weight loss has been shown in some studies to reduce postoperative complications [12], hospital length of stay [13], operating room time [14], and improved 1 year weight loss [15], other studies have not shown a benefit in longer-term weight-loss outcomes [16–18]. An additional compelling reason to endorse preoperative weight loss is to optimize the operative field by reducing liver volume and visceral adipose tissue (VAT). Two prospective studies have confirmed the benefit of prescribing a very low calorie liquid diet (VLCD) for 9–12 weeks on preoperative loss of body weight, VAT and subcutaneous adipose tissue (SAT), liver volume and comorbid risk factors [19,20]. Based on the existing literature, it is reasonable to include preoperative weight loss as an expectation during the preoperative period [21].

WEIGHT-LOSS OUTCOMES AND IMPROVEMENT IN OBESITY-RELATED MEDICAL CONDITIONS

Several meta-analyses and systematic reviews of bariatric surgery outcomes have been conducted [9,22,23]. In general, weight loss is greatest with the malabsorptive procedures (BPD, BPDDS), followed by the restrictive–malabsorptive procedure (RYGB), and least with the restrictive procedures (LAGB, LSG). Percent excess weight loss at 3–6 years ranges from 62% to 81%, 53% to 77%, and 45% to 72% for each surgical type, respectively [24]. Significant improvement in multiple obesity-related comorbid conditions have been reported including type 2 diabetes, hypertension, dyslipidemia, and obstructive sleep apnea [24,25]. Readers are referred to a recent comprehensive guideline for further information on perioperative medical care and outcomes from bariatric surgery [24].

LIFESTYLE INTERVENTIONS IN THE POSTOPERATIVE CARE OF BARIATRIC SURGICAL PATIENTS

National guidelines suggest that continued attention to diet, physical activity, and emotional health after bariatric surgery is essential to ensure optimal outcomes [1]. Accordingly, patients are encouraged to participate in postoperative programs that support lifestyle modification.

NUTRITIONAL CARE

Dietary Changes after Bariatric Surgery

A variety of dietary changes occur after bariatric surgery. Most importantly, there is a significant and sustained reduction in caloric intake. Although portion sizes tend to increase gradually over time in postoperative patients, caloric intake is typically still reduced by 25% or more for years after surgery [26–28].

Food intolerances may occur and can lead to alterations in dietary patterns after bariatric surgery. Lactose intolerance can develop in patients who have undergone gastric bypass; as a result, nearly one-third of patients report avoiding milk after this procedure [29]. Dumping syndrome

occurs in up to 76% of patients after RYGB and may lead patients to reduce their intake of concentrated sweets and fatty foods to avoid associated postprandial symptoms, such as abdominal cramping, nausea, diarrhea, lightheadedness, sweating, and tachycardia [30]. In fact, over 60% of patients report avoiding sweets and nearly 30% avoid fatty foods after gastric bypass surgery [29,31]. Other food intolerances may occur as well. Among patients who have undergone VBG, for example, nearly two-thirds avoid consuming whole meats, one-third eschew bread, and one-third avoid fresh fruits and raw vegetables, presumably to avoid the phenomenon referred to as "plugging," when a food becomes lodged in the gastric pouch [31,32]. Similar eating patterns have been seen among patients who have undergone LAGB [33]. On the other hand, only around 10% or less of gastric bypass patients report avoidance of meats, fruits, and vegetables [31]. As a result, patients who have had RYGB may consume fewer fatty foods and sweets and more fruits and vegetables than patients who have had purely restrictive procedures, such as LAGB or VBG [27,31,33,34].

Regardless of the types of foods consumed, regurgitation or vomiting can occur when patients eat too quickly, fail to chew food thoroughly, or eat in excess of what the gastric pouch will hold. However, it should be noted that vomiting is not an intended consequence of bariatric surgery and it should not be viewed as normal, particularly in the late postoperative period. Patients who have persistent vomiting or regurgitation after surgery should be evaluated for the presence of maladaptive eating behaviors, as well as anatomical or functional issues such as stomal stenosis or ulceration, reflux, and gastric dysmotility [24,35].

Patients with symptoms of dumping syndrome can usually be managed by dietary modification, including avoidance of concentrated sweets and simple sugars, consumption of small frequent meals, and inclusion of protein at every meal. Patients with symptoms suggestive of postprandial hypoglycemia that are not ameliorated by dietary modification should undergo evaluation for the presence of endogenous (or "post-bypass") hyperinsulinemic hypoglycemia [24,36]. Patients with more severe neuroglycopenic symptoms (such as confusion or loss of consciousness) should also undergo evaluation for this condition, which can occur after gastric bypass.

Recommended Dietary Patterns and Eating Behaviors

As a result of the reductions in gastric capacity and caloric intake after surgery, patients must take care to ensure that nutritional needs are met. Postoperative patients should be advised to consume small portions, have—four to six small meals daily, and ensure an adequate intake of lean protein (60–120 g/day), fruits and vegetables (more than five servings per day), and whole grains [24,37]. Patients should also eat slowly, chew thoroughly, avoid fatty foods, sweets, and sugar-sweetened beverages, and avoid ingestion of liquids within 30 min of meals. Unfortunately, many postoperative patients fail to follow the recommended guidelines, particularly regarding fruit and vegetable consumption and avoidance of sweets and caloric beverages [37]. For this reason, clinicians should routinely assess patients' dietary intake during postoperative visits and reinforce recommended dietary goals.

Prevention of Micronutrient Deficiencies after Bariatric Surgery

Patients who have undergone bariatric surgery should be counseled that they are at risk for the development of micronutrient deficiencies after surgery. After RYGB, the most common micronutrient deficiencies include those of vitamin B_{12}, vitamin D, calcium, and iron [38,39]. Folic acid deficiency has also been reported but is largely preventable with regular use of a standard multivitamin preparation [38]. Sleeve gastrectomy has been reported to produce similar deficiencies as gastric bypass but at a somewhat lower frequency [39]. As compared to gastric bypass, the BPDDS is much more likely to produce deficiencies of the fat-soluble vitamins, including vitamin A [40]. Purely restrictive procedures such as LAGB are infrequently associated with specific nutritional deficiencies [41].

In many cases, micronutrient deficiencies can be prevented by regular vitamin and mineral supplementation along with appropriate clinical follow up and routine biochemical surveillance. Expert guidelines are available regarding recommended vitamin and mineral supplementation after surgery and the frequency of laboratory screening for deficiency states [24]. Tables 45.1 and 45.2 summarize these recommendations. Patients who are found to have evidence of specific micronutrient deficiencies will need additional vitamin or mineral supplementation, as indicated.

PHYSICAL ACTIVITY

Among individuals who have lost weight with nonsurgical treatment approaches, physical activity clearly plays a vital role in long-term maintenance of weight loss [42,43]. Much less is known about the role of physical activity in weight control after bariatric surgery, but it may be an important factor.

Physical Activity Levels after Bariatric Surgery

Numerous studies suggest that self-reported levels of physical activity increase significantly after bariatric surgery [44,45]. However, there is little objective data regarding changes in physical activity levels in the postoperative period. In one surprising study, patients reported a large increase in moderate to vigorous intensity activity after surgery, but accelerometer data suggested that such an increase did not actually occur in most individuals [46]. In fact, data suggest that only 10%–24% of postbariatric surgery patients

TABLE 45.1
Recommended Micronutrient Supplementation after Bariatric Surgery

Supplement	Dose and Frequency
Multivitamin	1–2 daily
Calcium citrate (after RYGB, SG, or BPD/DS)	1200–2000 mg/day in 2 or 3 divided doses
Calcium citrate or carbonate (after LAGB only)	1200 mg/day in 2 divided doses
Vitamin D (in calcium supplement or separate)	400–800 IU/day
Elemental iron (for menstruating women)	40–65 mg/day
Vitamin B_{12} (after RYGB, SG, or BPD/DS only)	≥350 mcg/day oral Or 500 mcg every week intranasally Or 1000 mcg/month intramuscularly Or 3000 mcg every 6 months intramuscularly

Source: Adapted from Mechanick, J. et al., *Obesity*, 17(Suppl 1), S1, 2009.

Note: Patients with micronutrient deficiency states will require additional supplementation as indicated.

LAGB, laparoscopic adjustable gastric banding; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; BPD/DS, bilipancreatic diversion with duodenal switch.

meet national guidelines regarding minimal physical activity levels for general health promotion (i.e., ≥150 min/week or moderate-to-vigorous physical activity in bouts of 10 min or more) [37,47]. Data from the National Weight Control Registry indicate that patients who have lost weight through bariatric surgery tend to be less physically active than individuals who have lost similar amounts of weight through nonsurgical approaches [48].

Benefits of Physical Activity in Postoperative Bariatric Surgery Patients

In epidemiologic studies of postoperative patients, increased self-reported physical activity has been repeatedly associated with improved weight loss, mood, and psychosocial functioning [44,49,50]. Similarly, in a cross-sectional study that used armband accelerometers to measure activity in patients who had undergone gastric bypass 2–5 years earlier, higher levels of moderate-to-vigorous physical activity were associated with greater postoperative weight loss [47].

However, data from intervention studies are lacking. In one small, nonrandomized, prospective study, participation in a postoperative exercise program (including 75 min of supervised aerobic exercise and resistance training three times a week) for 3 months did not significantly increase weight loss after RYGB surgery [51]. However, the intervention did prevent the observed decrease in dynamic muscle strength that was seen in postoperative patients who did not exercise, and it was also associated with an increase in functional and aerobic capacity. In a small, randomized, controlled trial, Shah and colleagues randomly assigned 33 obese (BMI ≥ 35.5 kg/m^2) postoperative patients to either high-volume exercise (with a goal of expending ≥2000 kcal/week in moderate intensity aerobic exercise) or a usual activity control for 12 weeks [52]. Subjects assigned to the exercise intervention reported a greater than threefold increase in time spent in moderate physical activity and a nearly twofold increase in recorded step counts. In this small study, intervention group subjects did not have greater weight loss or greater improvements in body composition, fasting glucose, or insulin levels, lipids, or blood pressure, as compared to controls. However, they did have significantly greater improvements in physical fitness and glucose levels after an oral glucose challenge. Additional data are needed to further characterize the benefits of exercise in postoperative bariatric surgery patients and to determine the optimal physical activity levels in this group.

TABLE 45.2
Recommended Laboratory Tests and Frequency of Routine Biochemical Surveillance

Procedure	Recommended Frequency of Biochemical Surveillance	Recommended Laboratory Tests
LAGB, RYGB, and SG	*First year*: every 3–6 months *Thereafter*: annually	CBC, electrolytes, glucose, iron studies, ferritin, vitamin B_{12}, liver function, lipids, 25-hydroxyvitamin D *As needed*: intact PTH, thiamine, RBC folate, MMA, HCy
BPD/DS	*First year*: every 3 months *Thereafter*: every 3–6 months	*Every 3–6 months*: CBC, electrolytes, glucose, iron studies, ferritin, vitamin B_{12}, RBC folate, liver function, albumin, prealbumin, lipids *Every 6–12 months*: 25-hydroxyvitamin D, vitamin A, vitamin E, vitamin K, INR, intact PTH *Every 12 months*: urine N-telopeptide, metabolic stone evaluation (24 h urine calcium, citrate, uric acid and oxalate), zinc and selenium *As needed*: osteocalcin, carnitine, essential fatty acid chromatography

Source: Adapted from Mechanick, J. et al., *Obesity*, 17(Suppl 1), S1, 2009.

LAGB, laparoscopic adjustable gastric banding; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; BPD/DS, bilipancreatic diversion with duodenal switch; CBC, complete blood count; PTH, parathyroid hormone; RBC, red blood cell; MMA, methylmalonic acid; HCy, homocysteine; INR, international normalized ratio.

Barriers to Physical Activity after Bariatric Surgery

Significant weight loss, such as that achieved after bariatric surgery, may enable severely obese patients to become more active. However, cognitive barriers to physical activity may persist after bariatric surgery and may influence patients' activity levels [45]. These barriers include reduced awareness of the health benefits of exercise, fear of injury, a lack of confidence in the ability to participate in physical activity, and self-consciousness, or embarrassment. Treatment strategies that address these barriers may help patients become more physically active.

Recommendations for Physical Activity after Bariatric Surgery

National guidelines suggest that, for optimal weight control, most overweight individuals will need to accumulate at least 150–300 min of moderate physical activity per week, or 30–60 min most days of the week [53]. In one recent study of subjects who have successfully maintained large weight losses over time after surgical or nonsurgical treatments, nearly 70% engage in 150 min or more of moderate to vigorous physical activity per week, and over 30% are physically active for at least 300 min/week [43]. Other data from the National Weight Control Registry indicate that walking is the preferred form of physical activity in this group of individuals [54]. In randomized controlled trials as well as epidemiologic studies, individuals who use pedometers to reach a specific step-count goal (such as >10,000 steps/day) increase their activity levels more and lose slightly more weight than those who do not use pedometers [55]. Regular pedometer use may therefore be a practical and helpful strategy for patients who have had bariatric surgery.

BEHAVIORAL/PSYCHOLOGICAL CARE

Bariatric surgical patients experience a variety of psychosocial challenges in the postoperative period. Initially, patients must adjust to the postoperative diet and to their altered relationship with food. As weight loss progresses, patients must adapt to changes in their appearance and their interactions with others. Dramatic weight loss, however desirable to the patient, can lead to unexpected consequences, such as body image issues related to excess skin, unwanted sexual attention from others, and jealousy from friends and loved ones. As a result of these many challenges, mood disorders, disordered eating patterns, and substance abuse are common among postoperative patients.

Mood Disorders

Mood disorders are prevalent among candidates for bariatric surgery. For example, in one prospective study utilizing structured clinical interviews to assess mood pre- and postoperatively, clinical depression was present in approximately one-third and anxiety was present in almost 20% of preoperative patients [56]. In this population, the prevalence of clinical depression decreased by over 50% in the 3 years following surgery, but the prevalence of anxiety remained relatively stable. Other studies have reported significant improvements in depressive symptoms that persist for up to 5 years postoperatively [57–59]. Data from the large Swedish Obese Subjects (SOS) study suggest that after dramatic improvements in both depression and anxiety in the first postoperative year, there may be some deterioration of mood over time [60]. However, even 10 years postoperatively, the prevalence of mood disorders did not return to baseline levels in this cohort.

It is important to note that some studies have yielded less encouraging findings. In one small cohort, levels of depression and anxiety did not change significantly after surgery [28]. In another cohort, improvements in mood seen in the first postoperative year eroded after 2 years [61]. Other reports suggest that clinical depression may occur for the first time in some postoperative patients, despite good weight-loss outcomes [62]. Furthermore, patients who have undergone bariatric surgery may be at an increased risk of suicide, particularly in the first 3 years after surgery [62–64]. In one large retrospective cohort study, individuals who had undergone gastric bypass surgery were twice as likely to commit suicide as obese control subjects matched for sex, age, and baseline BMI [64]. Case studies suggest that patients who commit suicide after bariatric surgery often have a history of recurrent major depression, both before and after surgery, and that their depression persists even if they have excellent weight-loss results [65]. These reports highlight the importance of continued attention to psychosocial health in the postoperative period, regardless of weight-loss outcomes.

Disordered Eating

The prevalence of disordered eating appears to be high after bariatric surgery. In fact, studies suggest that half of all postoperative patients experience recurrent episodes of loss of control over eating [28,66,67]. Patients who have disordered eating patterns before surgery often continue to exhibit similar behaviors after surgery. In one prospective study, two-thirds of patients with preoperative binge eating disorder reported persistent eating pathology after surgery [68]. In many cases, patients may no longer be able to consume large amounts of food in a short period of time, due to the restriction in gastric capacity after surgery. However, emotional eating and grazing, which is defined as repeated episodes of consumption of small amounts of food, along with a perceived lack of control, are common in this population [69]. Patients may not report these behaviors unless they are prompted by a clinician.

Alcohol Misuse

As a result of media attention in recent years, there has been heightened concern about the potential for development of

alcohol dependence or abuse in postoperative patients [70]. There is a lack of published studies that have evaluated this issue prospectively with an appropriate control group. However, in one small cross-sectional study, structured clinical interviews were employed to determine the rates of current and lifetime alcohol use disorders in a group of 51 postoperative patients [71]. In this study, 35.3% of individuals met DSM-IV criteria for a lifetime history of alcohol use disorder, and 11.8% had a current alcohol use disorder, comparable to published rates in the general population (30.3% and 8.5%, for lifetime and current disorders, respectively). Patients with a prior history of alcohol use disorders (in remission at the time of surgery) appear to be at risk for recurrence after surgery [71]. Fortunately, anecdotal reports suggest that only a very small number (<3%) of patients significantly increase their alcohol intake after surgery [72].

The absorption and metabolism of alcohol may be altered after bariatric surgery, and as a result, postoperative patients may be more susceptible to the intoxicating effects of alcohol [73–76]. Patients should therefore be counseled to exercise caution when consuming alcohol after surgery. In addition, clinicians who care for bariatric surgery patients should ask patients about alcohol intake after surgery and remain alert to the possible presence of alcohol use disorders in this population.

Psychological Counseling and Peer Support in the Postoperative Period

Data suggest that patients with postoperative depression experience poorer weight loss than those who are not depressed [56]. Similarly, postoperative patients who exhibit disordered eating patterns, such as grazing and loss of control over eating, have poorer weight loss and greater weight regain [67,68]. Clearly, patients who are found to have mood disorders, disordered eating behavior, or substance abuse after bariatric surgery should be offered expert psychological counseling and support. It is not known, however, whether such treatment improves weight loss or other outcomes.

In epidemiologic studies, attendance at postoperative support groups is associated with improved weight-loss outcomes [77–79]. There is a lack of data regarding the effects of other types of postoperative psychological support, such as group or individual therapy, on weight loss and other outcomes.

Interestingly, patients who exhibit disordered eating patterns may be more receptive to a behavioral intervention after surgery than before surgery. In one small nonrandomized prospective study, pre- and postoperative bariatric surgical patients with binge eating or other disordered eating patterns were referred to a 10 week cognitive behavioral therapy program designed to address and improve the maladaptive eating patterns [80]. Patients who were referred to the program postoperatively were much more likely to attend the initial session and to complete the program than patients referred preoperatively.

COMPREHENSIVE LIFESTYLE INTERVENTIONS AFTER BARIATRIC SURGERY

There is limited data regarding the benefits of comprehensive lifestyle interventions in the postoperative period. However, in one small, randomized controlled trial, subjects who were assigned to a multifaceted lifestyle intervention after vertically banded gastroplasty reported improved dietary habits, increased physical activity levels, and reduced television viewing, as compared to subjects assigned to usual care [81]. Furthermore, subjects in the lifestyle intervention group lost significantly more weight at 1, 2, and 3 years after surgery than subjects in the usual care group.

The timing of the intervention may be important. Kalarchian and colleagues recently reported the results of a small randomized, controlled study (n = 36) involving patients who had undergone bariatric surgery at least 3 years earlier but who had failed to lose 50% or more of their excess weight [82]. Participants were randomly assigned to a comprehensive lifestyle intervention, including 12 weekly group education sessions and 5 individual telephone coaching sessions over 6 months, or a waitlisted control group. Subjects randomized to the intervention group lost slightly more weight (3.3 ± 8.1 kg) than those in the control group (1.3 ± 6.8 kg), but the difference was not statistically significant. Interestingly, in this study, the presence of depressive symptoms at the beginning

TABLE 45.3
Etiological Factors for Weight Regain Following Bariatric Surgery

Anatomical
LAGB malfunction or mismanagement
Band or port breakage, band to lose
RYGB
Pouch enlargement
Gastrojejunal anastomosis dilation
Gastro-gastro fistula
Physiological
Pregnancy
Menopause
Weight gaining medications
Smoking Cessation
Endocrine disorder: hypothyroidism, Cushing's disease
Intestinal or hormonal adaptation
Behavioral
Dietary
Unhealthy eating patterns, grazing, nibbling, mindless eating
Consumption of high energy foods and beverages
Loss of dumping syndrome symptoms
Loss of control over urges, binges
Reduced vigilance
Physical Activity
Reduced leisure time activity
Increased sedentary behaviors
Insufficient moderately and vigorously intensity exercise
Development of physical limitations to exercise

of the study was associated with greater weight loss in the intervention group but not the control group, suggesting that the behavioral component of the intervention may have been helpful for patients with depression.

WEIGHT REGAIN FOLLOWING BARIATRIC SURGERY

Although clinicians commonly see bariatric surgery patients regain some weight postoperatively, the prevalence and incidence of weight regain has not been well characterized. Using cross-sectional data, weight regain has been estimated to occur in 20%–35% of patients, depending upon the procedure performed and duration of time following surgery [23,35,38,83]. The causes of weight regain are likely to be multifactorial, similar to patients who regain weight after nonsurgical approaches. Table 45.3 provides a categorical list of potential etiologies that should be explored with all patients who present with weight regain. The physiological and behavioral (diet and physical activity) causes are common to surgical and nonsurgical patients. Depending on the patient's age and gender, a through history should be performed that reviews all of these reasons followed by appropriate counseling. In contrast, the anatomical factors for weight regain result directly from either malfunction or disruption of the surgical procedure. These causes need to be evaluated by an imaging procedure or upper endoscopy. Additional studies are needed to better understand the frequency, etiology, and treatment for weight regain.

CONCLUSION

Bariatric surgery is an effective and acceptable treatment for individuals with severe obesity who are at risk for or have complications associated with obesity. Several surgical procedures are available with variable risk and weight-loss outcomes. However, regardless of the procedure performed, surgery is considered a tool that is adjunctive to choosing a healthy, calorie-controlled diet and engaging in daily physical activity. For patients who undergo restrictive-malabsorptive or malabsorptive operations, dietary supplementation is necessary to avoid nutritional deficiencies. Patients are at risk for weight regain following surgery due to several biopsychosocial factors. In order to maximize successful outcomes, all patients should be monitored and managed by a multidisciplinary team of health care providers knowledgeable in bariatric surgical care.

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46 Future Directions in Obesity Research and Treatment

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CONTENTS

Changes in Dietary Patterns over Time 584
Insulin-Sensitivity Hypothesis 585
LCDs and Physiological Markers 587
Insulin and Physical Activity 587
Weight Gain, Sleep, and Stress 588
Summary 589
References 590

The numbers are clear and the trajectory has been obvious for years: Overweight and obesity are rampant in the United States and obesity-related diseases are at epidemic levels. Prior to the launch of the Food Guide Pyramid in the mid-1970s, the weight status of the U.S. population was relatively stable and the prevalence of obesity was relatively low. Subsequent to the 1970s, in the 1980s and 1990s the rate of obesity increased by 50% per decade [1]. Between 1980 and 1994, the prevalence of obesity among U.S. children grew by 100% [2]. The NHANES results from 2007 to 2008 demonstrated that out of U.S. citizens 20 years and older, over 34% were overweight, 33% were obese, and close to 6% were extremely obese [1]. From 2007 to 2009 alone, the number of obese U.S. residents grew by 2.5 million. Despite presidential backing, as of 2010 no state had met the *Healthy People 2010* goals of obesity rates at or below 15%. In fact, from 2009 to 2010, the number of states with an obesity prevalence of 30% or more increased from 9 to 12 [3]. If current trends continue, by 2023 it is estimated that 80% of Americans will be overweight or obese [4].

As the rates of overweight and obesity continue to increase so does the prevalence of diseases associated with excess adiposity. In the United States, obesity constitutes a leading cause of mortality, second only to smoking [5]. Of the host of disease states associated with obesity are the components of metabolic syndrome, cardiovascular disease (CVD), and the growth and proliferation of certain types of cancer cells. Obesity also affects an individual's quality of life by negatively impacting their social and occupation functioning along with their mental health. If the problems of obesity and overweight cannot be controlled, particularly among children, the current U.S. generation may actually experience decreased longevity compared to their parents. Rather than a singular focus on weight reduction for the purpose of improved health, future obesity treatments should be developed, which positively impact the cluster of disorders accompanying weight gain.

Despite concern over the obesity epidemic and immense effort and investment in developing weight-loss interventions over the past 40 years, the impact of obesity treatments have been largely disappointing. Regardless, Jeffrey et al. [6] report 47% and 75% lifetime prevalence rates for dieting among men and women, respectively, and it is reasonable to believe that as overweight and obesity rates climbed over the subsequent 20 years that these numbers would have commensurately increased. Optimistic reports suggest that the majority of weight-loss interventions demonstrate some success in the short-term [7] and approximately 20% of overweight individuals are successful at maintaining at least a fraction of weight lost. On the other hand, numerous reports have also suggested that weight lost is usually regained within a few years of treatment, with perhaps as many as 30%–64% of weight-loss intervention participants gaining back weight in excess of what they had initially lost [8]. In general, the more time between cessation of intervention and follow-up, the more weight is regained [8].

Additional evidence for the lack of practical success of weight-loss interventions come from the methodology typically employed in weight-loss trials. Most weight-loss studies have compared a low-fat diet group to a control group. Despite the control groups receiving no intervention and the low-fat diet groups receiving intensive intervention typically consisting of food diaries, food weighing, group and individual counseling, the intervention groups do not fare significantly better than the control groups [7]. In studies where low-fat diet protocols are compared to other diet types of similar intensity, the low-fat diets generally perform worse [7]. As a result of the lack of long-term success

experienced by many individuals on low-fat diet regimens, and the frequency with which many individuals engage in dieting, the development of any new dietary approach should carefully consider the potentially very negative ramifications of weight cycling [8].

Although long-term outcomes are generally poor, the typical low-fat caloric-restriction weight-loss prescription is still widely endorsed. Interestingly, this continued allegiance persists without respect to outcome or complaints from participants in such programs of feeling unsatisfied and hungry. Even on low-fat diet plans that do not encourage strict energy restriction, participants often report feelings of hunger, which may be a result of declines in blood glucose subsequent to the metabolism of a high glycemic meal. Unfortunately, such feelings of hunger have been associated with the development of adverse mood states. Cheatham et al. [9] found that over the course of a 6 month study, a group of participants following a high glycemic diet reported significant consistent worsening of mood. Wells et al. [10] also found that after just 1 month, individuals following a low-fat diet reported increasing scores on a measure of anger and hostility. An increasingly negative mood, particularly with regard to the development of worsening depressive symptoms as is frequently noted in those following low-fat, high-carbohydrate diet protocols, have been shown to adversely impact the long-term commitment to such weight-loss programs [9]. Six of the seven studies and meta-analyses included in the Nutrition Evidence Library indicate greater attrition rates for low-fat diets as compared to low- or very-low carbohydrate diets [11]. On average, studies reporting attrition in nonpharmacological behavioral weight-loss interventions report rates ranging from 22% at 6 months [12] to 70% at 12 weeks in a commercial weight-loss program [13]. As an aside, outcomes for weight-loss medications are often no better due to 1 and 2 year adherence rates of less than 10% and 2%, respectively [14].

To move forward in addressing the challenges of overweight and obesity in the coming decades will require reexamination of the approaches most heavily relied upon for weight control. Since weight loss over time is negligible, negative mood states are increased, attrition is high, and participants report a lack of satisfaction with energy restriction and low-fat diets, the investigation and development of alternative approaches is imperative. Moreover, since obesity is so strongly correlated with a plethora of metabolic dysfunctions, trends in diet and contributions to understanding metabolism from anthropology and biochemistry are warranted. This chapter will address emerging lines of research that incorporate interdisciplinary approaches to the development of unifying theories of overweight, obesity, and modern diseases of civilization.

CHANGES IN DIETARY PATTERNS OVER TIME

Prior to the introduction of agriculture and animal husbandry (~10,000 years ago), hominins largely relied on animal meat (including internal organs), fish, fruit, vegetables, and nuts for sustenance [15,16]. Although for years it was thought that hunter gatherers (HG) subsisted primarily upon vegetation, this inference was a result of limited study by Lee [17], whose data were misrepresented and misinterpreted over the years [18]. More recent ethnographic and quantitative analyses of archaeological data in addition to studies of modern foraging populations indicate that animal products comprised the majority of the HG diet [18]. Richards and colleagues analyzed isotopic evidence from Neanderthal skeletons [19] and Paleolithic humans [20] and found strong evidence of a diet predicated heavily on animal products. Moreover, contrary to popular belief that HG lead short difficult lives riddled with disease, archaeological evidence suggests that our HG ancestors were fit, strong, lean, and tall with healthy teeth and bones [21]. In fact, it was the assimilation to a carnivore diet that throughout evolution facilitated the development of a larger brain, a smaller jaw, a faster metabolism, and a reduction of gut size [22–24]. However, there simply has not been a sufficient amount of time for the human genome to adapt to a diet based on the genetically manipulated monocrops of modern agriculture (e.g., wheat, soy, etc.), factory farming, and processed foods since the past 10,000 years constitutes only about 1% of our evolutionary history [15,25,26].

While patterns of macronutrient consumption varied by region, culture, season, and other factors, HG, and the animals consumed by HG, foraged on native and natural foods. Current protein intake estimates for modern worldwide HG cultures range from 19% to 35% [27] well above the current estimates for protein consumption in the United States (~15% of total energy intake) and at the upper end of government recommended levels for adults (10%–35%; [28]). This rate of intake has been relatively stable since 1970, with the average intake of meat, eggs, and nuts having increased over time by only 70 cal [29].

The primary macronutrient difference, however, between the HG diet and modern Western diets is centered on the consumption of carbohydrates. While current estimates of the percentage of total caloric intake from carbohydrates ranges from 49% to 52% [28] for men and women in the United States, well-aligned with the government recommended level of 45%–65%, HG diets likely ranged from 22% to 40% carbohydrate [27]. Moreover, important qualitative differences should be noted. Carbohydrates consumed by HG consisted primarily of low-glycemic high-fiber wild vegetables with honey on occasion when seasonally available [30]. In contrast, an examination of the top 25 sources for calories among adult Americans, reveals an inherent reliance on high-glycemic carbohydrates in the form of (in descending order) grain-based desserts, yeast breads, soda/energy/sports drinks, alcohol drinks, pizza, tortillas/burrito/tacos, pasta, potato/corn/other chips, fried white potatoes, ready-to-eat cereals, candy, rice, quickbreads, and fruit drinks. These types of foods comprise approximately 72% of the total daily caloric intake by people in the United States [31] and contributed to the

131.9 lb/person/year consumption of refined sugar in the United States in 2010 [32]. Overall, of the calories consumed by most Americans, 75% come in the form of highly processed foods containing high levels of sugars and high glycemic carbohydrates [33].

In addition to the changing role of carbohydrates in the human diet, particularly the Western diet, a similar pattern, albeit in the opposite direction, is noted for fat intake. The majority of modern foraging cultures, much like our HG ancestors, consume a diet comprised of approximately 36%–43% of total caloric intake from fat with no adverse health effects [27]. These numbers are somewhat higher than the current fat intake of Westerners [28] and higher than government recommended levels for adults (20%–35%; [31]. During the late 1960–early 1970s, the government began advising the American public to replace saturated fats with polyunsaturated fat. Then during the 1980s that message shifted to one advising the elimination of all fats. By 1990, the American Heart Association was calling for the use of nonfat dietary products [7]. Among nutrition and diet researchers, virtually sole emphasis has been placed on reducing fat intake as a method to promote weight loss and improve health parameters. The American public has dutifully responded to advice to reduce fat intake and from 1971 to 2000 reduced the percent of energy from fat from approximately 37% to 33% [28]. The consumption of saturated fat also declined from approximately 13.5% to 11% during this time period as the U.S. government began making recommendations to keep saturated fat below 10% of total daily caloric intake [28]. Unfortunately, according to Willett ([7]: p. 30), "we probably have collectively as a nutrition community contributed to the overweight problem" as a result of this line of thinking since the American public has been led to believe that so long as they avoid fats they can consume as much carbohydrate as they wish.

Despite the widespread belief that fat is "bad," the claim has never received empirical support and a large body of evidence suggests just the opposite. In fact, Zelman [34], stated in the *Journal of the American Dietetic Association* that targeting dietary fat as a cause of obesity and harm to health was misguided. Over the past 30 years numerous high-profile, large longitudinal studies failed to support the lipid-hypothesis in relation to obesity and indicators of poor health. These include the Framingham Heart Study [35], the Multiple Risk Factors Intervention Trial [36], and the Women's Health Initiative [37]. Hoenselaar ([38]: p. 122), in his review of the discrepancies between scientific evidence and dietary advice, summarized that "(t)he results and conclusions about saturated fat intake in relation to CVD, from leading advisory committees, do not reflect the available scientific literature."

In the Nurse's Health Study, which investigated the relationship between intake of various types of fats and the subsequent development of CVD, women with a high-consumption of trans fats in relation to polyunsaturated fats ran a three times greater risk of developing CVD. Overall, though, level of dietary fat was not associated with risk of CVD [7,16], in their review of the relationship between various fats and coronary heart disease (CHD) prevention called for the reduction or elimination of trans fats, while suggesting that the elimination of saturated fats and monounsaturated fats will have negligible to no impact on CHD risk, and the increased consumption of polyunsaturated fats may be cardioprotective.

In addition to addressing the lipid hypothesis, any effort to influence a change in the eating behavior of the American public will need to be accompanied by a clear explanation of macronutrient metabolism. It simply is not the case that all calories are created equal and continued advocacy for energy restriction with disregard for this evidence will perpetuate failure in attempts to reduce obesity. Although the government continues to call for the reduction of excessive caloric intake through the *Dietary Guidelines for Americans* [31] even the DGA committee recognized that caloric intake has remained relatively stable over time and within recommended guideline levels.

It has long been accepted, although not entirely among weight-loss researchers, that different macronutrients vary in their thermogenic properties. The rates of thermogenesis for carbohydrate are approximately 5% while protein is approximately 20% [39]. Hence, very low carbohydrate ketogenic diets (VLCKDs) due to protein driven gluconeogenesis provide metabolic conditions favorable for mass and fat loss. Under ketogenic conditions, established via low carbohydrate consumption, energy is provided through exogenous protein and fat sources. In instances where caloric-expenditure exceeds caloric intake, endogenous glycogen and fat stores are burned as well. In this state, similar to conditions of starvation, fatty acids and ketones are used as fuel [39]. However, unlike starvation, with adequate levels of protein and fat intake and restricted carbohydrate consumption, glucose levels are maintained and feelings of hunger are thwarted.

A relatively recent re-evaluation of the lipid hypothesis in conjunction with increased awareness of the role of carbohydrates in insulin production and weight gain has resulted in the proliferation of research examining the impact of fats vs. high-glycemic carbohydrates on weight status and health parameters. Such dietary comparisons are very instructive for the weight-loss practitioner and should be examined carefully given the relative lack of significant impact from the conventional weight-loss approaches focusing on thermodynamics and the lipid hypothesis [40,41].

INSULIN-SENSITIVITY HYPOTHESIS

In an effort to further elucidate the role of insulin in weight status and health, as well as investigate the applicability of the lipid hypothesis in comparison to the insulin-sensitivity hypothesis, comparisons of weight lost on low-fat diets (LFD) and low-carbohydrate diets (LCD) have received increasing consideration. Interventions in which the fidelity of each approach is maintained may expose potentially

constructive theoretical and pragmatic conceptualizations of the obesity epidemic. Although dietary protocols among LCD interventions are relatively inconsistent with regard to total kcal/day, percent of energy from fat and protein, and fat and protein sources, results indicate a clear trend. Volek et al. [42] found that among LFDs and LCDs with equivalent caloric intake, weight loss among individuals following an LCD was significantly greater than among participants in LFD groups (10.1 vs. 5.2 kg). Results from the A to Z Weight Loss Study [43] demonstrated that individuals adhering to the Atkins diet, which is low in carbohydrate, evidenced two times the weight loss in comparison to individuals on other diets. Hession et al. [44] reviewed the literature comparing LFDs to LCDs and reported that LCDs are more effective at 6 months and as, if not more, effective than LFDs at 1 year. Foster et al. [45], in the only 2 year randomized clinical control trial to date, reported greater 2 year weight loss on LCDs than LFDs despite a lower energy intake in the LFD.

In fact, studies comparing LFDs to LCDs often restrict the caloric intake of the LFD groups while allowing the LCD group to consume ad libitum. Despite caloric differences, weight loss is generally comparable if not greater in the LCD condition and the LCD groups report greater satiety and satisfaction with the diet [46–48]. Moreover, as is typical for LFD and low-calorie diets, any weight lost is only maintained for as long as the individual remains in a calorically deprived state.

A confound in many studies involving LCDs is the gradual reintroduction of carbohydrates. Evidence suggests that such a methodology compromises weight loss and results in weight regain over time. An additional source of bias involves studies including exclusively vegetarian sources of protein and fat, limited or no red meat, and high dairy protocols as part of LCDs. These aspects appear to mitigate weight loss as well.

The extent to which carbohydrates should be limited in an effort to impact health and weight status is not entirely clear; although, it now seems evident that any reduction of carbohydrates below 100 g/day is likely to yield positive results. The very low carbohydrate ketogenic diet (VLCKD), in which carbohydrate intake is sufficiently low to create the presence of detectable ketones, generally requires carbohydrate intake no greater than 10% of total energy. VLCKDs typically involve unrestricted intake of saturated and unsaturated fat, meat products, fish, eggs, heavy cream, and oil with limited amounts of hard cheeses and low-carbohydrate vegetables and a small amount of nuts and seeds. Restricted foods include fruits and juices, other dairy products, all grains and cereals, high-carbohydrate vegetables, and desserts.

Aside from absolute weight loss, distinct patterns of change are noted in comparing LFD to LCD weight loss. Percent of weight loss due to fat loss is significantly greater on LCDs than on LFDs. According to Garrow and Summerbell [49], a weight loss of 10 kg achieved through dieting alone should consist of 71% fat mass loss. However, studies examining fat loss patterns in individuals consuming an LCD suggest a preferential loss of fat mass [48,50]. Volek et al. [48] found that for obese males, LCDs ranging from 30 to 104 g of carbohydrate per day result in a corresponding weight loss comprised of 95%–75% fat mass, respectively. Moreover, individuals on LCD protocols evidence greater midsection and abdominal weight loss than is seen with those following an LFD regimen. Volek et al. [48] noted body fat loss in the trunk region three times greater in a very low-carbohydrate diet group than in a low-fat diet group. While the most significant differences occurred with men, within-group examination of women alternately consuming both a VLCKD and an LFD reveal slightly greater reductions in body mass, total fat mass, and trunk fat mass while consuming the VLCKD, as well. In fact, Volek et al. [48] demonstrated that many subjects regained fat subsequent to switching from a VLCKD to an LFD. However, no subjects regained weight or fat on the alternate protocol. This pattern of fat loss, likely a product of the five to seven times greater reactivity to insulin molecules of abdominal fat than more distally located subcutaneous adipocytes, should be of great interest to obesity researchers since abdominal adiposity is often mostly closely related to the health problems associated with metabolic syndrome [51].

In addition to frequently noted weight loss and higher than predicted percent fat loss, an LCD may constitute the most promising future direction in obesity for other reasons. First, free-living individuals on an LCD often naturally reduce their caloric intake as a result of decreased appetite and hunger resulting from higher consumption of fat and protein. In a controlled study, researchers found that hunger level on an LFD was equivalent to hunger level experienced on a 1000 kcal/day less LCD [52]. Increased ketones have been shown to inhibit appetite while low-glycemic intake prevents dips in blood glucose, which occur on higher carbohydrate diets and which may produce carbohydrate cravings, resulting in increased intake. While high-protein and fat diets reduce appetite and increase feelings of fullness, diets creating a high-insulin response (e.g., high-carbohydrate diets) are shown to increase food intake, are experienced as less satisfying, and may result in an overall higher energy intake. It is perhaps a result of decreased feelings of hunger on an LCD that also results in higher rates of compliance among participants on LCDs than on LFDs [39]. Furthermore, while many studies of weight loss are inherently problematic with regard to objective measurement of intake and relationship between intake and physiological measures, fidelity to a VLCKD is directly verifiable through daily urine testing with reagent strips for the presence of acetoacetic acid. During approximately 10 weeks of testing, Volek et al. [48] noted 85% compliance to a VLCKD through urine testing for ketones. The ability to objectively measure fidelity, in combination with decreased attrition rates and greater satiety, contributes to the demonstrated feasibility of implementing LCDs in output settings.

Fidelity to an LCD and decreased attrition may also be the result of improved mood promoted by these diets. Multiple

reports indicate that an LCD may be more protective of mood during weight loss than an LFD. Evidence suggests that consumption of a high-fat/low-carbohydrate meal results in greater feelings of relaxation and friendliness and decreased feelings of tension and antagonism as compared to consumption of a low-fat/high-carbohydrate meal [10,53,54] Cheatham et al. [9] also examined the impact of diet on subclinical depression among participants in a weight-loss study. Their results indicated lower levels of subclinical depression and negative mood among participants following an LCD as compared to those on an LFD.

Overall, it appears that an LCD may provide a potentially effective means for weight control over traditional calorie restriction and low-fat diets without concomitant hunger and decline in mood. Moreover, improvement in health parameters generally occurs rapidly and regardless of weight loss.

LCDs AND PHYSIOLOGICAL MARKERS

The emphasis, over the years, on reduction in overweight and obesity has primarily been driven by the relationship between weight loss and improved markers for health. Of primary concern to obesity researchers is the relationship between weight and CVD, the current leading cause of death in the United States. Coronary artery disease (CAD), a rarity in the early 1900s [55], is thought to have increased in prevalence due to dietary changes brought about through industrialization [56]. Since obesity rates began to climb the emphasis with regards to weight loss and health has rested almost exclusively on lipid profiles and cholesterol. The LDL of healthy newborns is between 30 and 70 mg/dL; however, as soon as infants are weaned and started on a modern diet LDL increases [33]. The average LDL of American adults is approximately 130 mg/dL, well above the physiologically normal range. Approximately 80% of CAD events occur within the 90–130 mg/dL range [57], and prognosis of CAD event improves as LDL levels approach the physiologically normal range [58]. However, as research into lipid profiles has proliferated, it has become clear that the atherogenic risk with regard to LDL comes almost entirely from the small, dense particles rather than the overall LDL cholesterol concentration [59–61]. Moreover, the small dense LDL particles are now considered to be an associated feature of metabolic syndrome [42].

Since it is now clear from epidemiological studies that there exists a positive, inverse, or at minimum, no relationship between saturated fat and CVD morbidity and mortality, the hypothesis that fats contribute to higher risk of CAD needs to be replaced with the greater likelihood that excess carbohydrate intake results in increased levels of small dense LDL particles [42]. Evidence from multiple studies points to improvement in lipid markers of CVD subsequent to a VLCKD, which is typically high in fat including saturated fat [59–61]. Small dense LDL particles are often converted to larger LDL and decreases in plasma saturated fatty acids are noted, despite higher saturated fat intake. While LFDs often produce reductions in LDL when participants lose weight, reductions in HDL-cholesterol (HDL-C, along with triglycerides, the lipid component most strongly associated with insulin resistance) are also generally noted [62,63]. Conversely, LCDs typically result in increased HDL-C levels [45]. Overall, Frassetto et al. [15] found consistent improvement in the physiology and metabolism of carbohydrate and lipids on LCDs. On VLCKDs reduction in CVD risk has been noted during weight loss and weight maintenance phases after only 8–12 weeks [64–67]. Overall Volek et al. ([42]: p. 307) conclude that "carbohydrate restriction has the ability to target the range of markers with a single intervention" and thus represents an unified approach to improved overall health. These findings are consistent with the 2005 Institute of Medicine Macronutrient Report stating that in comparison to diets higher in fat, low-fat and high-carbohydrate diets may be more deleterious with regard to the development of CHD and diabetes [31].

In addition to improved lipid profiles, subjects on an LCD typically evidence improvement on numerous additional physiological markers. Frassetto et al. [15] found that among healthy sedentary adults a LCD improved not only lipid profiles, but glucose tolerance, blood pressure, insulin secretion and sensitivity, and vascular reactivity without weight loss, increase in physical activity, or use of medications among healthy sedentary subjects after only 2 weeks. Westman et al. [39] and Johnstone et al. [68] noted significantly decreased insulin secretions and increased insulin sensitivity among individuals following a LCD, within 3–4 days on the diet, as well. Yancy et al. [69] also reported significantly greater improvements in blood pressure in a VLCKD group compared to a LFD plus Orlistat group. LCDs have proven beneficial for individuals suffering from epilepsy [70,71], narcolepsy [72], heartburn [73,74], and dermatitis herpetiformis [75]. Moreover, intracellular changes resulting in decreases of reactive oxygen species (ROS) are evident with the metabolism of fatty acids and ketones [39]. Since ROS facilitates apoptosis, a VLCKD may reduce the risk of diseases associated with ROS generation including Alzheimer's diseases and a variety of cancers [76].

INSULIN AND PHYSICAL ACTIVITY

Any discussion of weight loss and maintenance invariably includes the role of physical activity (PA). Over the past 40 years, as a result of the adoption of the thermodynamics hypotheses, the relationship between exercise and weight loss/maintenance has focused on creating a negative energy balance through exercise. As has been the case with nutrition, this advice has been predicated upon faulty logic and information. Exercise plays an undeniably important role in maintaining health. However, the role of PA in reducing overweight and obesity is far more complex than the achievement of a negative energy balance. The same insulin-sensitivity hypothesis applicable to weight loss is relevant to the role PA plays in achieving maximum health.

An examination of trends in PA over the same course of time in which the rise in weight status has been noted is very

revealing. A random annual telephone survey conducted by the Centers for Disease Control and Prevention from 1990 to 1998 showed that although many Americans were not meeting health activity recommendations, the self-reported level of PA in which the U.S. population engaged remained stable [77]. A more rigorous test of the relationship between PA and weight status involves the use of the doubly labeled water (DLW) technique to assess energy expenditure. Numerous such studies, reviewed by Westerterp and Speakman [78], showed that from 1988 to 2006, a slight increase in PA was noted across Europe and North America. However, during that same time period, obesity rates rose from 5% to 10% in the European samples and 8% to 22% in the North American samples [79].

Perhaps the rise in obesity despite an increase in PA is reflective of increased caloric consumption among those who are physically active. Another study using the DLW technique followed 40 healthy nonobese adults with an average age of 27 over 11 years [79]. This study assessed activity related energy expenditure, PA levels, and BMI. Interestingly, participants with high-baseline PA gained more weight at follow-up than those participants with lower baseline PA. In addition, on average, all members, regardless of PA level gained approximately 5 lb/year. The authors suggest that although many participants changed from a physically active lifestyle to one that was less active across the study's 11 year span, participants' caloric intake was not commensurately reduced [79].

It is generally accepted among PA researchers that weight loss cannot be accomplished by PA alone [80–82]. Although recommended activity levels of moderate intensity are related to improved health indices, they are not associated with clinically significant weight loss. In fact, the position statement of the organization arguably the most likely to declare an association between PA and weight loss (American College of Sports Medicine) states, "despite the intuitive appeal of the idea that physical activity helps in losing weight, it appears to produce only modest increments of weight loss beyond those achieved by dietary measures and its effects no doubt vary among people" [83; p. 1087, 84].

Although theories involving increased PA in an effort to balance a thermogenic energy equation have failed, there are other metabolic advantages of PA that indirectly contribute to weight stability and loss. Exercises designed to increase muscle tissue may decrease the amount of free-floating glucose eventually stored in fat cells. Not because of the sheer number of calories burned, but due to the impact of increased myocytes on glucose clearance. A greater amount of muscle mass in relation to fat mass results in a greater balance and regulation of insulin delivery and metabolism. Because muscle burns approximately 7–10 times more glucose than fat [85,86], a physiological balance in favor of greater muscle mass than fat mass increases the efficiency and expediency through which glucose is metabolized and cleared [51].

In order to fully appreciate the role of PA in weight loss and maintenance, attention must shift from energy expenditure to insulin regulation and the role myocytes and adipocytes play in conjunction with energy intake. An optimal diet and PA regimen is one which limits carbohydrate intake (and thus insulin production) and involves the engagement of muscle tissue in clearing remaining glucose in addition to burning protein and ketones for energy. Unfortunately, even a cursory review of the PA components of obesity treatments reveals a predominance of prescriptions for long periods of moderate activity. These approaches often require long and repetitive periods of PA, which do not maximize neuroendocrine adaptation. In contrast, an approach to physical fitness receiving increased focus is high intensity functional training (HIFT), which appears to maximize the benefits of exercise including metabolic and physiological adaptations in cardiac muscle cells and endothelial function, blood pressure, cardiac contractility, lipid oxidation, glucose and insulin levels, body composition, and skeletal muscle adaptations [87–90]. HIFT facilitates these improvements in substantially less time, or training volume, than traditional exercise approaches. Importantly, HIFT has been found to be safe even for medically compromised individuals, including patients with heart failure (HF), CAD, and chronic obstructive pulmonary disease (COPD) [88,91,92].

WEIGHT GAIN, SLEEP, AND STRESS

As the link between hormones and weight gain becomes increasingly clear, the relationships between sleep and stress and their impact on obesity, are gaining further attention. It is very likely that HG slept and worked in accordance with the rising and setting sun, establishing circadian rhythm patterns, which influence the release of hormones in a similar fashion still for modern man [93]. Studies involving participants including children, adolescents, and adults have confirmed a link between sleep and weight status. A lack of sleep clearly decreases leptin secretions, which generally peak during nighttime sleep [94]. In addition, ghrelin, which signals hunger, becomes elevated in a sleep-deprived state [95,96]. The decrease in leptin and concomitant increase in ghrelin result in sleep-deprived individuals reporting increased hunger and appetite. However, even more significantly, individuals in such a state crave sugary, starchy, and salty foods over all others [95]. While a metabolic or thermodynamic explanation would suggest that such cravings would be necessary to account for increased energy expenditure during wakeful times, participants in sleep-restriction studies were often required to remain in bed or sitting in a comfortable chair [95]. While HG may have benefitted from a metabolic advantage when hunting at night, modern man, when experiencing a sleepless night, rarely engages in PA to counterbalance the hormone-driven cravings and hunger.

To make matters worse, in addition to increased ghrelin and decreased leptin, sugary and starchy food cravings, and the resultant hunger, sleep-deprived individuals typically evidence decreased glucose tolerance. A 4 h sleep reduction across six nights produced a 30% reduction in insulin response to glucose in healthy men [97]. Individuals who remain sleep deprived can reach a state of insulin resistance bordering on prediabetes [98]. Across longitudinal

and cross-sectional studies, an inverse relationship has been established between sleep and BMI. A study of 1772 participants over 15 years of age in Spain found that those sleeping more than 9 h a night had less than half the risk of obesity in comparison with their counterparts sleeping 6 or fewer hours per night [99]. Gangwisch et al. [93] in analyzing data from NHANES I from 1982 to 1992, reported similar results leading them to suggest that weight control efforts should place greater emphasis on sleep quality and quantity.

In addition to direct effects, sleep deprivation is also associated with stress and depression, which, in turn, are related to weight gain. Stress, whether brought on by sleeplessness or environmental conditions, is associated with metabolic changes as well as changes in eating patterns. Metabolically, stress can moderate the responsiveness of the hypothalamic-pituitary-adrenocortical (HPA) pathway [100]. There is strong evidence to suggest that weight status is impacted via elevations of cortisol produced under conditions of prolonged activation of the HPA axis and thus resulting in insulin resistance [100–104]. Frequent dieting is correlated with emotional stress [105] perhaps due to the negative emotional consequences of calorie restriction or low-fat intake or the associated repetitive chores including calorie counting and food monitoring [106]. Tomiyama et al. [107] found participants in a 2 (calorie restriction vs. no calorie restriction) × 2 (caloric-monitoring vs. no caloric-monitoring) study who were tasked with monitoring caloric intake reported increased perceived stress and participants in groups restricting caloric intake evidenced increased total cortisol production.

Prolonged stress may also contribute to quantitatively and qualitatively different patterns of food intake. Among college students, studies suggest that stress and depression are associated with less fresh fruit and vegetable consumption, greater intake of sweets and fast foods [108,109], and binge eating [110,111]. Vicennati et al. [112] have demonstrated that subsequent to the culmination of a stressful event, a preference for carbohydrates persists. This phenomenon may be particularly strong among women [113]. The preference for carbohydrate foods as a result of stress can be understood in light of the relationship between cortisol, glucose, and insulin. Elevated secretions of cortisol, a stress hormone and insulin antagonist [114], are related to increased glucose intolerance [115]. Glucocorticoids directly impact insulin action and down-regulate sensitivity to lipase while inhibiting peripheral tissue uptake of glucose. This in turn, drives the cravings for starchy, high glycemic, carbohydrates. Therefore, chronic hypercorticolemia results in increased fat mass, particularly in visceral adipose tissue where glucocorticoid receptor density is high [116]. Thus, a strong relationship exists between chronic stress, high cortisol levels, and metabolic syndrome [117,118]. In one study of work-related stress, employees with chronic stress were two times more likely to develop metabolic syndrome than their nonstressed colleagues [119]. Overall, clinical, as well as epidemiological studies, document a significant relationship between stress due to adverse life events and psychological as well as psychosocial challenges and abdominal obesity and metabolic syndrome.

SUMMARY

For the past three decades, conventional wisdom has concluded that obesity is the result of an imbalance between energy intake and expenditure as predicted by the energy balance equation. Also, the theoretical basis for dietary prescription was dominated by the lipid hypothesis, which warned that dietary fat, particularly saturated fat, promoted heart disease. Obesity, it has been argued, is the result of sloth (declining rates of physical activity) and gluttony (increasing intake of dietary fat and total calories). These two hypotheses remain highly influential among segments of the academic community and still largely guide advice from government agencies. For instance, a recent ranking presented in U.S. News and World Reports' "Best Diets" focus on low-fat, semistarvation diets despite their anemic outcomes in clinical trials. In this chapter it is argued that a comprehensive analysis of nutritional science, biochemistry, epidemiology, and evolutionary biology literature presents a significant challenge to the conventional wisdom about obesity. Evidence is mounting that, as Hite et al. ([11]: p. 922) have concluded, although the initial goals were admirable, the application of the dietary recommendations for low-fat and reduced-calorie diets have "constituted a population-wide dietary experiment that should be brought to a halt" as the "'potential for harmful effects' has in fact been realized." In addition, a critical analysis of the literature on PA rates over that past several decades casts doubt on the notion that sloth is a significant cause of the obesity epidemic. We argue that obesity research is ripe for a paradigm shift away from the conventional wisdom which has failed to adequately impact the global obesity epidemic toward fresh approaches, which are better grounded in the larger scientific literature and which offer new hope for those who suffer from obesity and its related disorders.

It seems clear that future investigations should strive to increase understanding of the insulin-sensitivity hypothesis of weight gain, potentially assist in creating new U.S. dietary guidelines based on this appreciation, and help inform the public of metabolic pathways to health and wellness. To do so, the public must first be educated about the influence of carbohydrates, insulin, and other hormones in weight gain and health parameters. The role insulin plays in a host of seemingly unrelated physiological markers including poor lipid profiles, hyperinsulinemia, hyperglycemia, increased inflammation, and decreased apoptosis in endocrinological cancer cells should also be of primary concern to nutrition researchers. Moreover, the increased prevalence rates corresponding to the population-wide increased consumption of carbohydrates have been noted in such varying conditions as diabetes, metabolic syndrome, allergies, headache, gout, acne, Alzheimer's disease, heartburn and reflux, irritable bowel syndrome, ADD/ADHD, epilepsy, schizophrenia, and narcolepsy and are potentially due to inflammation resulting from excessive carbohydrate intake deserves further investigation. The existence of such a unifying explanation for so many modern medical conditions is strong evidence for the insulin-sensitivity hypothesis. Carbohydrate restriction,

consistent with the hominin genotype can potentially target the majority of markers in one singular unifying approach while concomitantly reducing rates of overweight and obesity.

Given the relative newness of the insulin-sensitivity hypothesis with regard to weight gain and its physiological correlates specific additional areas of study warrant consideration. First, it appears clear that various hormones play significant roles in the gain and loss of weight as well as nutrient metabolism. It would therefore, be prudent to devote additional research efforts to expanding our understanding of the differences such hormones play in weight gain and loss between the sexes and among pre- and postmenopausal women. Second, further research efforts should be directed toward the study of free-living participants and their ability to maintain a LCD or a VLCKD over time. As these areas and more are further defined and explicated, a strong alliance between biochemists, food scientists, weight-loss researchers, and other specialists should be forged. Continuing to partition knowledge among professionals will continue to hinder advancement. Along similar lines, the creation and delivery of an unified message from various specialists to policy makers should be explored. Obesity, and morbidity, and mortality rates will not decline while political interests in certain agricultural commodities continue to take precedence.

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Part X

Immunology and Infectious Disease

David Nieman, DrPH, FACSM

47 Exercise, Inflammation, and Respiratory Infection

David C. Nieman, DrPH, FACSM

CONTENTS

Introduction 597
Chronic Anti-Inflammatory Influence of Exercise Training 597
Physical Activity, Fitness, and Chronic Inflammation 597
Potential Mechanisms 598
URTI Risk Reduction from Regular Moderate Exercise Training 599
Moderate Physical Activity and URTI Risk 599
Moderate Physical Activity and Enhanced Immunosurveillance 601
Conclusions 602
References 602

INTRODUCTION

Exercise immunology is a relatively new area of scientific endeavor, with the majority of papers published during the past 25 years [1]. Most studies have focused on the acute and chronic effects of various exercise workloads on the immune system and immunosurveillance against pathogens. For the practicing physician, two areas of investigation from exercise immunology have the greatest clinical and public health implications: (1) chronic anti-inflammatory influence of exercise training and (2) reduction in risk of upper respiratory tract infections (URTI) from regular moderate exercise training.

CHRONIC ANTI-INFLAMMATORY INFLUENCE OF EXERCISE TRAINING

Acute inflammation is a normal response of the immune system to infection and trauma. Intense and prolonged exercise similar to marathon race competition causes large but transient increases in total white blood cells (WBC) and a variety of cytokines including interleukin-6 (IL-6), IL-8, IL-10, IL-1 receptor antagonist (IL-1ra), granulocyte colony stimulating factor (GCSF), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 beta (MIP-1β), tumor necrosis factor-alpha (TNF-α), and macrophage migration inhibitory factor (MIF) [2,3]. C-reactive protein (CRP) is also elevated following heavy exertion, but the increase is delayed in comparison to most cytokines. Despite regular increases in these inflammation biomarkers during each intense exercise bout, endurance athletes have lower levels when measured during rest in contrast to overweight and unfit adults. For example, mean CRP levels in long-distance runners (rested state) typically fall below 0.5 mg/L in comparison to 4.0 mg/L and higher in obese, postmenopausal women [3,4].

The persistent increase in inflammation biomarkers is defined as chronic or systemic inflammation, and is linked with multiple disorders and diseases including atherosclerosis and cardiovascular disease (CVD), the metabolic syndrome, diabetes mellitus, sarcopenia, arthritis, osteoporosis, chronic obstructive pulmonary disease, dementia, depression, and various types of cancers [5–7]. CRP is the most frequently measured inflammatory biomarker, and individuals with CRP values in the upper tertile of the adult population (>3.0 mg/L) have a twofold increase in CVD risk compared to those with a CRP concentration below 1.0 mg/L [7]. An elevated fasting IL-6 concentration is a significant component of the chronic low-grade inflammation that underlies the metabolic syndrome, CVD, diabetes, and various cancers [8]. Athletes typically have plasma IL-6 concentrations that fall below 1.0 pg/mL in contrast to values above 2.0 pg/mL in older and obese individuals [3,8].

Physical Activity, Fitness, and Chronic Inflammation

Large population observational studies consistently show reduced WBC, CRP, IL-6, TNF-α, and other inflammatory biomarkers in adults with higher levels of physical activity and fitness, even after adjustment for potential confounders [9–14]. The inverse association between physical activity/fitness and inflammation is related in part to the effect of activity on fat mass [11]. In most studies, however, adjustment for body mass index (BMI) and adiposity attenuates but does not negate the strength of the relationship between inflammatory biomarkers and physical activity/fitness [11,15]. For example, in a study of 1002 community-dwelling adults (age range, 18–85 years), a general linear model (GLM) analysis adjusted CRP means for frequency of physical activity, BMI, and several other lifestyle and demographic factors [15].

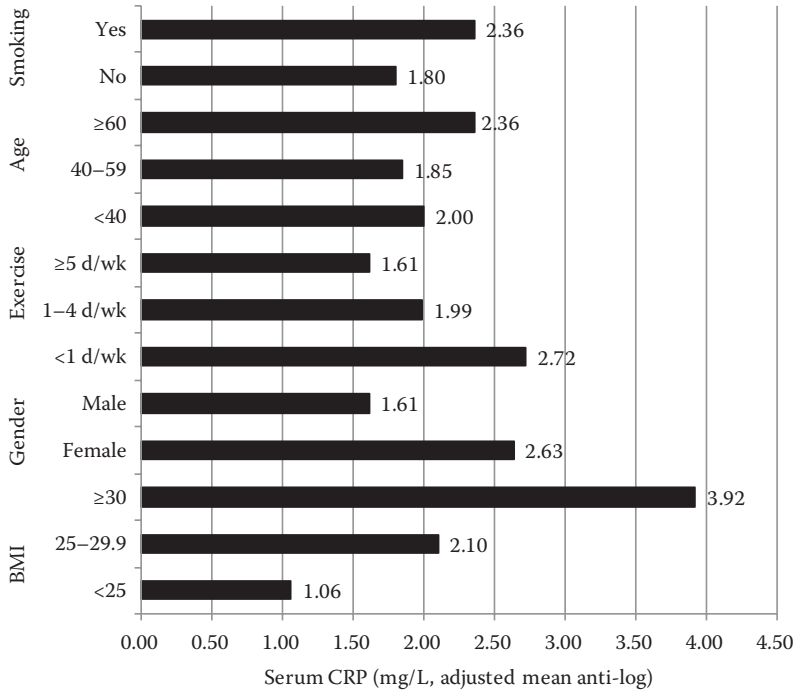


FIGURE 47.1 The relative influence of aerobic exercise frequency and other lifestyle and demographic factors on C-reactive protein. Means are adjusted statistically after weighting for each factor through a general linear model. (From Shanely, R.A. et al., *Scand. Med. Sci. Sports Exerc*., 2011, in press.)

BMI had the strongest effect on CRP followed by gender (higher in females), exercise frequency, age, and smoking status (Figure 47.1).

Randomized, controlled exercise-intervention studies provide equivocal support for the inverse relationship between increased physical activity and reduced systemic inflammation [11,16–22]. One explanation is that in comparison to the large variance evaluated in observational studies, the change in aerobic fitness and activity levels is typically of low magnitude in randomized exercise trials, the duration of training seldom extends beyond 6 months, and the number of subjects is relatively low [17,18,20,21]. Nonetheless, data from both study formats support that in order for reductions in chronic inflammation to be experienced, a large change in a combination of lifestyle factors is needed including weight loss, near-daily moderate-to-vigorous physical activity of 30–60 min duration, avoidance of cigarette smoking, and increased intake of fruits and vegetables [22,23]. For example, if an obese, older individual adds three weekly 30 min walking sessions to the lifestyle, reductions in chronic inflammation are unlikely to be experienced unless the exercise workload is increased in combination with significant weight loss and improved diet quality.

Potential Mechanisms

When successful, exercise training may exert anti-inflammatory influences through a reduction in visceral fat mass and the induction of an acute anti-inflammatory environment with each bout of exercise that over time becomes chronic [24,25]. These effects may be mediated in part through muscle-derived peptides or myokines, but this proposed mechanism needs further testing [25]. Contracting skeletal muscles release myokines (e.g., IL-6, IL-8, IL-15) that may exert both direct and chronic anti-inflammatory effects.

The first identified and most studied myokine is IL-6. During prolonged and intense exercise, IL-6 is produced by muscle fibers and stimulates the appearance in the circulation of other anti-inflammatory cytokines such as IL-1ra and IL-10 [26]. IL-6 also inhibits the production of the proinflammatory cytokine TNF-α and stimulates lipolysis and fat oxidation [26]. With weight loss from energy restriction and exercise, plasma levels of IL-6 fall, skeletal muscle TNF-α decreases, and insulin sensitivity improves [27,28]. Thus IL-6 release from the exercising muscle may help mediate some of the health benefits of exercise including metabolic control of type 2 diabetes [27,28].

Muscle IL-6 release, however, is very low during moderate physical activity. For example, during a 30 min brisk walk on a treadmill, plasma IL-6 concentrations increased from 1.3 to 2.0 pg/mL in female subjects [29]. The increase in IL-6 during brisk walking is probably insufficient to mediate anti-inflammatory and other beneficial health effects, and additional research is needed to determine the relative contribution of myokines compared to other exercise-induced factors. The acute exercise-induced increase in IL-6 after heavy exertion (e.g., typically above 5, 10, and 50 pg/mL following 1, 2 h, and marathon-race running bouts, respectively) may indeed orchestrate anti-inflammatory influences, lipolysis, and improved insulin sensitivity, but this amount of physical activity is beyond levels achievable by most overweight/obese individuals.

A moderate exercise program of near-daily 30 min walking bouts, without diet control, has small influences on visceral fat, even in long-term studies [30]. This is further evidence that the myokine hypothesis does not apply at the activity level attainable by most middle-aged and elderly individuals. Thus moderate physical activity training must be increased to the highest levels acceptable to an individual (e.g., 60 min/day) and combined with weight loss through tight control of energy intake and improved diet quality to achieve reductions in systemic inflammation.

URTI RISK REDUCTION FROM REGULAR MODERATE EXERCISE TRAINING

URTI is the most frequently occurring infectious disease in humans worldwide [31–33]. More than 200 different viruses cause the common cold, and rhinoviruses, and coronaviruses are the culprits 25%–60% of the time. The National Institute of Allergy and Infectious Diseases reports that people in the United States suffer 1 billion colds each year with an incidence of 2–4 for the average adult and 6–10 for children [31]. URTI imposes an estimated $40 billion burden in direct and indirect costs on the U.S. economy [32].

Low- to high-exercise workloads have a unique effect on URTI risk, and can be modeled using a J-curve relationship [34] (Figure 47.2). Regular physical activity improves immune function and lowers URTI risk while sustained and intense exertion has the opposite effect. Marathon race competitions and heavy exercise training regimens increase URTI risk, but relatively few individuals exercise at this level, limiting public health concerns. The second half of this chapter will review the benefits of regular, moderate activity in improving immunosurveillance against pathogens and lowering URTI risk. This information has broad public health significance and appeal, and provides the clinician with an additional inducement to encourage increased physical activity among patients.

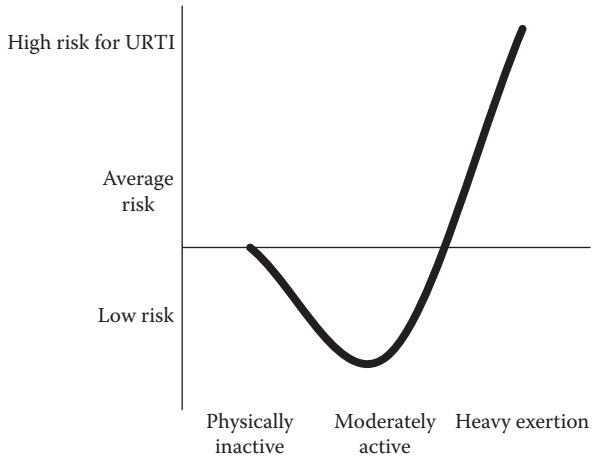


FIGURE 47.2 J-Curve model on the relationship between exercise workload, and URTI risk. Animal and human data support a reduction in URTI risk with moderate activity in contrast to an elevated risk following heavy exertion.

Moderate Physical Activity and URTI Risk

Several lines of evidence support the linkage between moderate physical activity and improved immunity and lowered infection rates: survey, animal, epidemiologic, and randomized training data. Survey data consistently support the common belief among fitness enthusiasts that regular exercise confers resistance against infection. In surveys, 80%–90% of regular exercisers perceive themselves as less vulnerable to viral illnesses compared to sedentary peers (Figure 47.3) [35,36].

Animal studies are difficult to apply to the human condition, but in general, support the finding that moderate exercise lowers morbidity and mortality following pathogen inoculation, especially when compared to prolonged and intense exertion or physical inactivity. Mice infected with the herpes simplex virus, for example, and then exposed to 30 min of moderate exercise experience a lower mortality during a 21 day period compared to higher mortality rates after 2.5 h of exhaustive exercise or rest [37]. Another study with mice showed that 3.5 months of moderate exercise training compared to no exercise prior to induced influenza infection decreased symptom severity and lung viral loads and inflammation [38].

Retrospective and prospective epidemiologic studies have measured URTI incidence in large groups of moderately active and sedentary individuals. Collectively, the epidemiologic studies consistently show reduced URTI rates in physically active or fit individuals. A 1 year epidemiological study of 547 adults showed a 23% reduction in URTI risk in those engaging in regular versus irregular

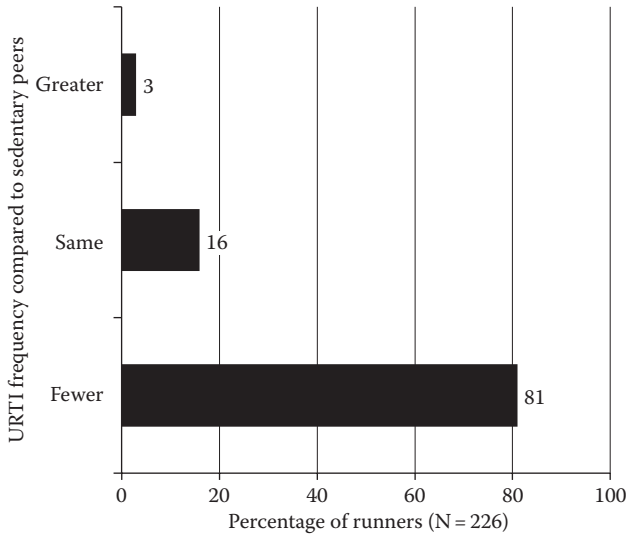


FIGURE 47.3 Survey responses by endurance athletes in response to this question: "Compared to others who do no run or exercise do you feel that you generally have _____ episodes of sickness with the common cold or flu?." (From Nieman, D.C., *Med. Sportiva*, 13, 189, 2009.)

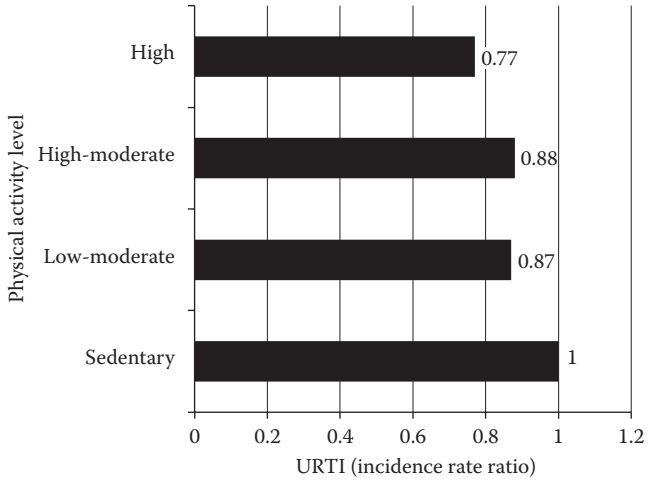


FIGURE 47.4 This 1 year epidemiological study of 547 adults showed a 23% reduction in URTI risk in those engaging in regular versus irregular physical activity. (From Matthews, C.E. et al., *Med. Sci. Sports Exerc.*, 34, 1242, 2002.)

moderate-to-vigorous physical activity (Figure 47.4) [39]. In a group of 145 elderly subjects, URTI symptomatology during a 1 year period was reduced among those engaging in higher compared to lower amounts of moderate physical activity [40]. During a 1 year study of 142 males aged 33–90, the odds of having at least 15 days with URTI was 64% lower among those with higher physical activity patterns [41]. A cohort of 1509 Swedish men and women aged 20–60 were followed for 15 weeks during the winter/spring [42]. Subjects in the upper tertile for physical activity experienced an 18% reduction in URTI risk, but this proportion improved to 42% among those with high perceived mental stress.

A group of 1002 adults (ages 18–85 years, 60% female, 40% male) were followed for 12 weeks (half during the winter, half during the fall) while monitoring URTI symptoms and severity using the Wisconsin Upper Respiratory Symptom Survey [43,44]. Subjects reported frequency of moderate-to-vigorous aerobic activity, and rated their physical fitness level using a 10-point Likert scale. The number of days with URTI was 43% lower in subjects reporting an average of 5 or more days of aerobic exercise (20 min bouts or longer) compared to those who were largely sedentary (≤1 day/week). (Figure 47.5). This relationship occurred after adjustment for important confounders including age, education level, marital status, gender, BMI, and perceived mental stress. The number of days with URTI was 46% lower when comparing subjects in the highest versus lowest tertile for perceived physical fitness, even after adjustment for confounders.

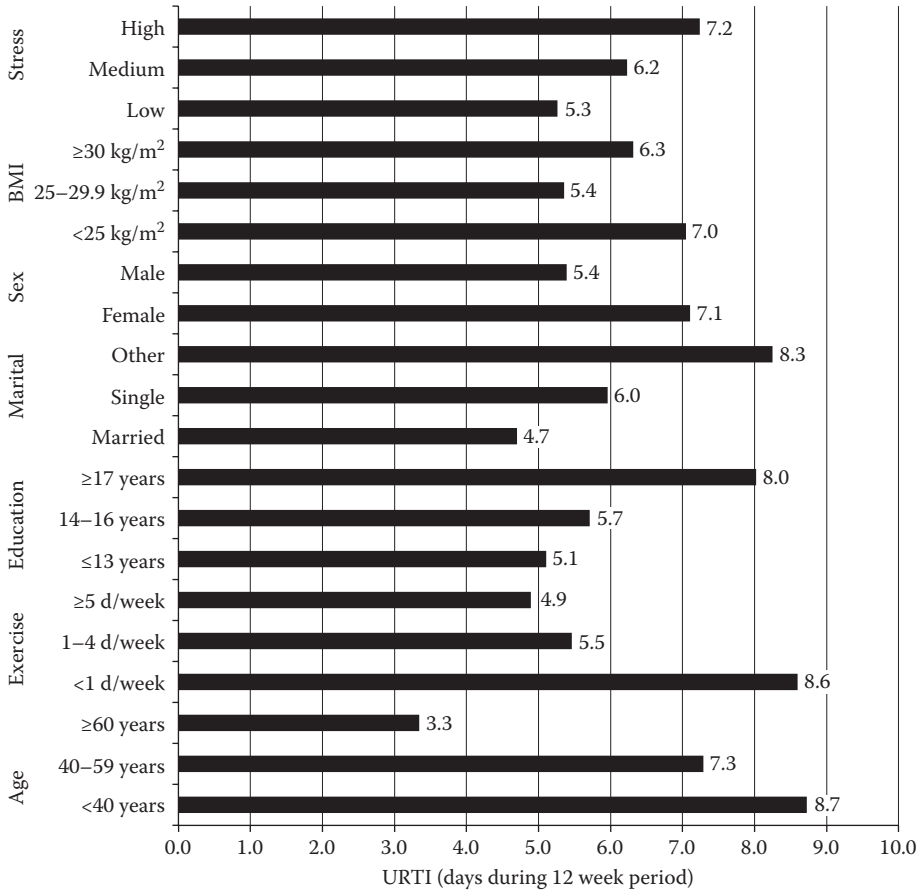


FIGURE 47.5 The number of days with URTI during a 12 week period (winter or fall) in a group of 1002 adults (ages 18–85 years) by exercise frequency and other lifestyle and demographic factors. Means are adjusted statistically after weighting for each factor through a general linear model. (From Nieman, D.C. et al., *Br. J. Sports Med.*, 2011, in press.)

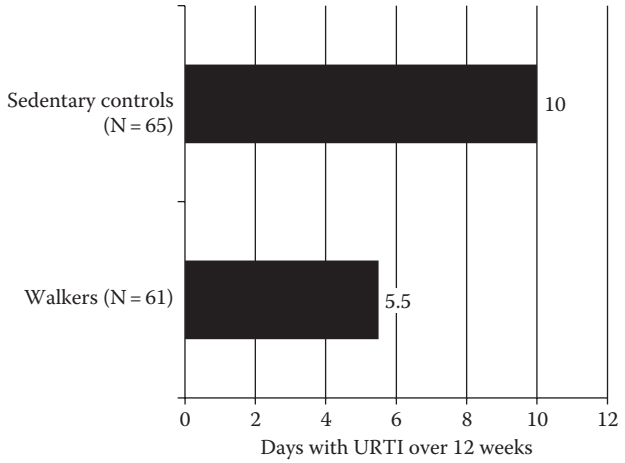


FIGURE 47.6 The number of URTI symptom days was decreased by approximately half through a walking program (5 days/week, 45 min/session, for 15 weeks) by previously sedentary, overweight adult women. (From Nieman, D.C. et al., *Int. J. Sports Med*., 11, 467, 1990; Nieman, D.C. et al., *Med. Sci. Sports Exerc*., 30, 679, 1998.)

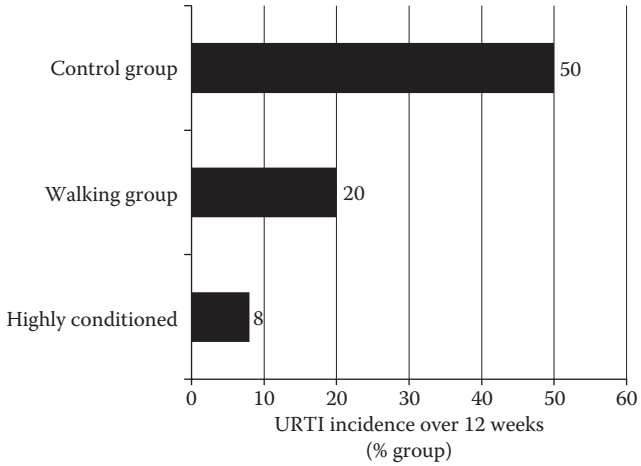


FIGURE 47.7 URTI incidence in three groups of elderly women during 12 weeks: highly conditioned, walkers, and controls. (From Nieman, D.C. et al., *Med. Sci. Sports Exerc*., 25, 823, 1993.) Physically inactive controls had the highest URTI incidence during the fall cold season.

Regular physical activity may lower rates of infection for other types of diseases, but data are limited due to low disease prevalence. For example, women with a high frequency of walking experienced an 18% lower risk of pneumonia compared with women who walked the least [45]. In the same cohort, women who reported running or jogging more than 2 h/week had a reduced pneumonia risk compared with women who spent no time running or jogging [45].

Randomized experimental trials provide important data in support of the viewpoint that moderate physical activity reduces URTI symptomatology. In a randomized, controlled study of 36 women (mean age 35 years), subjects walked briskly for 45 min, 5 days/week, and experienced ½ the days with URTI symptoms (5.1 versus 10.8) during the 15 week period compared to that of the sedentary control group (Figure 47.6) [46].

The effect of exercise training (45 min walking sessions/week at 60%–75% maximum heart rate) and/or moderate energy restriction (1200–1300 kcal/day) on URTI was studied in obese women (N = 91, body mass index 33.1 ± 0.6 kg/m^2) randomized to one of four groups: control, exercise, diet, exercise, and diet [47]. Energy restriction had no significant effect on URTI incidence, and subjects from the two exercise groups were contrasted with subjects from the two nonexercise groups. The number of days with URTI for subjects in the exercise groups was reduced 40% relative to the nonexercise groups (5.6 versus 9.4), similar to the level of nonobese, physically active controls (N = 30, 4.8 days with URTI).

In another study, 30 sedentary elderly women (mean age, 73 years) were assigned to walking or sedentary groups [48,49]. The exercise group walked 30–40 min, 5 days/week, for 12 weeks at 60% heart rate reserve. Incidence of URTI in the walking groups was 21% compared to 50% in the calisthenic control group during the study (September through November) (Figure 47.7).

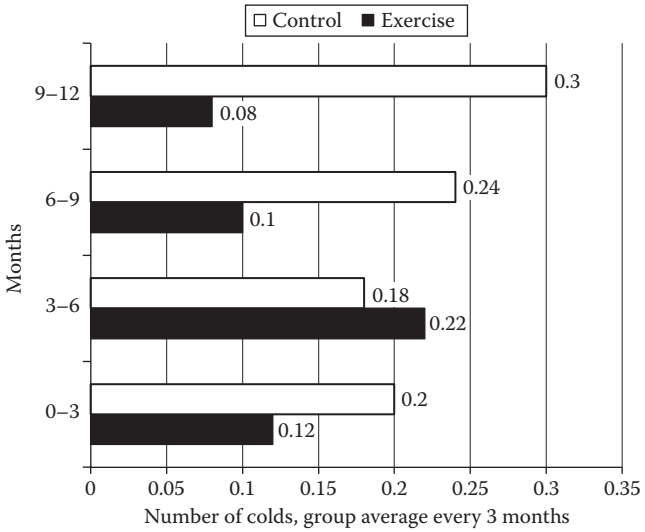


FIGURE 47.8 A 1 year randomized study of 115 overweight, postmenopausal women showed that 166 min/week (~4 days/week) of moderate exercise lowered URTI risk compared to controls (stretching), especially during the last 3 months. (From Chubak, J. et al., *Am. J. Med*., 119, 937, 2006.)

A 1 year randomized study of 115 overweight, postmenopausal women showed that regular moderate exercise (166 min/week, ~4 days/week) lowered URTI risk compared to controls (who engaged in a stretching program) [50]. In the final 3 months of the study, the risk of colds in the control group was more than threefold that of the exercisers (Figure 47.8).

MODERATE PHYSICAL ACTIVITY AND ENHANCED IMMUNOSURVEILLANCE

During moderate exercise several transient changes occur in the immune system [29,51–53]. Moderate exercise increases the recirculation of immunoglobulins, and neutrophils, and

natural killer cells, two cells that play a critical role in innate immune defenses. Animal data indicate that lung macrophages play an important role in mediating the beneficial effects of moderate exercise on lowered susceptibility to infection [54]. Stress hormones, which can suppress immunity, and pro- and anti-inflammatory cytokines, indicative of intense metabolic activity, are not elevated during moderate exercise [29].

Although the immune system returns to preexercise levels within a few hours after the exercise session is over, each session may represent an improvement in immune surveillance that reduces the risk of infection over the long term. Other exercise-immune-related benefits include enhanced antibody-specific responses to vaccinations. For example, several studies indicate that both acute and chronic moderate exercise training improves the body's antibody response to the influenza vaccine [55–58]. In one study, a 45 min moderate exercise bout just before influenza vaccination improved the antibody response [55].

These data provide additional evidence that moderate exercise favorably influences overall immune surveillance against pathogens. Taken together, the data on the relationship between moderate exercise, enhanced immunity, and lowered URTI risk are consistent with guidelines urging the general public to engage in near-daily brisk walking.

CONCLUSIONS

Although methodology varies widely and evidence is still emerging [59], epidemiologic and randomized exercise training studies consistently report a reduction in URTI incidence or risk of 18%–67%. This is the most important finding for the practicing physician that has emerged from exercise immunology studies during the past two decades. Animal and human data indicate that during each exercise bout, transient immune changes take place that over time may improve immunosurveillance against pathogens, thereby reducing URTI risk. The magnitude of reduction in URTI risk with near-daily moderate physical activity exceeds levels reported for most medications and supplements, and bolsters public health guidelines urging individuals to be physically active on a regular basis.

Regular physical activity should be combined with other lifestyle strategies to more effectively reduce URTI risk. These strategies include stress management, regular sleep, avoidance of malnutrition, and proper hygiene [33,60–63]. URTI is caused by multiple and diverse pathogens, making it unlikely that a unifying vaccine will be developed [33]. Thus lifestyle strategies are receiving increased attention by investigators and public health officials, and a comprehensive lifestyle approach is more likely to lower the burden of URTI than a focus on physical activity alone.

The anti-inflammatory effect of near-daily physical activity may play a key role in many health benefits, including reduced CVD, type 2 diabetes, various types of cancer, sarcopenia, and dementia [9–18]. This is an exciting area of scientific endeavor, and additional research is needed to determine how immune perturbations during each exercise bout accumulate over time to produce an anti-inflammatory influence. As with URTI, multiple lifestyle approaches to reducing chronic inflammation should be employed with a focus on weight loss, high volume of physical activity, avoidance of smoking, and improved diet quality.

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48 Chronic Exercise and Immunity
Practical Applications

Paul M. Coen, PhD and Michael G. Flynn, PhD

CONTENTS

Effect of Chronic Exercise on Leukocyte Number and Function 605
Effect of Chronic Exercise on Innate Immunity 605
Monocytes and Tissue Macrophage 605
Natural Killer Cells 606
Neutrophils 606
Effect of Chronic Exercise on Adaptive Immunity 607
T- and B-Lymphocytes 607
Excessive Training and Immunity 607
Th1/Th2 Balance 607
Toll-Like Receptors 608
Excessive Training: URS or URTI? 608
Glutamine 609
Prostaglandin E2 609
Moderate Training and Immunity 609
Exercise and Inflammation 609
Wound Healing 610
Exercise and Efficacy of Vaccines 611
Summary 611
References 612

The influence of exercise training on host defense and indices of immune function have been studied for over four decades. There is strong evidence that exercise training plays a role in altering immunity, but there are a number of unresolved issues. The potential changes in immunity that may be induced by regular exercise or strenuous exercise training will be addressed in this chapter. The objective of this chapter is to identify practical implications of chronic exercise that are applicable to both fitness exercisers and athletes. The influence of chronic exercise on innate and adaptive immunity will be reviewed along with the effect of excessive exercise training on selected immune parameters and resistance to infection. The chapter will further address the influence of moderate exercise training on inflammation, wound healing, and the efficacy of vaccines.

EFFECT OF CHRONIC EXERCISE ON LEUKOCYTE NUMBER AND FUNCTION

Leukocytes are the circulating cells of the immune system and are involved in all stages of mounting an immune response to foreign organisms. Leukocytes are found in the blood and lymphatic system and are derived from bone marrow hematopoietic stem cells. Regular intense exercise does not appear to alter resting peripheral blood leukocyte number [1–3]. However, regular moderate physical activity can alter phenotype and influence the function of specific subsets of leukocytes. These changes potentially mediate the systemic anti-inflammatory effects of chronic exercise as evidenced by lower levels of circulating markers of inflammation (IL-6 and CRP). In this section we will summarize current literature to show how regular exercise can elicit changes in number, function, and phenotype of the major leukocyte subsets.

EFFECT OF CHRONIC EXERCISE ON INNATE IMMUNITY

Monocytes and Tissue Macrophage

Monocytes are circulating cells of the innate immune system. They are immature precursor cells for tissue macrophage and dendritic cells. Monocytes can respond to infection or tissue damage by migrating to the site of insult and differentiating into tissue-specific macrophage or dendritic cells (e.g., Kupffer cells in liver, macrophage in adipose tissue). These resident cells have multiple roles, including phagocytosis and responding to inflammatory signals (both exogenous and endogenous) via germ line–encoded pattern recognition receptors (e.g., toll-like receptors). Antigen presentation and

subsequent cytokine release help to coordinate the responses of the adaptive immune system. Chronic low-grade activation of the monocyte/macrophage lineage is thought to contribute to the pathophysiology of obesity, insulin resistance [4], and development of atherosclerosis [5].

Several researchers have highlighted the role of chronic exercise-induced alterations in monocyte phenotype/inflammatory response as a possible mechanism underlying the anti-inflammatory effects of exercise. Cross-sectional and longitudinal training studies show that chronic exercise can reduce *ex vivo* mitogen-stimulated whole blood production of inflammatory cytokines [6,7]. Further investigation suggested that the degree to which toll-like receptor (TLR) 4 is expressed on circulating monocytes mediates mitogen-stimulated cytokine production [8]. This finding may be significant as monocyte/macrophage TLR4 activation is implicated in the pathophysiology of atherosclerotic plaque development and peripheral tissue insulin resistance. Exercise training per se has also decreased monocyte TLR4 expression [8–10]. Taken together, this emerging evidence implies that regular exercise can reduce expression and reactivity of the innate immune receptor TLR4, an important factor in monocyte/macrophage activation.

Circulating monocytes are phenotypically classified based on cell-surface expression of CD14 and CD16. CD14++CD16− cells are called classical monocytes and make up ~90% of the circulating monocyte population [11]. CD14+CD16+ monocytes are called inflammatory monocytes and are a subpopulation (~10% of total monocytes) with a proclivity for production of inflammatory cytokines. For example, when stimulated cultures are depleted of CD14+CD16+ monocytes, roughly 80% of inflammatory cytokine production is lost [12]. Researchers recently reported that the circulating inflammatory monocyte percentage was elevated in patients with subclinical atherosclerosis and obesity [13]. Compared with classical monocytes, inflammatory monocytes adhere more robustly to activated endothelial cells [14] and may be precursors to CD16+ macrophages found distributed throughout atherosclerotic lesions and adipose tissue [15,16]. Based on these studies, researchers believe that inflammatory monocytes play a role in the pathogenesis of several diseases linked to inflammation. Recent data indicate that aerobic/resistance training program can reduce the inflammatory monocyte population [17,18], thus providing another potential mechanism by which exercise reduces inflammation.

More recently, researchers have begun to examine the effect of exercise training on adipose tissue macrophage recruitment and activation. Activation of adipose tissue macrophages is associated with obesity and peripheral tissue insulin resistance [19]. Production of TNF-α by activated adipose tissue macrophages is believed to be a major contributor to peripheral tissue insulin resistance in obesity and type 2 diabetes [20]. Bruun et al. reported that a 15 week hypocaloric diet and exercise intervention reduced macrophage-specific markers and inflammatory cytokines in adipose tissue [21]. This effect was concomitant with improved insulin sensitivity. However, a 12 week exercise only and exercise with diet intervention in 79 obese subjects did not elicit changes in adipose tissue markers of inflammation [22]. Others have also found no effect of exercise training on markers of adipose tissue inflammation [23]. Currently, these are the only human studies to examine the effects of exercise on adipose tissue macrophage activation and recruitment and it is clear that further studies are needed.

There is strong evidence in support of the concept that regular exercise can reduce monocyte/macrophage inflammation, possibly through modulation of TLR4 expression and/or altering the phenotype of circulating monocyte subpopulations. However, more studies need to be conducted to clarify the effect of regular exercise on adipose tissue macrophage recruitment and activation. This body of work is clinically important as activation of the monocyte/macrophage lineage is implicated in the pathophysiology of diseases such as diabetes and cardiovascular disease (CVD).

Natural Killer Cells

Natural killer cells are cytotoxic lymphocytes and are a major constituent of the innate immune system. They protect against certain tumors and virally infected cells by releasing granules containing proteases and perforins that induce apoptosis in the target cell. A number of cross-sectional and training intervention studies have been conducted in which the effects of chronic exercise on basal NK-cell number or activity were examined. The results of these studies are varied, with exercise reported to suppress [24], increase [25–28], or not change the cytotoxic activity or number of natural killers cell [6,29–32]. For example, Yan et al. reported that the concentration of NK-cells (CD16+CD56+) significantly increased in elderly subjects who exercised regularly, compared to that of the age-matched control subjects [33]. On the other hand, a baseline comparison revealed that endurance-trained elderly women had greater NK-cell activity compared to sedentary elderly women. However, 12 weeks of moderate aerobic exercise did not alter NK-cell activity or number in these previously sedentary women [3]. It should be noted that a number of these studies were conducted on elderly subjects [6,26,32] and cancer survivors [27,28]. Given the development of immunosenescence that occurs with aging and the confounding effect this may have, data generated from elderly cohorts should be interpreted with caution. Furthermore, a paucity of data exists on the effects of chronic exercise on basal NK function/activity in younger and middle-aged adults. In summary, despite a good deal of research examining the effect of exercise training on NK-cells, it appears that a consensus has not been reached.

Neutrophils

Neutrophils are polymorphonuclear cells and are the most abundant leukocyte subtype. Neutrophils are the first responders of the innate immune system and migrate to the site of infection or injury within minutes. In athletes,

resting circulating neutrophil number is similar to sedentary individuals [2,34]. However, there was a recent report on the effects of moderate exercise on neutrophil number. An exercise training program lowered neutrophil number in overweight women with multiple risk factors for CVD [35]. Furthermore, the decrease in neutrophil number was correlated with improvements in insulin sensitivity. It may be that in the context of chronic inflammation, such as is evident with CVD, exercise training can impact neutrophil number. In athletes however, it appears that regular intense exercise may reduce neutrophil function [3,36,37].

EFFECT OF CHRONIC EXERCISE ON ADAPTIVE IMMUNITY

T- and B-Lymphocytes

T- and B-cells are the primary circulating cells of the adaptive immune system. T-cells are involved in cell-mediated immunity and B-cells are primarily responsible for producing antigen-specific antibodies (humoral immunity). Immunosenescence refers to the natural decline in immune function that occurs with aging and is thought to contribute to age-associated morbidity [38]. Hallmarks of immunosenescence include, among others, a reduced population of antibody-producing B-cells and T-cell functional dysregulation brought about primarily by thymic involution [39]. Regular exercise may also impact number, function, and *ex vivo* proliferative response of T-cell populations in elderly subjects and, as such, may be an important modality for maintaining immune health as one grows older. Cross-sectional studies in which elderly runners were compared to sedentary individuals showed that *ex vivo* lymphocyte proliferative response to PHA was significantly higher in elderly runners [40,41]. Koizumi et al. reported that exercise training increased the absolute numbers of T-cells and T-helper cells in elderly humans (2003). T-cell proliferation in response to mitogen increased following a 6 month aerobic exercise intervention [32]. However, others have shown that *ex vivo* lymphocyte responses are not affected by regular exercise [42]. *Ex vivo* T-cell proliferation did not change after 12 weeks of exercise training [3]. Resistance training for 10–12 weeks did not alter proliferative response to mitogens [30,43]. Finally, a 12-month moderate resistance exercise program for elderly women did not alter circulating numbers of lymphocytes [31]. Currently, there is a lack of consensus on the effects of regular exercise on *ex vivo* lymphocyte proliferative response.

A number of studies have examined the effects of regular exercise on the immune response to antigens *in vivo* in older adults. The assays of lymphocyte response utilized in these studies may have greater physiological relevance than studies using *ex vivo* mitogen-induced stimulation of lymphocytes. In fact, the *in vivo* measure of immune response employed can be compared to a live challenge with a pathogen. Kohut et al. showed that regularly exercising older adults had a greater titer for anti-influenza IgG and IgM following immunization when compared to sedentary controls [44]. The response to keyhole-limpet hemocyanin (KLH) antigen was determined in cohorts of young and old, active and inactive individuals [45]. Anti-KLH antibodies (IgM, IgG, IgG1) were all elevated in the older active adults compared with the sedentary controls following intramuscular injection of KLH. In these studies, measures of B-cell function and T-cell function were enhanced in the older adults. Taken together, these studies suggest that immune response to antigen challenge may be improved with regular exercise in older adults. For the fitness enthusiast, a successful exercise program will result in improved physical performance, such as endurance or strength, and perhaps a desirable change in weight or body composition. However, it is clear that in addition to changes at the whole body level, there are also benefits at the cellular level. Current research suggests that regular exercise can improve immune function at the cellular level, resulting in improved response to immunization and lower levels of chronic inflammation. These potential benefits of exercise are vital to maintaining good health.

Excessive Training and Immunity

Excessive training can result in a wide range of negative clinical signs and symptoms. This symptom complex is quite often referred to as overtraining syndrome, but the reader will also frequently see "overtraining" used as a synonym. Clinical symptoms of overtraining syndrome are many and include lethargy, fatigue, mood disturbances, underperformance, poor healing of cuts and scratches, and immune suppression. Athletes who train intensely are believed to become ill more frequently and there are several anecdotal examples of elite athletes forced to leave high-level competition due to a mysterious illness or infection.

As noted previously, resting immunity is not substantially different between athletes and healthy, sedentary individuals, but it appears that intensive training could negatively affect several immune measures. Changes in NK-cell activity and T-cell function have been observed after intensified training programs, but it is unclear whether the changes in the immune system induced by hard training are to blame for a higher incidence of infection in athletes [32]. Nevertheless, the collective toll of excessive training on the immune system would appear to render athletes more susceptible to infection.

The immune variable that responds most consistently to repeated, hard exercise is the mucosal secretion or secretion rate of immunoglobulin A (IgA), considered a first line of defense against infection. IgA has also been more strongly and consistently linked to infection risk in athletes than other measurable aspects of immunity [46].

Th1/Th2 Balance

CD4+ T-helper cells can be divided into two distinct subpopulations, type 1 (Th1) and type 2 (Th2). Activated Th1 cells are generally considered proinflammatory, producing TNF-α and INFγ, whereas activated Th2 cells are considered antiinflammatory and produce IL-4, IL-5, and IL-10. The ratio of

Th1/Th2 cytokines is often used as an index of the inflammatory signaling milieu. The Th1/Th2 distribution has been consistently shown to be influenced by intensive training, with a shift toward Th2 dominance [47]. A pronounced shift in cytokine production typical of the Th2 antiinflammatory milieu likely renders the vigorous exerciser more susceptible to infection [46,48]. However, moderate training appears to induce a positive, subtle shift toward a Th2 cytokine profile, balancing the Th1/Th2 response and inducing the antiinflammatory influences of regular exercise [48].

A shift toward Th2 dominance is frequently found in elderly subjects, but Th1 dominance may be regained after 6 months of moderate training [49]. Thus, while it appears that both moderate and intensive exercise can alter Th1/Th2 balance, there appears to be an optimal balance that may be both age and training status specific. Intense training, tilting the balance too far in favor of Th2, is associated with a reduction in cell-mediated immunity and immunosuppression.

An important part of the Th1/Th2 ratio that has not been well studied in an exercise or intensified training context is the T regulatory cells or T regs (CC4+CD25+). T regs play an important role in suppressing the activity of other immune cells and maintaining discrimination between self and nonself antigens during an immune response, thereby preventing autoimmune diseases. The only available exercise training studies examining T reg function were conducted with a Tai Chi intervention. Yeh et al. found evidence of increased T reg function in both healthy middle-aged adults [50] and subjects with type 2 diabetes [51] after 12 weeks of Tai Chi training. It is not known how T regs respond to a period of intensified training and there is little evidence to show how T regs respond to a period of moderate training.

Toll-Like Receptors

Hard bouts of exercise have also been linked to downregulation of TLR4 cell-surface expression [52]. Oliveira and Gleeson found that cycling for 90 min (75% VO_{2peak}) resulted in a transient reduction in TLR4 that was sustained for 1–4 h after exercise [52]. TLRs help orchestrate the innate immune response to a wide range of pathogens, which led the authors to conclude that postexercise TLR4 depression could contribute to postexercise immune depression. This premise, however, was based on a single bout of exercise and there is a lack of research examining the response of sustained, intensified training on TLR downregulation. Therefore, while it is possible that regular bouts of hard exercise might transiently reduce TLR expression increasing susceptibility to infection, moderate intensity, long-term training has been shown to reduce TLR4 expression in hyper-inflammatory groups (sedentary, overweight/obese, and elderly). Reduced TLR4 expression is generally viewed as a positive adaptation due to its potential to influence systemic inflammation. Thus, there is likely a differential response to repeated bouts of intense exercise where the goal is improved performance, which could lead to immune depression, and long-term moderate exercise programs, in which the goal is to improve fitness and the outcome improve overall health.

Excessive Training: URS or URTI?

Athletes who train hard are frequently reported to have an increased incidence of upper-respiratory symptoms (URS) related to upper-respiratory tract infection (URTI) [53]. Elite athletes are believed to have a higher incidence of URTI than fitness exercisers or sedentary individuals. These findings, along with the fact that several indices of immune function are suppressed by heavy exercise, led to the assertion that heavy exercise lowers immune defenses and increases URTI risk. Two important factors remain unclear in this regard. First, whether excessive training suppresses immune function to the extent possible to result in an increased susceptibility to infection has not been determined [32]. There is a general consensus that several immune parameters are depressed following prolonged or severe exercise, most notably and consistently mucosal immunoglobulin A (IgA), but it is not known whether the immune depression is causative of an increased incidence of URTI. Second, it is not clear whether the URTIs reported by athletes in the majority of studies are pathogen based or a result of local airway irritation or inflammation [54]. Problematically, most of the studies in which the incidence of URTI has been assessed in conjunction with heavy training largely relied on self-report. Researchers from a small number of studies have called that practice into question, largely due to a lack of the presence of an infectious pathogen in sputum of athletes reporting symptoms of URTI [54]. However, most researchers also acknowledge that the ability to detect these pathogens in sputum is far from an exact science. It is interesting to note that the daily use of an antiinflammatory throat spray, 1 week before and 2 weeks after a half-marathon, did not influence the number of reported URTI episodes in a relatively small group of runners (n = 25 treatment; n = 20 controls) but may have influenced the severity scores (trend) [55]. Thus, while evidence is mounting that regular, modest exercise reduces the risk of URTI [3] and prolonged, intense, or excessive exercise training increases the risk of URTI [53], there is considerable controversy in this area which prevents us from making concrete conclusions about the links between hard exercise and illness.

No increase in the rate of infectious episodes was found in marathon runners when runners with a prerace infection were removed from the cohort [56], casting further doubt on the relationship between hard exercise and URTI. Thus, while there are conflicting data on the relationship between infection risk and hard training, the conflict is difficult to rectify when considering feasibility and research design issues. Logistically, the excessive time and cost make it difficult to include quantitative cellular immune measures in large cohort studies of infection incidence and prevalence. There are some larger scale studies in which salivary IgA has been measured and negatively correlated with URTI

incidence [29]. Gleeson et al. [46] monitored 80 athletes for several months, with training and illness logs recorded and blood and saliva samples obtained. These authors identified a subgroup of "illness-prone" subjects who had higher training loads, higher levels of multi-antigen-stimulated anti-inflammatory cytokines—illustrating a Th2-dominant response—and lower salivary sIgA secretion and flow rates. In addition, the highest quartile of IL-10 producers had higher training loads, higher production of inflammatory and anti-inflammatory cytokines, lower IgA, and higher URTI incidence than the lowest quartile. The authors suggested that IL-10 might be a useful predictor of infection risk in physically active individuals [46]. There is clearly an increase in upper-respiratory symptoms associated with hard training. Further research is required to document what proportion of these illnesses are pathogen based or linked to airway inflammation/irritation.

Glutamine

Glutamine showed promise as a marker of overtraining syndrome and a potential cause of immune suppression associated with hard training [57]. Glutamine is a preferred substrate of rapidly dividing cells and is favored by immune cells. Glutamine levels are believed to be challenged when gluconeogenesis-related liver uptake is increased during prolonged exercise [58]. Kargotich et al. [59] found that plasma glutamine levels were lowered by high-intensity exercise in swimmers and glutamine was proposed as a marker of overtraining syndrome. Others have found less consistent results when glutamine levels were monitored along with normal training or intense training, leading to overtraining and reported that glutamine levels were not linked with URTI [2], casting doubt on the premise that glutamine provides a sensitive marker of overtraining syndrome.

Branched chain amino acid supplements could help sustain plasma glutamine levels during hard training and reduce potential immunosuppressant effects, as suggested in studies from Bassit et al. [60]. These researchers provided BCAA supplements or placebo to elite male triathletes (Olympic distance) and/or marathoners for 30 days before and 1 week after competition. There was a substantial reduction in plasma glutamine levels postrace in the placebo groups, but glutamine did not decline in BCAA group. Lowered glutamine occurred concomitant with impaired lymphocyte and monocyte function, suggesting that maintaining glutamine levels is linked to postrace susceptibility to infection [61].

Prostaglandin E2

Prostaglandin (PG) E2 is produced from arachidonic acid through the cyclooxygenase pathway by macrophages and dendritic cells and has inhibitory effects on immune function. Specifically, PGE2 can polarize dendritic cells, resulting in a suppression of Th1 and activation of Th2 subpopulations [62]. The influence of exercise training on PGE2 has not been closely studied; however, damaging exercise is linked to elevated PGE2 levels, which in turn are likely related to the pain associated with delayed-onset muscle soreness [63].

An intriguing hypothesis to explain the immune suppression associated with overtraining syndrome was proffered by Smith [47]. Athletes who are training intensely undergo repeated tissue trauma, which results in the production of stress hormones (catecholamines and cortisol) and inflammatory cytokines (e.g., PGE2). These endocrine shifts promote Th2 dominance and suppress cell-mediated immunity [47]. Thus, the repeated tissue trauma is deemed responsible for the Th2 dominance, which Smith claims is not immunosuppression but rather aggressive activation of Th2 cells and a loss of cell-mediated immunity.

PGE2 has been clearly shown to inhibit interferon-gamma and promote Th2 dominance [64]. Cortisol, which may also be elevated in overtrained athletes, has also been shown to favor Th2 balance [65]. There is some support in the literature for Smith's hypothesis [46], but there are few studies in which PGE2 has been studied in an overtraining or moderate exercise training context in healthy humans.

Production of the immune-suppressing PGE2 from monocytes is known to be higher in aged humans and animals [66], which helps explain the Th2 dominance frequently observed in older humans. High levels of PGE2 might also help explain the immunosenescence observed in older subjects [66], but there are no studies in which the effect of exercise training on PGE2 production has been examined in older humans.

MODERATE TRAINING AND IMMUNITY

Exercise and Inflammation

The role that inflammation plays in the development and exacerbation of chronic disease has grown substantially in importance over the last decade. Inflammation or inflammatory biomarkers have been clearly linked to CVD [67], type 2 diabetes [68], osteoporosis [69], and several other chronic diseases not previously believed to have an inflammatory etiology. For example, CVD was long believed to be a disease of deranged lipid storage; however it is now clear that inflammation plays a major role in the pathophysiology of atherosclerosis and CVD. In fact, inflammation is known to contribute to every stage of vessel plaque development [70], up to and including the potentially lethal plaque rupture [25].

Exercise is known to provide substantial benefits for individuals with chronic diseases, with a strong role in prevention of disease and amelioration of symptoms in those with disease. There is growing evidence that exercise has anti-inflammatory effects, but it is not clearly known to what extent the anti-inflammatory effects of exercise prevent or help ameliorate the symptoms of chronic disease. Early evidence suggests that this effect may be substantial.

Observational or population studies provide consistent evidence of an anti-inflammatory benefit of exercise. That is to say, inflammatory biomarkers are significantly lower

in segments of the population with moderate to high levels of physical activity [71]. Not surprisingly, intervention studies provide less consistent support of an anti-inflammatory effect of exercise. Small subject numbers, different exercise modes and intensities, supervised versus unsupervised exercise, and different choice of biomarkers all likely contribute to these inconsistencies. Nevertheless, there is a fairly strong intervention literature to support the observation that exercise training has anti-inflammatory effects in serum or circulating cells [10,17], muscle [72,73], and to a lesser extent, adipose tissue [21,22].

There is some support for a required intensity threshold, such that lower doses of exercise or home-based exercise studies may not elicit a significant anti-inflammatory effect. In contrast, Butcher et al. [74] showed an anti-inflammatory action via PPAR gamma when subjects increased their pedometer counts to above 10,000 steps 3 days/week, suggesting that regularly performed, low-intensity exercise may be sufficient to exert an anti-inflammatory action.

It seems reasonably clear that increasing physical activity level or engaging in an exercise training regimen can exert anti-inflammatory effects. An issue that remains unresolved is whether exercise training can exert an anti-inflammatory effect in the absence of changes in body fat [22,75]. The literature in this area is mixed, but there are several examples of exercise providing an independent anti-inflammatory effect. In a recent review by Beavers, Brinkley, and Nicklas [71] (2010), the authors identified 19 studies in which self-reported physical activity level was linked to biomarkers of inflammation, and an additional nine studies during which the fitness level was measured. These authors concluded that accounting for obesity "… attenuated, but did not negate, the strength of the relationship between inflammatory biomarkers and physical activity." There are few studies in which an exercise intervention with and without fat losses have been compared. Christiansen et al. [22] recently reported that both diet and diet + exercise reduced blood and tissue markers of inflammation, but exercise training alone did not exert significant anti-inflammatory effects.

If exercise training can exert anti-inflammatory effects independent of reductions in total body adiposity, we speculate that it could be due to small but significant reductions in visceral fat. These changes in visceral fat with exercise training, at a level that does not significantly alter total body fat [76], could be responsible for exercise's ability to exert anti-inflammatory effects. However, there are a myriad of additional potential mechanisms for the anti-inflammatory effect of exercise that remain to be tested.

Inflammatory biomarkers and inflammation have been linked to the risk of several chronic diseases, the risk of physical frailty, and linked to the risk of dementia in older adults [77]. A practical example is the link between inflammation and type 2 diabetes. High levels of inflammation are linked to peripheral tissue insulin resistance, impaired insulin receptor function, and severity of diabetic complications. Exercise training has been shown to reduce NFKB expression and TLR4 expression in type 2 diabetics. TLR4 activation has also been shown to mimic several features of the diabetic state, but regular exercise reduces nuclear factor kappaB (NFκB) and TLR4 expression in diabetic subjects [78,79]. Thus, it appears that the ability of exercise to ameliorate the symptoms of chronic disease may be linked, in part, to the anti-inflammatory action.

In summary, moderate exercise has anti-inflammatory effects. It is possible that there is an intensity threshold, but evidence in support of low-intensity exercise exerting anti-inflammatory effects suggests the need for further study. It appears that exercise can exert anti-inflammatory effects in the absence of significant changes in body fat, but the lack of controlled studies in which exercise and diet have been studied alone and in combination preclude definitive conclusions. Exercise is known to exert anti-inflammatory effects in persons with type 2 diabetes and a concomitant improvement in diabetic state and amelioration of symptoms without significant body fat changes. Thus, while some mechanisms remain to be determined, the anti-inflammatory effect of exercise has important health implications.

Wound Healing

Aging and several chronic conditions, such as diabetes, are known to slow the rate at which wounds heal. Bed sores are fairly common in older, institutionalized patients and are difficult and expensive to treat. Thus, it is important to examine potential low-cost interventions such as diet and exercise on wound healing. The nutrition literature is fairly strong and the positive effects of improved nutrition—especially in cases of malnutrition—on wound healing are well documented. The influence of exercise training or physical activity levels on wound healing have been studied in a relatively small number of investigations [80,81], but the limited, available information looks promising. As such, the inability of aging macrophages to produce angiogenic proteins could be modified by exercise training, and the anti-inflammatory effect of exercise training could also play a role in enhanced wound healing. Keylock et al. [81] showed significantly improved wound healing in older, exercise-trained mice; the trained mice also had lower TNF-α and MCP-1 levels in the wound. Emery et al. [80] divided 28 older adults into an exercise and nonexercise group and found a significantly improved healing rate of an experimental wound in the exercised group, compared with the nonexercised group. Although this research was limited by a fairly small number of subjects, the exercise effect in Emery's study was substantial, with 55% of the subjects in the exercised group having complete healing at day four compared with 0% on the nonexercised group. More work is needed to determine if simple, cost-effective interventions such as exercise training can alter the rate at which wounds heal. However, the paucity of literature on the topic prevents us from

making solid conclusions regarding practical strategies for clinicians or patients.

Exercise and Efficacy of Vaccines

Aging is associated with a decline in immune function [82], which is often characterized by a decreased ability of the adaptive immune system to respond to novel antigens [83] and can also result in low-grade chronic inflammation through activation of the innate immune system [84]. Aging-related immunosenescence contributes to the increased incidence and severity of infectious disease among elderly adults. Older adults experience a greater mortality rate from influenza infection and generally exhibit reduced vaccine efficiency. Influenza vaccine efficacy for older adults may be as low as 56% [85], compared to 68%–88% in younger adults [86,87].

Recently, exercise has been shown to improve immunocompetence among older adults who have been administered an influenza vaccine. Several cross-sectional studies in which physically active elderly subjects were compared to sedentary controls, have shown a greater influenza vaccine response [40,44,81]. Endurance-trained older adults exhibit greater T-cell response and production of cytokines responsible for mediating viral immunity including IL-2 and IFNγ, compared to sedentary controls [40]. A cross-sectional comparison of elderly physically active, moderately active, and sedentary groups showed that physical activity was associated with greater response to influenza immunization. The older physically active group developed greater flu-specific IgG and IgM titers 2 weeks postimmunization, compared to moderate activity and sedentary groups [44]. Peripheral blood mononuclear cell proliferation in vitro was also lower in the sedentary group. Keylock et al. demonstrated that physically active highly fit elderly individuals have higher antibody responses to fluzone vaccine and a Th2 skewing of the antibody response to tetanus toxoid when compared to sedentary low-fit older adults [81]. Taken together these studies suggest that lifestyle factors, including regular exercise may influence immune response to influenza immunization.

A number of longitudinal studies have also been conducted to examine the role of exercise training per se on influenza vaccine response. Kohut et al. reported that a 10 month exercise intervention resulted in a greater increase in influenza-specific antibody titer and IFN-γ production following flu vaccine [88]. These researchers also identified psychosocial factors such as depression and sense of coherence as potential mediators of response to influenza vaccine. In a larger trial 144 sedentary older adults were randomized to either a 10 month aerobic training (n = 74) or a flexibility and balance program (n = 70) [32]. The intervention resulted in a significant increase in seroprotection, determined as a hemagglutination inhibition (HI) titer of >40, 24 weeks after vaccination (30%–100%). This is significant as it suggests that an enhanced vaccine response following exercise training can be maintained over a period greater than the length of a typical flu season. However, and possibly more significantly, there was no difference in the incidence of URTI between the two groups, although the aerobic exercise group exhibited reduced overall illness severity and less sleep disturbance. To date the effects of exercise on vaccine response have not been reported to influence the incidence of URTI.

Several research groups have also examined the effects of an acute bout of exercise on influenza vaccine response. A single bout of eccentric exercise was shown to enhance INFγ response in men, but not in women [89]. Interestingly, antibody titers in women were enhanced by eccentric exercise, but not in men. In a follow-up study, it was found that the intensity at which an acute bout of eccentric exercise is conducted does not affect antibody response to influenza vaccines [90]. However, the authors found that exercise response was greatest with the low-immunogenicity antigen of the trivalent vaccine.

The timing of an eccentric bout of exercise relative to vaccination was also investigated to examine whether it affected the efficacy of the intervention. It was found that an acute bout of exercise immediately 6 or 48 h prior to administration of a standard trivalent influenza vaccine had no effect on antigen-specific serum antibody titers at 28 days postvaccination compared to control [91]. Cell-mediated immunity (in vitro stimulation of IFN production by blood with whole vaccine) was not different between groups. Campbell et al. suggested that exercise-induced immune enhancement was only observed when the control group had relatively poor responses [91].

The mechanisms responsible for mediating the effects of exercise on vaccine efficacy are not fully understood. However, a number of studies have shed some light on potential mediators of improvement. Immunosenescence in aging is associated with an elevation in the ratio of memory T-cells to naive T-cells, potentially reducing the ability of the adaptive immune system to respond to novel antigen. Exercise training has been previously shown to reduce the memory-naïve T-cell ratio [32]. In a mouse study, voluntary running enhanced OVA-specific CD4+ T-cell cytokine production and proliferation in all lymphoid organs [32]. Suzuki et al. found that voluntary wheel running can increase the rate of production and half-life of IgG when immunized against tetanus toxoid [92]. These studies suggest that exercise can prolong antibody response, potentially by restoring the naive T-cell level and subsequent ability to respond to novel antigen.

While most studies have concentrated on the effects of exercise on influenza vaccine, some suggest that being physically active may improve autoantibody response to HIV antigens. The sera of well-trained athletic individuals showed high reactivity with peptide NTM1 [93]. Autoantibody response to this antigen has been previously shown to contribute to control of HIV disease.

SUMMARY

It is clear that regular, moderate, or extreme exercise has the potential to alter indices of immune function. While it appears that regular exercise may offer some protection against URTI, provide anti-inflammatory actions, and enhance the

response to vaccine, many unanswered questions remain. For example, excessive training (overtraining) has been linked to increased risk of URTI, but researchers have questioned the reliability of both self-report of URTI and the direct method to detect pathogens in sputum.

The ability of exercise to improve the course of chronic disease via anti-inflammatory and other immune changes is an exciting avenue for researchers. These studies will help to close the gap between the myriad benefits of exercise training and the available mechanisms to explain the benefits. Despite the gaps in our knowledge, it is clear that athletes can train effectively without excessive illness and that fitness exercisers adapt in primarily positive immunological fashion to regular, moderate exercise.

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49 HIV Infection
Exercise and Immune Function

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CONTENTS

Introduction....615
Virology and Infection....615
Primary HIV Infection....615
Asymptomatic (Active Latency)....616
Symptomatic (Accelerated Aging)....616
Symptomatology of HIV Infection....616
Psychological Consequences....616
Physical Consequences....616
Antiretroviral Therapy....618
Toxic Side Effects....618
Treating the Side Effects....618
Treatment of HIV-Related Symptoms....618
Exercise as an Alternative Treatment to ART-Related Toxicities....619
Psychological Improvements Following Exercise....619
Physiological Improvements with Exercise....620
Recommendations for Exercise....620
Changing Demographics....620
Conclusion....621
References....621

INTRODUCTION

Although advances in the treatment of HIV and AIDS have reduced the number of AIDS-related cases and deaths worldwide, new cases of reported HIV infections have remained relatively stable, resulting in a continued increase in overall prevalence. Approximately 40,000 new infections of HIV are reported every year in the United States alone [1]. Since the discovery of antiretroviral therapy (ART) medications there have also been drastic changes in the pathogenesis of HIV disease and symptomatology of infection. People living with HIV/AIDS (PLWHA) no longer exhibit high rates of muscle wasting or AIDS-related opportunistic infections [2]. PLWHA have a variety of psychological and physiological symptoms associated with the virus itself, the related medications, or a combination of both. Due to the nature of concurrent symptoms being experienced at frequent rates, the general well-being and overall quality of life are often reduced [3,4]. Further, the frequency of reported symptoms is associated with increased disease progression, decreased functional capacity, reduced adherence to pharmacological treatment, self-medication, and increased psychological disturbances such as anxiety and depression [5–10]. Recent data indicate that the primary cause of death among PLWHA are chronic diseases generally associated with aging such as cardiovascular disease (CVD) and kidney failure, among others [11].

The use of exercise training to reduce the risk of chronic disease is supported within the literature and could potentially have similar health benefits among HIV-infected persons. The benefits of aerobic and resistance exercise have been established among general populations and various clinical groups from longitudinal investigations such as the Aerobics Center Longitudinal Study (ACLS) [12–14] and the Framingham Heart study (among others) [15–17]. Although shorter in duration, a number of studies indicate that PLWHA can obtain similar benefits within 6 weeks following a prescribed physical activity routine [18–21].

VIROLOGY AND INFECTION

Primary HIV Infection

The stage known as primary HIV infection (PHI) is best defined as the time between acute viral transmission lasting anywhere from 2 to 6 weeks until the onset of antibody production [22]. Current evidence indicates a massive CD4+ cell depletion occurring at mucosal sites within 2–3 days following viral transmission. Using polymerase chain reaction (PCR) techniques, Piatak and colleagues indicated that viral

reproduction was capable of reaching 10^6 or 10^7 viral particles/mL of plasma within the first 2 weeks of transmission [23,24]. At the onset of viral infection, symptoms generally appear anywhere from a few days to a couple of weeks. The majority of persons newly infected (70%) experience mild forms of symptoms generally associated with common colds, the flu, or stomach viruses. Due to these initial symptoms being mild in nature and the fact the PHI is short in duration, the initial infection often goes unnoticed until more severe symptoms appear, causing the person to seek medical attention. It is believed that the severity of these initial symptoms and how the immune system reacts is an indication for disease progression.

Asymptomatic (Active Latency)

Following PHI there is a sharp increase in plasma viral load as the virion is being disseminated throughout the entire body and spreading the infection to nearby peripheral and distal sites. Generally within 2–4 weeks, the sudden peak in viral load begins to regress, which is believed to be the result of the primary immune response involving cell-mediated immunity in addition to antibody production [22,25–27]. The appearance of HIV antibodies detected within plasma begins a period of clinical latency also referred to as seroconversion. With more advanced measurement techniques, it has been shown that during this stage of clinical latency the virus is actually in a state of active reproduction. Even though it appears to be in a state of inactivity, there is continued infection of nearby cells and production of viral strands.

Symptomatic (Accelerated Aging)

The widespread use of ART has successfully increased the lifespan of PLWHA with AIDS-related deaths declining annually. Instead, PLWHA are more likely to reach a stage of "accelerated aging," referring to the increased risk of developing chronic disease(s) known to primarily affect uninfected aging populations. Recent evidence indicates PLWHA are being diagnosed with and/or dying from CVD, diabetes, and other metabolic disorders with an early age of onset [28,29]. Mainly due to the toxic effects of some antiretrovirals, these adverse side effects can be found in Table 49.1.

SYMPTOMATOLOGY OF HIV INFECTION

Psychological Consequences

PLWHA are burdened with multiple psychosocial stressors at all stages of illness. Immediately upon diagnosis, patients must face life-changing issues such as managing the illness, affording appropriate health care, and the daily struggles that accompany living with the stigmatization of HIV. In addition to these personal stressors, various environmental factors could potentially exacerbate the levels of stress already experienced such as the living in a lower socioeconomic status, facing unemployment, reduced access to health care, and many others. The patients' ability to cope with these burdens ultimately depends on their psychological state, social support network, and their stage of HIV disease.

As is the case with any chronic disease patients, PLWHA are at an increased risk for psychiatric disorders like depression, anxiety, delirium, mania, HIV-related dementia, and psychosis. Many of these psychological complications are known to be treatable, and therefore it is imperative for caregivers and health care providers to learn to recognize the signs of these conditions so they may either treat the patient or refer them to a specialist for further evaluation. Effective treatment for depression, a common psychiatric disorder among PLWHA, has been shown to result in fewer physical symptoms, better sleep quality, and improvements in health-related quality of life.

Many studies of various chronic diseases have investigated consequences of distress among patients and reported positive associations with mood disturbances, poor treatment adherence, and negative health outcomes [10,30–33]. Similar findings have been reported among HIV-related investigations. Although distress has been identified as an important measure to manage mental health, and self-reported symptoms have become a common method used to indicate health status, the literature on self-reported symptom distress within the HIV-infected population is scarce.

Generally a level of distress is experienced when symptoms are present and emerging data have shown a negative impact of psychological distress on HIV disease progression [34–37]. Increases in symptom distress potentially have negative consequences to both physical and psychological health that have recently been discovered with a growing body of evidence supporting the psychoneuroimmunology (PNI) framework as discussed by McCain et al. [37,38]. Recent investigations have begun to show consistent reports of psychological distress and disturbances impairing immune function [39,40] as well as cytokine-induced changes in neurotransmitter and neuroendocrine function, which have been shown to correlate with onset of depression and/or fatigue [41,42]. The burden of frequent symptoms is known to negatively affect disease management and mental health [4,5,9,43]. Identifying factors that are associated with increased symptom distress may provide possible strategies to lessen the burden of HIV-infection and related symptoms while also improving treatment adherence.

Physical Consequences

All clinical populations face a large variety of disease-related physical and psychological symptoms, but prevalence rates of self-reported symptoms are generally over 50% among PLWHA ranging from a single symptom to multiple concurrent symptoms [3–5,44]. Common physical symptoms reported include diarrhea, loss of appetite, nausea, muscle weakness, peripheral neuropathy, fever, dry skin, and persistent cough. These are often experienced in conjunction with antiretroviral side effects for those placed on

TABLE 49.1
Antiretroviral Toxicities

Nucleoside Analogs

Drug	Zidovudine (ZDV AZT, Retrovir)	Didanosine (ddI, Videx)	Stavudine (d4T, Zerit)	Lamivudine (3TC, Epivir)	Emtriva (FTC)	Viread (Tenofovir)	Abacavir (ABC, Ziagen)
Side effects	Headaches, fever, muscle soreness, nausea, lipodystrophy, fatigue	Peripheral neuropathy, upset stomach, diarrhea, insomnia	Peripheral neuropathy, lipodystrophy, headache, insomnia, anxiety	Headache, nausea, diarrhea, fatigue, insomnia	Headache, diarrhea, nausea, rash	Nausea, diarrhea, bone changes	Hypersensitivity reaction, vomiting, fatigue

Protease Inhibitors

Drug	Invirase (Saquinavir)	Reyataz (Atazanavir sulfate)	Aptivus (Tipranavir)	Lexiva/ Nelfinavir (Viracept)	Kaletra (Lopinavir/ Ritonavir)	Indinavir	Ritonavir (Norvir)
Side effects	Diarrhea, abdominal discomfort, vomiting	Dizziness, rash, elevated liver function	Nausea, vomiting, abdominal pain, headaches, fever, dizziness, liver toxicities	Nausea, rash, diarrhea, headache, vomiting, fatigue	Rash, diarrhea, nausea, muscle weakness, increased blood lipids	Headache, fatigue, nausea, diarrhea, joint pain	Weakness, peripheral neuropathy, weight loss, increased muscle enzymes

NNRTI

Drug	Intelence (Etravirine)	Nevirapine (Viramune)	Delavirdine (Rescriptor)	Efavirenz (Sustiva)
Side effects	Rash, diarrhea, nausea, headache, hypersensitivity	Headaches, nausea, vomiting, fever, rash, drug-induced hepatitis	Headaches, nausea, vomiting, fever, rash, lipodystrophy	Rash, nausea, diarrhea, insomnia, increased lipids

Entry Inhibitors: Integrase Inhibitor/Dual-Class Fixed Dose Combo

Drug	Fuzeon (Enfuvirtide)	Selzentry (Maraviroc)	Isentress (Raltegravir)	Atripla (Sustiva/ Truvada)
Side effects	Pneumonia, diarrhea, nausea, fatigue, possible hypersensitivity	Cough, fever, cold, rash, muscle and joint pain, dizziness, low blood pressure	Diarrhea, nausea, vomiting, headache, fever, abdominal pain, fatigue, weakness, dizziness, lipodystrophy	See Sustiva and Truvada

Source: Adapted from Bartlett and Gallant, *Medical Management of HIV Infection*, John Hopkins University School of Medicine, 2000.

an ART regimen. As a result, the management of multiple symptoms has become a daily task for PLWHA in an effort to maintain an optimal quality of life [4,45].

As was the case before the discovery of antiretrovirals, the association between the number of self-reported symptoms and disease status still allows for the use of reported symptom frequency as an indicator of disease progression and health-related quality of life. More recently, this has begun to assist health professionals with monitoring how well a patient is responding to current antiretroviral combinations [4,46]. Symptoms lasting anywhere between a few days to a few weeks increase the burden of disease among individuals, often resulting in negative lifestyle habits. The side effects and symptoms of HIV infection often have many patients turning to self-medication by either altering their daily ART regimen or seeking additional alternative treatments that may include illegal narcotics [8,9,43,47]. Although the discovery of ART has led to an increased life span and decreased reports of AIDS and AIDS-related deaths, many scientists have reported a complex variety of symptoms and side effects associated with ART regimens creating a metabolic syndrome effect.

ANTIRETROVIRAL THERAPY

The total amount of time in which the virus replicates while evading immune system detection without proper treatment can be up to 10 years, but the total timeframe in which this occurs will vary between cases. Some viral genotypes can act swiftly and aggressively to destroy the immune system within 2–4 years following infection, whereas others focus on replicating before mutating into a more aggressive strand ensuring successful destruction of the invaded host. Recent data indicate ART medications are successful with preventing viral replication, increasing life expectancy, improving immunologic function and nearly eradicating AIDS cases and related deaths [48–50].

The timing for initiating treatment varies tremendously depending on viral infection as well as the patient's primary health care provider, but generally it is recommended that patients begin an antiretroviral regimen if asymptomatic but with a CD4 cell count ≤ 500 μL or symptomatic. For optimal results, treatment is suggested for asymptomatic patients with CD4 cell counts ≥ 500 μL [51]. Options for treatment range from early, aggressive intervention to postponing ART until a measurable increase in disease progression has been observed. Recent recommendations were released by the International AIDS Society–USA Panel in early 2010 (Table 49.2) stating the decision as to when patients should start treatment needs to be established after weighing "the benefits of treatment on morbidity and mortality against its risks, including toxicity, resistance, drug interactions, and the costs and inconvenience of lifelong treatment" [50]. Ultimately the primary factor determining success when deciding to begin ART is patient "readiness" to live with the daily burdens resulting from the treatment. But now with options becoming available for combination ART that can be administered with one pill there is hope that these treatments lead to a possible decrease in the risks associated with ART.

TABLE 49.2
2010 Recommendations of the International AIDS Society-USA Panel to Initiating Antiretroviral Treatment

Measure	Recommendation
Specific conditions	ART is recommended regardless of CD4 cell count
• Symptomatic HIV disease	
• Pregnant women	
• HIV-1 RNA > 100,000 copies/ml	
• Rapid decline in CD4 cell count > 100/μL per year	
• Active hepatitis B or C virus coinfection	
• Active or high risk for CVD	
• HIV-associated nephropathy	
• Symptomatic PHI	
• Risk for secondary HIV transmission is high, e.g., serodiscordant couples	
Asymptomatic, CD4 cell count ≤ 500 μL	ART is recommended
• CD4 cell count < 350/μL	
• CD4 cell count 350–500/μL	

TOXIC SIDE EFFECTS

The majority of side effects associated with ART are physiological in nature and directly alter metabolic processes, resulting in increased circulating blood lipids, lipodystrophy, and insulin resistance, thus creating a metabolic syndrome [28,29,44,50,52–54]. What was once a short-term muscle-wasting disease for PLWHA that ended in death over a period of several months has evolved into a chronic metabolic disorder with primary causes of mortality no longer being HIV/AIDS-related.

Symptoms and side effects from ART medications will vary depending upon specific antiretrovirals included in the patient's pharmacological regimen, as well as the total number of antiretroviral medications included. Table 49.1 provides a detailed list of antiretrovirals currently available, their toxic side effects, as well as other drug interactions. For example, NRTIs are associated with lactic acidosis, hepatic steatosis, and lipodystrophy. Evidence has shown lipodystrophy is more prevalent among individuals currently taking a combination of NRTI and a PI, both of which have known side effects disrupting metabolic function and disrupting adipocyte mitochondrial function [51,55]. Other symptoms specific to the type of NRTI being taken include pancreatitis, nausea, diarrhea, headache, insomnia, peripheral neuropathy, fatigue, malaise, anemia, and many others. The common side effects outlined in Table 49.1 are those that may directly inhibit exercise performance and/or adherence. For a more extensive list of all symptoms and side effects please refer to Bartlett 2000, *Medical Management of HIV Infection* [51].

Further caution must be considered for the possibility of drug interactions such as PI ritonavir, which has demonstrated interactions with the analgesics, cardiac medications, lipid-lowering agents, antimycobacterial, Ca^{++} channel blockers, antihistamines, antidepressants, neuroleptics, psychotropics, and ergot alkaloids (vasoconstrictors). The interactions with ritonavir appear to be through the use of these drugs of the cytochrome p450 activation system [51].

TREATING THE SIDE EFFECTS

Treatment of HIV-Related Symptoms

Additional medications are generally prescribed for viral symptoms and treatment-related side effects. Common prescription medications taken in addition to ARTs may include appetite stimulants, psychoactive drugs, soporific agents, antidiabetic drugs, analgesics, antibiotics, antilipemics, bisphosphonates, calcitonin, or hormone replacements. Some of the more common antidepressants and anxiolytics may be prescribed among those beginning an ART regimen to assist with maintaining treatment adherence.

Studies have consistently shown beneficial results in adherence to HAART when patients are treated with antidepressants as well [56,57].

The use of additional prescription medications in response to disease and ART side effects has not always yielded beneficial results. Each ART can have different interactions with other pharmaceuticals that could further exacerbate symptoms or even prevent the ARTs primary mechanism of action from working altogether without the patient's knowledge [58–62]. For example, in the treatment of anxiety in which someone taking a daily Valium or Klonopin to treat their anxiety at the same time as starting ART, the mechanism responsible for inhibiting serotonin reuptake may no longer be effective due to specific antiretroviral mechanisms. In fact, there are some PI medications, such as ritonavir, which metabolizes the antianxiety and other antidepressant medications completely [63,64]. Because of the unpredictable reactions that an antiretroviral may have on new prescriptions, or even over the counter medications, new treatment strategies are imperative.

A complementary treatment that may help address ART toxicities and viral-related side effects is exercise training [20,21,29]. Similar metabolic abnormalities within the general population respond positively to prescribed dosages of routine exercise. These exercise-induced changes include decreases in total cholesterol and triglycerides, decreased fat mass, increased lean tissue mass, decreased waste circumference, and increased insulin sensitivity [65–71].

Exercise as an Alternative Treatment to ART-Related Toxicities

In populations with a broad range of chronic diseases, there is a growing body of evidence showing that health benefits can be obtained by incorporating structured aerobic exercise into an individual's recovery and/or treatment plan. For those stricken with conditions such as HIV, cancer, and type 2 diabetes, aerobic combined with resistance exercises can have positive effects in alleviating symptoms associated with the diseases and side effects of the medical interventions. Only in the last few years has there been an association established between HIV and increased risk of chronic diseases such as CVD and diabetes. As a result, there is limited evidence to make a definitive statement as to whether or not exercise is a beneficial alternative to decreasing the risk of CVD among PLWHA. Although limited, the data that are available suggest even modest amounts of routine exercise can yield both psychological and physiological health improvements. Table 49.3 provides a list of studies completed after the implementation of ART indicating the form of exercise training and its effects among PLWHA.

Psychological Improvements Following Exercise

Early investigations conducted prior to widespread use of ART compared the effects of aerobic exercise on psychological components, such as depression and anxiety. Eight weeks of moderate-intensity aerobic exercise completed twice weekly for 60 min have shown significant reductions in anxiety and depression [72]. Other investigators reported significant improvements after only 5 weeks of aerobic exercise. Men who exercised for 45 min a day, 3 days a week, reduced anxiety and depression upon learning of their seropositive status [73,74]. As these investigations were performed before ART, the results are limited to symptoms specific to viral progression and not treatment. Further, the majority of study demographics also consisted of middle class homosexual males. Due to the shift in patient demographics and treatments, these findings lack generalizability with today's predominantly impoverished minority seropositive populations. It is unknown whether or not the virus, or any ART medications, would inhibit specific exercise-induced adaptations that are observed among other clinical and healthy populations.

In the era of widespread use of ART, there has only been one investigation utilizing aerobic exercise as the primary intervention for HIV-associated depressive symptoms.

TABLE 49.3
Published Findings of Exercise Based Clinical Trials Since the Development of ART

References	Subjects	Outcomes/ Conclusions
Smith et al. [84]	Males (41) females (8)	↑ Time to fatigue, ↓ BMI, subcutaneous fat.
Thoni et al. [77]	Males (12) females (5)	↑ VO_2max and HDL ↓ Fat, cholesterol, and triglycerides
Neidig et al. [75]	Males (22) females (8)	↓Depressive symptoms and depressed mood.
Terry et al. [55]	Males (20) females (10)	↑ VO_2max ↓ BMI and body fat
Fairfield et al. [85]	Males (43)	↑ Muscle attenuation
Grinspoon et al. [86]	Males (43)	↑ Muscle and HDL
Hand et al. [20]	Males (40)	↑ VO_2max, endurance, muscle
Dolan et al. 2006 [87]	Females (40)	↑ VO_2max, endurance, muscle
Fillipas et al. [88]	Males (40)	↑ Cardio and cognitive function
Engelson et al. [89]	Females (18)	↑ Strength, fitness, and QOL
Robinson et al. [90]	Males (3); females (2)	↓ Fat
Sakkas et al. [91]	Males (40)	↑ Strength and LBM
Dudgeon et al. [92]	Males (38)	Acute changes post exercise: ↑ GH, ↑ IL-6, ↑ sTNFrII, ↓ cortisol

ART, antiretroviral therapy; BMI, body mass index; HDL, high-density lipoprotein; QOL, quality of life; LBM, lean body mass; GH, growth hormone; IL-6, interleukin-6; sTNFrII, soluble tumor necrosis factor receptor 2.

Like those investigations previously discussed, reductions in depressive symptoms and/or significant improvements in quality of life were shown [75]. Findings from this study suggest that 60 min of aerobic exercise conducted 3 days a week can be used as a beneficial method for improving the psychological disturbances experienced by PLWHA.

Physiological Improvements with Exercise

Studies have consistently shown physiological improvements across clinical measurements of health such as body mass index (BMI), waist circumference, blood lipids, strength, and CRF (among others). A 24 week exercise intervention utilizing two levels of intensity (medium or high) found both intensities yielded significant improvements in CRF and reduced perceived stress. The medium-intensity group exercised three times a week at 50%–60% of their VO_2max for 40 min and the high-intensity group exercised three times a week at 75%–85% of their VO_2max for 24 min. A major limitation to that study, however, was the high attrition rate of 76%, which was possibly due to the long duration and/or intensity of the study [76]. In a similar clinical trial, participants were randomized into either a high-intensity or moderate-intensity aerobic exercise group and exercised for a total of 30 min, 3 days a week for 12 weeks. Findings showed similar significant improvements in functional capacity in both groups [55].

Interventions consisting exclusively of low-intensity aerobic exercise, but with a longer duration of 16 weeks, also have shown significant improvements among CRF and serum HDL cholesterol among PLWHA when compared to a control group. Findings have also indicated significant decreases in total abdominal adipose tissue, total cholesterol, and circulating triglycerides [77]. Similar results have been reported by other researchers who have found significant increases in CRF, oxygen pulse, and maximum tidal volume. In addition, aerobic exercise has demonstrated decreases in BMI, waist-to-hip ratio, body density, and body fat after a 12 week moderate-intensity aerobic exercise intervention [55,78]. The reported findings would, thus, indicate that PLWHA are able to elicit significant health improvements when following a prescribed exercise routine lasting 5 weeks or longer. These effects have been observed with various combinations of the exercise intensity, participant disease status, and/or current antiretroviral treatment [20,21,29,55,76,78–80].

In addition to the findings on physiological and psychological variables, no significant changes in CD4+ cell count have been reported in high- or moderate-intensity exercise groups [76,77,80]. Further, there have been no significant changes from baseline reported in CD8+ cell count, leukocytes, or lymphocytes following moderate- or high-intensity exercise [55]. Recently it was shown that patients with dyslipidemia and lipodystrophy had no significant changes in immunological variables after completing 12 weeks of moderate-intensity aerobic exercise as well [55]. Notably, there are no published reports of exercise-induced immunosuppression in PLWHA who participated in physical activity regimens designed to reduce the psychological or physiological symptomatology associated with HIV.

TABLE 49.4
HIV-Associated Changes to Exercise Testing

Disease Status	Response to Exercise
Asymptomatic	• Physiological parameters within normal limits (e.g., blood pressure, heart rate, VO_2) • Possible functional aerobic impairments due to sedentary lifestyle
Symptomatic	• Reduced aerobic capacity and muscular strength • Possibility of increased heart rate at rest and submaximal work rates • Increased difficulty in adhering to exercise prescription • ART side effects (see Table 49.1)
AIDS	• Drastically reduced aerobic capacity and muscular strength • Possible abnormal neuroendocrine responses at moderate- and/or high- intensity work rates

Recommendations for Exercise

Current exercise training recommendations as described in ACSM's *Exercise Management for Persons with Chronic Disease and Disabilities* (3rd edition) for PLWHA suggest a moderate-intensity aerobic and resistance training regimen [81]. This includes accumulating a total of 150 min of moderate-intensity physical activity a week, as well as 2 days of full body resistance training at approximately 60% of one repetition maximum. Regardless of disease status, it is strongly recommended that anyone living with HIV or AIDS receive medical clearance from their primary health care provider prior to beginning an exercise program. Even though the majority of PLWHA have a reduced aerobic capacity, most of the standard physical fitness tests are applicable to this population and can be completed with little or no risk to the individual. Table 49.4 outlines potential HIV-associated changes that may be observed during exercise testing and/or training according to disease state.

CHANGING DEMOGRAPHICS

Over the last decade, the United States has seen a dramatic shift in the demographics of HIV/AIDS including a rapid rise in the incidence of HIV infection among minority communities, primarily African Americans [48]. Although prevalence and incidence rates indicate homosexual Caucasian men remain the most prevalent group with primary infection, the disproportionate incident rates of new infections among minority heterosexual populations is having a profound effect on prevention and treatment strategies. While the number of reported cases among Caucasians has remained relatively stable over the past 10 years, African American and Hispanic populations have shown increases in reported infection rates [48,82,83]. It is also of growing concern that within these minority populations of new HIV cases heterosexual females continuously show an increase in the number of

reported infections every year and that a large percentage of persons testing seropositive report a lower socioeconomic status.

CONCLUSION

Evidence would suggest that PLWHA, regardless of disease status, can obtain similar short-term health benefits from routine physical activity reported within general populations. Research has shown significant improvements among psychological and physiological variables after moderate levels of routine exercise in as little as 6 weeks. It is also clear that across various populations routine moderate-intensity physical activity reduces the risk of chronic disease and that many of these conditions have been established as major causes of morbidity and mortality among PLWHA.

Research among PLWHA has demonstrated that aerobic exercise performed at low-, moderate-, or high-intensity does not negatively impact immune function or disease progression in HIV-infected individuals. This suggests that aerobic exercise can be both beneficial and safe for this clinical population. However, it is recommended that if aerobic exercise is to be performed by this population, that they do so at a low- or moderate-intensity level as data are lacking to draw the conclusion that a high-intensity aerobic regimen will not have a negative impact on overall health or quality of life in this population [18,21,29].

Responses and adaptations to exercise training will vary depending on disease status and whether or not that patient is currently on an ART regimen. Asymptomatic individuals generally respond in a manner similar to someone without HIV of the same body size, age, and gender. However some may be more deconditioned due to psychological disturbances commonly associated with daily sedentary behavior such as depression or anxiety, among many others. Further, individuals with a symptomatic status will generally be on a current ART regimen. Side effects of common antiretrovirals that could potentially hinder exercise performance are outlined in Table 49.1.

Although exercise itself is not going to eliminate the burdens of health care costs, social stigmatization, or other daily stressors, it could potentially reduce the health consequences of chronic stress, improve quality of life, and possibly increase the reduced life span of PLWHA. Most of the negative side effects from both the virus itself and treatment-related toxicities, including impaired glucose tolerance, fatigue, increased blood lipid profile, chronic inflammation, anxiety, depression, circulating cortisol, and others, are known to improve with routine exercise in various populations. Additional evidence from longitudinal studies have clearly shown modest increases in cardiorespiratory fitness can decrease the risk of all-cause mortality as well as the risk of most chronic diseases. Whether or not PLWHA would have a similar response to long-term exercise is unknown due to insufficient research. Further, there are no reported exercise-related interventions lasting longer than 6 months, making it impossible to determine the long-term effects on overall health and life longevity. However, benefits of exercise that have been shown in a short time frame as reported by multiple investigations would suggest long-term gains in the physical and psychological well-being of PLWHA who participate in physical activity.

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50 Exercise, Aging, and Immunity

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CONTENTS

Introduction 625
Exercise and the Innate Immune System 625
Exercise and "Inflammaging" 625
Physical Activity, Cardiovascular Fitness, and "Inflammaging": Cross-Sectional Studies 625
Exercise Training and "Inflammaging": Prospective Training Studies 626
Potential Mechanisms of Anti-Inflammatory Effects of Exercise Training in the Aged 626
Adipose Tissue Modulation 626
Cholinergic Anti-Inflammatory Pathway 627
Aging and T-Cell-Mediated Immunity 627
Effect of Exercise on T-Cell-Mediated Immunity in the Aged 627
Exercise and Humoral Immunity 628
Cross-Sectional Studies 628
Prospective Training Studies 629
Summary 629
References 629

INTRODUCTION

Restoration of immunological function is important for the improvement of quality of life of the elderly as the aging population is rapidly increasing throughout the world. Potential strategies have included grafting of cells and tissues, dietary manipulation, antioxidant supplementation, thymic peptides, endocrine manipulation, and exercise [1]. To date, there have been no widely used strategies proven efficacious in restoring immune function in the aged. However, there is evidence that regular moderate cardiovascular exercise is related to overall improved immune function in the elderly [2].

EXERCISE AND THE INNATE IMMUNE SYSTEM

Innate immunity acts as the first line of defense against invading pathogens and is mediated primarily by cellular components including neutrophils, macrophages, dendritic cells, and natural killer (NK) cells and by humoral components including cytokines. Upon antigen recognition, the innate system initiates a rapid, nonspecific response intended to limit pathogen replication and further infection of host cells until the adaptive cellular immune response eliminates the pathogen. A central aspect of the innate response is inflammation, which describes the cellular milieu produced by activated macrophages, including a multitude of chemokines, cytokines, and other effector proteins, which coordinate the immune response and create an environment inhospitable to pathogen survival [3]. The inflammatory response may be acute, as in a transitory physical injury or infection, or it may be low grade and chronic, as in long-term infections and autoimmune diseases [3].

EXERCISE AND "INFLAMMAGING"

In more recent years, it has become recognized that normal aging is associated with a state of chronic low-grade inflammation characterized by elevated levels of circulating IL-6, C-reactive protein (CRP), and tumor necrosis factor (TNF)-α, all of which may be involved in the pathogenesis of numerous age-related diseases including cardiovascular disease, diabetes, cancer, sarcopenia, impaired wound healing, and dementia. This state has been termed "inflammaging" [1]. With these findings, therapies and interventions aimed at attenuating age-induced low-grade inflammation have come to the forefront of behavioral and biomedical research. Exercise may be one such therapy, as both epidemiological and longitudinal data suggest that increasing physical activity is an effective means of reducing systemic low-level inflammation and chronic inflammatory diseases in aged individuals.

Physical Activity, Cardiovascular Fitness, and "Inflammaging": Cross-Sectional Studies

Cumulative data from cross-sectional studies demonstrate an inverse relationship between physical activity levels and circulating inflammatory biomarkers. Several large population cohorts such as the Third National Health and Nutrition Examination Study (NHANES III), the Cardiovascular Health Study (CHS), and the Health ABC Study support

this inverse relationship having reported negative correlations between physical activity levels and circulating CRP (all), IL-6 (NHANES III), and TNF-α (NHANES III) [4]. Furthermore, this relationship appears to occur in a dose-dependent manner, in that the lowest levels of inflammatory biomarkers were observed in elderly persons reporting the highest levels of physical activity [4].

While large cohort studies provide strong statistical power, they are often limited by their reliance on questionnaires to assess physical activity levels. For that reason, smaller cross-sectional studies that utilize accelerometry and fitness testing to assess physical activity/fitness may provide a more refined understanding of the relationship between physical activity and inflammation in aged adults. Interestingly, data from our laboratory found no significant relationship between accelerometry-based physical activity levels and circulating inflammatory markers, but did observe a negative correlation between body fat and CRP in 182 community-dwelling older adults [5]. These data partially coincide with our report demonstrating an inverse correlation between adiposity, cardiorespiratory fitness (VO_2 peak), heart rate recovery (HRR), and CRP in older adults, suggesting that elevated CRP levels may be related to increased visceral adipose tissue deposition and impaired parasympathetic activity frequently observed in aged adults [6]. Interpretation of these two studies supports the hypothesis that increasing physical activity levels alone may not be sufficient enough of a stimulus to reduce inflammation. Rather, physical activity volume or intensity must reach a threshold that reduces adiposity and/or increases parasympathetic tone in order to observe an improvement in inflammatory profile. Although the cross-sectional nature of these studies prevents the determination of cause-effect relationships, these data support the anti-inflammatory effect of exercise, which may be mediated by a reduction in adiposity and an increase in parasympathetic nervous system activity.

Exercise Training and "Inflammaging": Prospective Training Studies

Given the quantity of cross-sectional evidence suggesting a link between exercise and inflammation, several researchers have conducted longitudinal studies investigating whether exercise training reduces inflammation in aged adults. Our laboratory has recently published evidence that 10 months of aerobic exercise training (60%–70% VO_2 max) was able to reduce serum CRP levels in older adults, with no reduction in CRP levels of a similar group that underwent only flexibility exercise [7]. Additionally, we found that reductions in trunk fat associated with cardiovascular exercise were the best predictor of the reductions in systemic inflammation, further supporting the cross-sectional data, suggesting that adipose tissue accumulation may be at least partially responsible for the increases in basal inflammation seen in the elderly and other individuals [7]. In a similar study, Kohut et al. [8] examined the effects of 10 months of aerobic exercise (65%–80% VO_2 max) in elderly men and women compared to a flexibility control group. Results demonstrated that aerobic exercise induced significant reductions in serum IL-6, CRP, and IL-18, while both interventions were sufficient to cause a decrease in serum TNF-α.

The majority of the literature supports the anti-inflammatory effects of exercise observed in the previously cited studies; however, several longitudinal studies have failed to detect reductions in inflammatory biomarkers following exercise training intervention [9]. A potential explanation for the discrepancies between the studies could be attributed to differences in training intensity, duration, modality, subject population, and initial inflammatory profile. As body fat reduction and parasympathetic activity possibly mediate the relationship between training and inflammation, it is plausible the studies that failed to reduce inflammation did not reach an intensity or volume threshold significant enough to induce a reduction in adiposity and an increase in parasympathetic tone.

It must be noted that while the presence of a chronic inflammatory disease is one of the primary causes of mortality in the aged population, a normal innate immune response is necessary to protect against infectious disease. To this extent, further studies must examine the hormetic role of exercise mode, intensity, and duration on maintaining the necessary balance between an adequate inflammatory response and chronic inflammation in older adults.

POTENTIAL MECHANISMS OF ANTI-INFLAMMATORY EFFECTS OF EXERCISE TRAINING IN THE AGED

Adipose Tissue Modulation

Visceral adipose tissue has become increasingly recognized as a metabolically active organ capable of secreting inflammatory signals that can impact whole body physiology. Two recent reports indicate that *normal aging* leads to a dysregulated state in visceral adipose characterized by exaggerated inflammation and pinpoints adipose tissue as a primary source of inflammatory mediators during aging. Wu et al. [10] found that visceral adipose tissue from 22 to 24-month-old C57BL/6JNIA mice had increased gene expression of IL-1, TNF-α, IL-6, and COX-2 when compared to young counterparts. In another study, Starr et al. [11] demonstrated that the exaggerated systemic IL-6 response induced by intraperitoneal lipopolysaccharide administration was highly related to increased expression of IL-6 within visceral adipose depots of aged mice when compared to young controls. Accordingly, it has been hypothesized that exercise training may attenuate age-induced inflammation via a reduction in both visceral adipose tissue mass and inflammatory profile. Previous studies from our laboratory have demonstrated that moderate-intensity exercise training reduces adipose tissue and systemic inflammation in obese mice [12,13]. The biological mechanisms responsible for the antiinflammatory effects of exercise within adipose tissue are not known, but could be due to the regulation of cellular hypoxia, oxidative stress, adipocyte size, macrophage polarization, and energy

sensing pathways. Future elucidation of these factors will provide important data reconciling the relationship between adipose tissue inflammation and systemic inflammation.

Cholinergic Anti-Inflammatory Pathway

Work from Kevin Tracey's laboratory suggests that stimulation of the parasympathetic nervous system, via the efferent vagus nerve, inhibits proinflammatory cytokine production and protects against systemic inflammation [14]. They referred to this pathway as the "cholinergic anti-inflammatory pathway" and described it as a central homeostatic mechanism by which the sympathetic division of the autonomic nervous system stimulates the inflammatory response through the release of epinephrine and norepinephrine, while the parasympathetic nervous system works reciprocally to suppress this release of proinflammatory cytokine [14]. A primary function of the vagus nerve is to control heart rate, which is typically measured by HRR following exercise and heart rate variability (HRV). A major adaptation to long-term exercise training is a decrease in HRR and HRV, signifying that the parasympathetic nervous system becomes more efficient in stimulating the reciprocating sympathetic nervous system. Thus, exercise training may increase efferent vagus nerve activity, and this increased activity may contribute to the anti-inflammatory effect of exercise. This hypothesis is supported by our cross-sectional study, which demonstrated that HRR was the best predictor of CRP in aged adults [6]. However, this hypothesis has not yet been fully investigated in a prospective or definitive manner.

AGING AND T-CELL-MEDIATED IMMUNITY

Cell-mediated immunity (CMI), which largely involves the antigen-specific activation of T cells that mediate the activation of other effector immune cells (e.g., macrophages, NK cells, B cells, and other T cells), is diminished in older individuals. Thymic involution, or the shrinkage of the organ responsible for T-cell maturation, starts at a young age and is linked to reduced immune capability in the elderly. The immune risk profile (IRP) [15–17] characterizes multiple immune function biomarkers that are used to predict morbidity and mortality in older adults. Individuals over 60 with an inverted $CD4^+/CD8^+$ T-cell ratio, the main characteristic of IRP, have significantly increased mortality rates [18]. Other important characteristics of the IRP include reductions in naïve T cells, corresponding increases in memory T cells, decreased T-cell proliferation and activation, reduced costimulatory molecules expression, and diminished cytokine signaling and latent cytomegalovirus (CMV) and Epstein Barr virus infection [17].

Whereas age-related alterations in antigen-presenting cells and antibody-producing B lymphocytes and their migration are apparent [19–21], the dramatic decline in humoral and CMI responses to many immune challenges is predominantly the consequence of senescent T cells [22]. Indeed, virus-activated $CD4^+$ T-helper (Th) cells provide critical cytokine signals that stimulate B cells to differentiate and produce antibodies. Th1 cells stimulate antibody responses, interferon (IFN)-γ production, and CTL memory, whereas Th2 cells stimulate antibody responses and IL-10, which attenuate Th1 responses [23,24]. Aging results in reduced Th1 cytokine production in response to stimulation, creating a cytokine imbalance represented by low-IFN-γ and high-IL-10 production, which is directly related to poor responses and higher risk for infection [25–29].

The reasons for the age-related T-cell defects are not entirely understood, but experiments in T-cell receptor transgenic mice have implicated reduced output of recent thymic emigrants by the involuted thymus and homeostatic proliferation of peripheral $CD4^+$ naïve T cells as key contributors to increased T-cell longevity and accumulation of age-related intrinsic defects [30]. Indeed, the amount of time a T cell spends in the periphery reduces its ability to respond to antigenic stimulation [30]. Aged $CD8^+$ T cells also exhibit reduced responsiveness to newly encountered antigens, profoundly reduced IFN-γ expression, telomerase activity, and, interestingly, clonal expansions of $CD28^-$ memory cells resulting in a reduced T-cell repertoire diversity [23,31–33]. Frequently, a large fraction of expanded memory cells are specific for ubiquitous latent β-herpes viruses including, most prominently, CMV [34], which leads to reduced T-cell diversity and a "clogging" of immunological space. Many studies have found that these terminally differentiated effector-memory cells are highly related not only to poor vaccination responses [35–37] but also to autoimmune diseases [31] and faster HIV-1 disease progression [38].

EFFECT OF EXERCISE ON T-CELL-MEDIATED IMMUNITY IN THE AGED

Cross-sectional studies report that elderly runners exhibited a higher in vitro stimulated T-cell proliferative response and improved effector cytokine production compared to elderly sedentary [39]. Also, highly conditioned elderly women [40] and older male recreational runners [40] at rest displayed higher T-cell proliferative responses to mitogens than those of age-matched sedentary peers without any differences in absolute T-cell number. In a study by Kohut et al., lymphocyte proliferation to influenza antigen was greater in the participants reporting either regular activity or less intense activity compared to sedentary individuals [41]. Therefore, regular exercise training may be an effective method of preventing or retarding impaired immune function in aging individuals. Results from these studies indicate that older regular exercisers may have an improved Th1 response, which may enhance CMI, improve defense against intracellular pathogens, and reduce the risk of morbidity due to infections. It is not known, however, if exercise only acts in a preventative manner to delay immunosenescence or whether exercise has immune restorative properties in previously sedentary individuals.

Results from exercise training studies in this population have not reported consistent findings. Although Kapsai et al. [42] found no effect 8 months of endurance and resistance training on $CD4^+/CD8^+$ T-cell coreceptor expression in frail elderly, Shimizu et al. [43] reported that 6 months of combined moderate exercise has shown to be effective in increasing costimulatory receptor CD28 expression on circulating T cells in elderly subjects. Since costimulation through CD28 enhances production of IL-2 and IFN-γ in T cells activated by antigens and/or mitogens, these results indicate that longer-term multimodal exercise interventions can be effective in restoring T-cell responsiveness in this population while promoting strength and cardiovascular fitness.

In order to gain a better understanding of the potential mechanisms by which exercise might improve CMI with aging, Woods et al. [44] have shown that 4 months of treadmill running in mice improved naïve to memory T-cell subset ratios in both $CD4^+$ and $CD8^+$ cells in the spleen of old mice and that 6 months of moderate aerobic exercise training in elderly individuals may be sufficient to lead to minimal increases in some measure of immune function, while not affecting others in previously sedentary elderly [45]. Furthermore, Kohut et al. [46] reported greater Th1 cytokine production, IL-2, and IFN-γ, in response to HSV-1 infection after 8 weeks of moderate aerobic training in mice [46]. Conversely, not all studies report conclusive evidence that exercise definitively improves CMI [47,48]. Reasons for this may be a product of small sample size, relatively short interventions, and differences in exercise modality and intensity in which exercise is performed during these interventions.

Few studies have examined the impact of exercise on in vivo measures of CMI. Delayed-type hypersensitivity (DTH) reactions in the skin have been used to assess CMI in vivo. Sedentary elderly men have been shown to have decreased DTH response when compared to their physically active counterparts [49]. High-intensity resistance training has not been shown to change DTH responsiveness in aged individuals [50] but aerobic exercise combined with an enriched diet in an elderly population found a small exercise effect on the DTH response that was sustained over a 17-week period when compared to the control group that exhibited a decline [51]. An important aspect of these studies is the clinical relevance of DTH response, which has long been used as an overall indicator of the strength of CMI. However, a major limitation to using DTH as a functional measure of CMI is the large variability typically observed, making it difficult to interpret studies with small sample numbers. Clearly, further study is warranted with larger samples sizes to determine the effects of exercise training on CMI in aged individuals.

In summary, there is evidence that regular physical activity can have a beneficial effect on specific aspects of T-cell-mediated immune status in elderly individuals, with endurance exercise being the most beneficial. Both animal and human cross-sectional and interventional studies support the hypothesis that moderate exercise enhances T-cell immune function in older adults. Unfortunately, at this time, the mechanism for these improvements is unknown.

EXERCISE AND HUMORAL IMMUNITY

Among the many effects of aging is a general decrease in the ability of the body to respond to antigenic agents including not only pathogens but also vaccines [52]. An immune response to infection or vaccination results in the production of antibodies, which are capable of binding to and neutralizing foreign invaders such as pathogenic bacteria and viruses. This response is commonly known as humoral immunity and is one of the major components of the adaptive immune system. Antibodies are secreted into body fluids by plasma cells, mature B cells that respond to pathogens in an antigen-specific manner. The aging process is associated with both a loss of B-cell number and a reduction in B-cell function [53]; thus, interventions that counteract this effect and allow for increased potency of B-cell responses are of major interest. Of the currently available therapies that have been shown to partially ameliorate this aging effect, endurance exercise training stands out as one which is at once cheap, safe, easy to perform, and available to a wide range of individuals in all parts of the world. Thus, the effects of exercise on B-cell function and antibody production as a response to exercise training are of major interest to a number of researchers in the field.

CROSS-SECTIONAL STUDIES

A cross-sectional examination of antibody response to influenza vaccine in older highly fit men and women compared to less fit older adults demonstrated that the highly fit, physically active individuals had a greater antibody response to both the H1N1 and B strains of the influenza vaccine than did their less active counterparts [54]. Additionally, the highly fit subjects had a greater production of more potent IgG2 versus less potent IgG1 antibodies after recall vaccination with a tetanus toxoid booster, suggesting an exercise effect on antibody isotype switching that may be important for defense against infection in older individuals. In a similar study, it was found that older individuals who exercised vigorously had higher antibody, including both IgM and IgG isotype, responses to influenza vaccine when compared to individuals of the same age who exercised either moderately or not at all [41].

This evidence is further supported by a study that found that physical activity level is positively correlated with antibody response to influenza vaccination in older adults [55]. Recently, a study of patients with coronary heart disease demonstrated that regular physical activity in this population is independently associated with increased anti-influenza antibody titer after vaccination [56], a result that extends this finding to a population that has risk factors for poor immunological responses beyond that of the normal aging process. In addition to these results from influenza and tetanus toxoid vaccination, some evidence exists that exercise can improve antibody response to novel immune activators. Administration of keyhole limpet hemocyanin (KLH) was found to elicit increased antibody responses in physically active compared to sedentary older adults [49], importantly

demonstrating that exercise can generate greater protective immune responses even to antigens to which an individual has no prior exposure history.

PROSPECTIVE TRAINING STUDIES

These cross-sectional studies are further supported by prospective exercise training studies that examine the antibody responses in previously sedentary older individuals who undergo a standardized training program under the supervision of the researchers. A 10-month aerobic exercise training program has been shown to increase antibody responses to influenza vaccine at time points out to 3 months postvaccination in older adults when compared to control subjects who remained sedentary during the course of the study [57]. A similar clinical study using a relatively large number of subjects (n = 144) found that although 10 months of aerobic exercise training did not induce higher peak anti-influenza antibody responses in older adults when compared to older individuals who underwent a nonaerobic flexibility-only training program, it did increase the duration of the protective antibody response, which was sufficient to cover the entire influenza season [58]. This was important to demonstrate because aging results in a quicker reduction in protective antibody levels when compared to younger individuals in response to vaccination [59]. Importantly, this increase in duration of protection was concomitant with reduced symptom severity of upper respiratory tract infections in this group. In a smaller cohort of the same group of participants, it was further demonstrated that the exercise training program increased the antibody response to KLH administration [60], thus providing more evidence that endurance exercise can increase immune responses to antigenic agents even in the absence of prior exposure.

Supporting the earlier data on plasma antibody responses, several investigators have found positive effects of exercise on general salivary antibody levels, an important first-line defense against pathogens introduced by oral routes. Moderate-intensity cycling for 6 months caused a 40% increase in salivary IgA levels in older men and women with no change in the sedentary control group in one study [61]. A separate study demonstrated that an acute bout of exercise can increase both concentration and secretion rate of salivary IgA even in individuals >75 years of age [62]. However, a similar study involving 16 weeks of aerobic exercise in older adults found no exercise-induced changes in salivary IgA levels, although exercise did increase plasma IgA as well as plasma IgG and IgM antibodies as seen in other studies [63], suggesting that duration, intensity, or mode of exercise may play a major role in determining immunological outcomes in this population. This is partially supported by a study that included both endurance and resistance exercise components in a training program for older adults, which resulted in significant increases in both salivary IgA concentrations and secretion rates compared to the preexercise intervention time point [64].

Several studies have examined some of the aforementioned measures in rodent models of aging, which allows for a more in-depth look at potential mechanisms by which exercise might cause these changes. However, results from these studies have not always been consistent with those undertaken in humans, sometimes for reasons that are not yet clear. A training program involving 8 weeks of treadmill running failed to elicit a higher antibody response to herpes simplex virus in mice, although other markers of immune function including lymphocyte production of cytokines were increased by exercise training [46]. A similar study that subjected rats to 10 weeks of treadmill training demonstrated no increase in antibody or other responses to administration of KLH when these rats were compared to sedentary control animals [65].

Despite these challenges, mechanistic studies in older rodents have shed some light as to possible causes for the changes in antibody responses to vaccination and infection seen in older adults. Blockage of β-adrenergic receptors via nadolol ablated the exercise-induced increase in antibody- and cell-mediated immune function seen in response to herpes simplex virus infection in mice [66]. Similarly, blockage of endogenous opioid activity, which is increased with exercise, decreased antibody response to albumin injection compared to exercised mice, which received a placebo implantation [67]. Although these studies provide some insight into possible causes for exercise-induced increases in immune responses in older adults, much more work remains to be done on this front before a satisfactory mechanism for these changes can be provided.

SUMMARY

Overall, in healthy older adults, regular aerobic exercise appears to reduce chronic low-level inflammation and augment both cell- and antibody-mediated immune responses. The benefits of regular exercise on the immune system and other systems should persuade practitioners to suggest regular exercise to otherwise healthy older adults. Unfortunately, at this time, the mechanism(s) responsible for the beneficial effects on the aged immune system are unknown.

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Part XI

Pulmonary Medicine

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51 Respiratory Symptoms

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CONTENTS

Introduction 635
Objective Assessment of Respiratory Symptoms 636
Pulmonary Function Tests 636
Spirometry 636
Lung Volume Testing 636
Diffusion Limitation of Carbon Monoxide 637
Pulse Oximetry 637
Dyspnea 637
Definition 637
Physiology of Dyspnea 638
Qualities of Dyspnea 639
Essentials of the History 640
Timing: Acute versus Chronic Dyspnea 640
Timing: Night versus Day 640
Position 641
Cough 641
Definition and Physiology 641
Clinical Causes of Cough 642
Acute Cough 642
Subacute and Chronic Cough with Clear Chest X-Ray 642
Chronic Cough with an Abnormal Chest X-Ray 643
Hemoptysis 644
Definition and Physiology 644
Etiology 644
Wheezing 645
Definition and Physiology 645
Etiology 645
Nocturnal Respiratory Symptoms: Snoring and Apnea 646
Definition and Physiology 646
Etiology 647
Essentials of the History 647
Summary 647
References 648

INTRODUCTION

Shortness of breath, cough, and wheezing are among the most common symptoms experienced by patients seeking medical care. As in most areas of medicine, the evaluation of patients with respiratory symptoms largely depends on a comprehensive and insightful history obtained by the physician. Information offered spontaneously by patients is the starting point in the evaluation of any problem, but knowledge of the pathophysiology and differential diagnoses underlying the symptoms allows the physician to probe further, to determine which areas of the physical examination require special attention, and ultimately to narrow, if not eliminate, the radiographic and laboratory testing required to confirm the diagnosis.

Often there is confusion between respiratory symptoms and signs. For example, patients are described as being "short of breath" as part of the physical examination. In fact, symptoms can only be described by the patient. Physicians may speculate that a patient is experiencing respiratory discomfort based on observing physical signs such as recruitment of accessory muscles of ventilation, tachypnea, or an inability to speak in full sentences. Nevertheless, *symptoms* characterize what patients are experiencing and can only come from them. The timing of respiratory symptoms and conditions that precipitate or alleviate the discomfort can clarify the impact of

the symptoms on the patient. Understanding the "language of dyspnea," developed from descriptive research of patients with a variety of respiratory diseases, can help clinicians understand the significance of their patients' symptoms.

This chapter focuses on the physiological and clinical significance of several common respiratory symptoms. The role for and utility of pulmonary function tests (PFTs) are briefly reviewed in the following text, but a more complete description is beyond the scope of this discussion. Clinical and pathophysiological details of specific disease states such as asthma and chronic obstructive pulmonary disease (COPD) will be addressed in other chapters. This chapter does cover how specific elements of the physical examination, in concert with reported symptoms, can narrow the differential diagnosis.

OBJECTIVE ASSESSMENT OF RESPIRATORY SYMPTOMS

Respiratory symptoms can be due to a variety of pathophysiological processes involving disparate organ systems. A general understanding of the use of PFTs is helpful in developing a preliminary physiologically based approach to respiratory symptoms. We will also comment briefly on some of the common pitfalls associated with the use of pulse oximetry.

Pulmonary Function Tests

Pulmonary function testing refers to maneuvers in which spirometry, lung volumes, and/or diffusion limitation of carbon monoxide (DLCO) are measured. Confusion regarding PFTs arises from imprecise use of the term "pulmonary function tests" in clinical practice to refer to measurements of spirometry alone. It is more precise to consider PFTs to include spirometry, lung volume, and DLCO measurements.

PFTs can provide objective data regarding a patient's specific respiratory impairment and can provide important insight into the cause of the patient's respiratory symptoms. Not all respiratory symptoms are best assessed by PFTs, but several common symptoms are due to diseases that may be diagnosed by PFTs. For example, the diagnosis of COPD, which may affect between 4% and 10% of adults in the United States [1], is dependent on spirometric measurements. COPD is typically suspected based on clinical symptoms, but further evaluation by measuring spirometry confirms or excludes the actual diagnosis.

When obtaining PFTs, a trained respiratory therapist or technologist can influence the quality of data obtained; the instructions, prompts, and encouragement provided to the patient prior to and during the test significantly affect the patient's respiratory maneuvers. Normal values for PFTs are determined from predictive equations developed from large descriptive studies and incorporate an individual patient's age, gender, ethnicity, and height [2].

Spirometry

Spirometry refers to measurements of the flow and volume generated when a patient performs a forced vital capacity (FVC) exhalation; these tests are critical for assessment of airway resistance. To perform an FVC exhalation, the patient takes in as big a breath as possible to completely fill the lungs with air (to total lung capacity [TLC]) and then forcibly exhales as rapidly as possible until no more air can be emptied from the lungs (to the residual volume [RV]). In addition to measuring the FVC, determining the volume of air the patient is able to exhale in 1 s (FEV1) is important in diagnosing obstructive airway diseases. If a patient has increased airway resistance and is unable to generate high flows from TLC, the FEV1 will be reduced.

Patients may develop increased airway resistance due to airway narrowing from airway inflammation, mucous buildup, and smooth muscle hypertrophy (e.g., as a consequence of chronic asthma) or from loss of tethering of the airways leading to airway collapse during active exhalation (e.g., COPD). Increased airway resistance causes obstruction of airflow during exhalation, which results in a decreased FEV1 out of proportion to the FVC. Therefore, the ratio of the FEV1 to the FVC (FEV1/FVC) will be reduced in such patients. In patients with severe airway resistance, expiratory time is insufficient to permit exhalation of a full vital capacity and RV may be elevated. Many clinicians and authors refer to this phenomenon as "air trapping."

Obstructive airway diseases are conditions that decrease the FEV1/FVC ratio. COPD and asthma are by far the most common causes of obstructive airway disease. Bronchiectasis and sarcoidosis are much less common causes. While a reduced FEV1, FVC, and a preserved (or increased) FEV1/FVC ratio suggest a restrictive pulmonary disease, lung volumes (particularly TLC) must be measured separately for confirmation.

Lung Volume Testing

Lung volumes may be measured by one of two methods. Plethysmography refers to measuring lung volumes based on the change of pressure and volume of a known quantity of air in a closed container (a so-called body box) to calculate a patient's lung volumes via Boyle's Law. Helium dilution refers to the measurement of lung volumes based on the difference in concentration of helium on exhalation after equilibrium has been established between the patient and a known quantity and volume of helium gas in an external container. Since helium is an inert gas that does not cross the alveolar–capillary basement membrane, the concentration of helium after the gas has equilibrated between a patient's lungs and the external container of helium provides a measurement of the patient's lung volumes. Helium dilution may underestimate lung volumes in patients with poor ventilation (e.g., patients with large bullae) or patients with global hypoventilation (e.g., patients with severe COPD and gas-trapping).

A TLC measurement below 80% of predicted is consistent with restrictive disease. When TLC and functional residual capacity (the volume of gas in the lung at the end of a relaxed exhalation) are greater than the predicted value, one should consider the presence of reduced elastic recoil of the lung, most commonly seen in a patient with significant emphysema. A TLC of >120% of predicted is consistent with

hyperinflation, usually the consequence of reduced lung elastic recoil. Gas-trapping and an elevated RV will commonly be present in such patients as well.

Diffusion Limitation of Carbon Monoxide

The DLCO measures the transfer of carbon monoxide (CO) across the alveolar–capillary basement membrane. DLCO is considered a surrogate for oxygen transfer across the basement membrane and into the circulation. A patient performs the DLCO maneuver by inhaling air with a small known concentration of CO up to TLC and holding his breath for 10 s to allow sufficient time for diffusion of CO into alveoli and for transfer of CO across the alveolar–capillary basement membrane. The amount of CO transferred into the blood stream is determined by the difference in the quantity of CO in the inhaled air (which is known) minus the quantity of CO in the exhaled air (which is measured).

The severity of the reduction is expressed as the percent predicted. A DLCO between 60% and 79% of predicted is considered to be consistent with a mild reduction in DLCO, between 40% and 59% a moderate reduction, and <40% a severe reduction. The DLCO is reduced when there is destruction of the alveolar–capillary interface (reduced surface is for diffusion) or there is an increase in the distance between the alveolus and the capillary across which the gas must diffuse. Table 51.1 lists diseases associated with a decreased DLCO.

Pulse Oximetry

Assessment of oxygen saturation with a pulse oximeter is common in both the inpatient and the ambulatory environment. Normal oxygen saturation does not mean that the patient's lungs are functioning appropriately. Patients with many cardiopulmonary conditions leading to dyspnea (e.g., asthma, pulmonary embolism, pneumonia, congestive heart failure [CHF]) may hyperventilate. This can lead to normal oxygen saturation with a low $PaCO_2$ and mask the presence of severe pulmonary disease. An accurate interpretation of the oxygen saturation must include an overall assessment of the patient's status and/or an accompanying arterial blood gas.

DYSPNEA

Definition

The word *dyspnea* derives from the Greek term for difficult breathing but has come to represent a more global set of sensations that can be grouped as "respiratory discomfort." Dyspnea, or breathlessness, may be experienced by healthy individuals when exercising to the limits of their aerobic capacity, may represent primary pulmonary or cardiac disease, or may be a manifestation of a severe metabolic acidosis. In a study of more than 1000 randomly selected adults, investigators discovered the presence of dyspnea in approximately 35% of adult patients without known, underlying cardiopulmonary pathophysiology [3]. Dyspnea was associated with increased morbidity and possibly mortality as compared to patients without dyspnea [3,4].

Given the frequency with which physicians encounter patients with dyspnea, having a clear understanding of the physiology and causes of dyspnea is critical in making the correct diagnosis. A summary of common cardiopulmonary conditions and the associated pathophysiological mechanisms that cause dyspnea is outlined in Table 51.2.

TABLE 51.1
Causes of Decreased DLCO Categorized Based on Lung Volume

	Causes of Decreased DLCO
High lung volumes	Advanced COPD
	Bronchiectasis
	Cystic fibrosis
Normal lung volumes	Pulmonary vascular disease (e.g., pulmonary vasculitis or primary pulmonary hypertension)
	Early pulmonary fibrosis
	Anemia[a]
Low lung volumes	Pulmonary fibrosis
	Sarcoidosis
	Congestive heart failure
	Pneumonectomy[b]

[a] Anemia causes reduced DLCO by reducing hemoglobin-binding sites for carbon monoxide; this will occur even in the presence of normal lungs and pulmonary vasculature.

[b] DLCO corrected for alveolar volume (DLCO/VA) should be normal assuming the remaining lung tissue functions normally.

TABLE 51.2
Relationship of Possible Mechanisms of Dyspnea to Selected Conditions

Asthma	Increased sense of effort
	Stimulation of irritant receptors in airways
Neuromuscular disease	Increased sense of effort
COPD	Increased sense of effort
	Hypoxia
	Hypercapnia
	Dynamic airway compression
Pulmonary embolism	Stimulation of receptors in pulmonary vasculature or right atrium (?)
Congestive heart failure	Stimulation of J-receptors in the lung
	Stimulation of receptors in pulmonary vasculature (?)
	Hypoxia
	Stimulation of ergoreceptors (?)
Deconditioning	Stimulation of ergoreceptors (?)

Question marks indicate that the data in support of the listed mechanism are limited.

Physiology of Dyspnea

Dyspnea associated with respiratory disorders appears to arise due to a variety of physiological mechanisms that involve stimulation of receptors in the upper airways, lungs, and chest wall as well as peripheral and central chemoreceptors (Figure 51.1). In addition, there are believed to be neural discharges, termed *corollary discharges*, between the motor and sensory cortices that are activated when ventilation is consciously increased. The physiology of cardiac dyspnea is less well understood but likely involves many of these mechanisms as well as others unique to low cardiac output states.

In the presence of increased mechanical load on the respiratory system, the motor cortex must increase the neural signals it sends to the ventilatory muscles to overcome the load. These outgoing messages, or efferent signals, are associated with a simultaneous corollary discharge to the sensory cortex that is hypothesized to provide the individual with a sense of how much "effort" or "work" is being expended in the act of breathing [5]. Dyspnea associated with muscle weakness (e.g., myasthenia gravis, Guillain–Barre syndrome) is also attributable to this mechanism. Dyspnea results when the system does not respond as expected for a given level of neural drive to breathe, and the larger the discrepancy, the more intense is the dyspnea experienced. This discrepancy between respiratory center output and the mechanical response of the system has been termed *efferent–afferent* or *neuromechanical dissociation* [6,7].

Conditions resulting in a reflexive or automatic increase in the neural output from the brainstem respiratory control centers are also associated with breathing discomfort, generally described as a sense of "air hunger" or an increased "urge to breathe." Stimulation of peripheral chemoreceptors by hypoxia and hypercapnia and central chemoreceptors by hypercapnia and metabolic acidosis is thought to produce dyspnea by this mechanism. Interestingly, inducing either hypoxia or hypercapnia in healthy volunteers results in similar levels of "air hunger" for each condition, demonstrating the importance of the corollary discharge from the brainstem in creating the sensation of dyspnea [8]. Stimulation of pulmonary receptors (e.g., from asthma or pulmonary embolism) may also result in an increase in ventilation and be responsible for part of the breathlessness in these conditions.

Bronchoconstriction is associated with a sensation of chest tightness [9–11], which is believed to arise from stimulation of pulmonary receptors by the bronchoconstriction [5]. Studies of the palliative effects of inhaled furosemide demonstrate decreased dyspnea scores in subjects experiencing limited tidal volume excursion, acute hypercapnia, and resultant breathlessness [12]. The mechanism of action of inhaled furosemide likely involves stimulation of pulmonary stretch receptors, thereby creating a sensation that the lung is inflating more than it actually is, resulting in a decreased sensation of breathlessness.

Cardiac dyspnea may occur due to impaired systolic or diastolic function and resultant high left ventricular diastolic pressure. This leads to increases in pulmonary capillary wedge pressure and, in some instances, transudation of fluid into the pulmonary interstitium and alveoli. As a result, the lung becomes less compliant, increasing the mechanical load

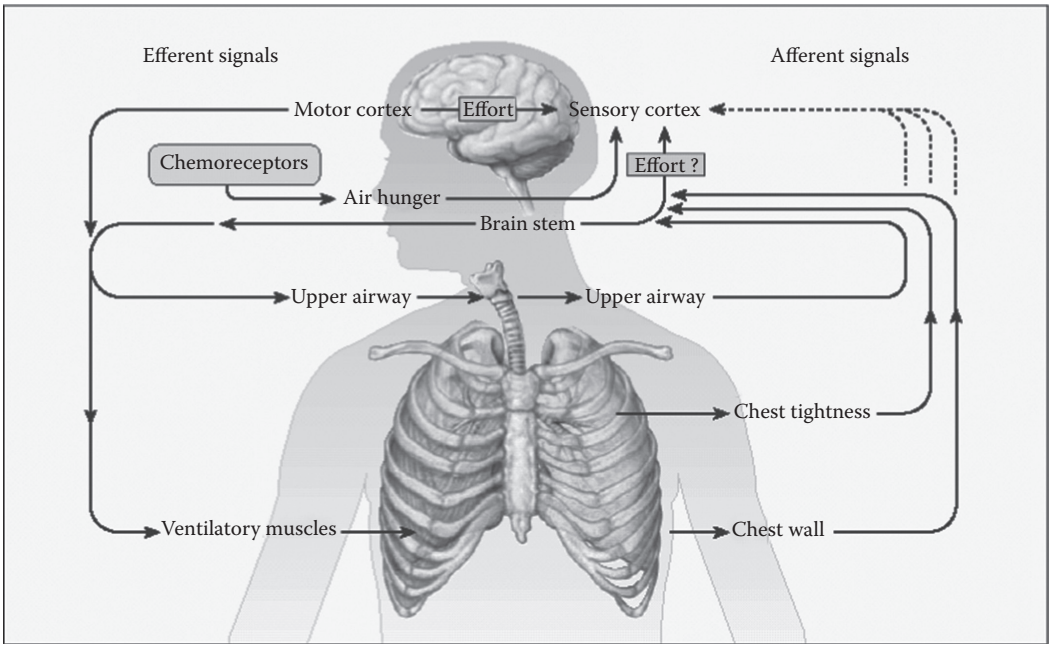


FIGURE 51.1 Physiological mechanisms producing dyspnea. Respiratory symptoms included in the term dyspnea result from stimulation of a range of receptors throughout the respiratory system as well as from corollary discharge thought to originate in the motor cortex when efferent neural discharges are sent to the ventilatory muscles. Qualitative phrases used to describe the sensations are noted based on research on and interviews with patients experiencing dyspnea. (From Manning, HL and Schwartzstein, RM, *N. Engl. J. Med.*, 333, 1547, 1995. Copyright 1995 Massachusetts Medical Society. All rights reserved.)

on the respiratory system, and hypoxia may occur. Increased pulmonary vascular pressures and stimulation of pulmonary receptors by interstitial fluid may also directly lead to respiratory discomfort. Low cardiac output states may also lead to reduced blood flow to the ventilatory muscles, resulting in muscle weakness and fatigue [13]. Furthermore, CHF appears to alter respiratory control mechanisms, leading to increased levels of ventilation compared to control subjects for any given level of exercise [14]. Stimulation of the neural drive to breathe may lead to dyspnea. Finally, there appear to be receptors (ergoreceptors) in the peripheral muscles that are sensitive to increases in the by-products of anaerobic metabolism and may contribute to the increased ventilation and breathing discomfort associated with low cardiac outputs [15].

Qualities of Dyspnea

Do patients with CHF, COPD, pulmonary embolism, and asthma all experience the same sensations of respiratory discomfort? Can we differentiate distinct types of dyspnea by the questions we ask patients? Studies demonstrate that dyspnea, like pain, is actually multiple qualitatively distinct sensations and that attention to the "language of dyspnea" can provide insights into a patient's disease.

Using a questionnaire (Table 51.3) derived from interviews with patients and studies in which normal subjects were made breathless while performing a range of ventilatory tasks [16], various cardiopulmonary conditions associated with dyspnea could be characterized by a unique set of verbal phrases [9]. These findings were confirmed in an investigation using a similar approach but with an expanded questionnaire [10]. Responses offered by patients when asked to describe their breathing discomfort have been shown to be reproducible over time [11].

TABLE 51.3
Descriptors of Dyspnea

1. My breath does not go in all the way
2. My breathing requires effort
3. I feel that I am smothering
4. I feel a hunger for more air
5. My breathing is heavy
6. I cannot take a deep breath
7. I feel out of breath
8. My chest feels tight
9. My breathing requires more work
10. I feel that I am suffocating
11. I feel that my breath stops
12. I am gasping for breath
13. My chest is constricted
14. I feel that my breathing is rapid
15. My breathing is shallow
16. I feel that I am breathing more
17. I cannot get enough air
18. My breath does not go out all the way
19. My breathing requires more concentration

TABLE 51.4
Language of Dyspnea: Association of Qualitative Descriptors and Physiological Mechanisms of Shortness of Breath

Qualitative Descriptors	Pathophysiology
Chest tightness or constriction	Bronchoconstriction, interstitial edema (asthma, myocardial ischemia)
Increased work or effort of breathing	Airway obstruction, neuromuscular disease, chest wall disease (COPD, moderate-to-severe asthma, myopathy, kyphoscoliosis)
Inability to get a deep breath	Hyperinflation (COPD, asthma)
Air hunger, need to breathe, urge to breathe	Increased drive to breathe (CHF, pulmonary embolism, moderate-to-severe airway obstruction)
Heavy breathing, rapid breathing, breathing more	Deconditioning

From these and related studies, a language of dyspnea has emerged (Table 51.4). Patients with bronchoconstriction commonly describe a sensation of "chest tightness." Increased mechanical loads (typical of airway obstruction), interstitial disease, and chest wall abnormalities usually result in increased "effort of work" of breathing. Neuromuscular weakness produces a sensation of increased effort to breathe. Significant hyperinflation, as in severe COPD, may cause a sensation of an "inability to get a deep breath" [17]. In experimental conditions, acute hypercapnia produces a discomfort characterized as "air hunger" or an increased urge to breathe [18]. Air hunger occurs in diseases associated with an increased urge to breathe (e.g., severe asthma, pulmonary embolism, acute hypoxia). Air hunger may include the sense of an inability to get a deep breath, seen with hyperinflation. Patients may express several of these sensations simultaneously, as many diseases are characterized by multiple pathophysiological derangements (e.g., asthma may result in chest tightness due to bronchoconstriction and increased effort of breathing due to hyperinflation and airway resistance).

Deconditioning, the inability to achieve maximal workloads with exertion because of reduced aerobic capacity of the heart and limb muscles, afflicts both healthy people and patients with cardiopulmonary diseases. It deserves special attention because deconditioning is a state that can be corrected with an exercise program [19,20]. Often patients with underlying cardiopulmonary diseases are assumed to be limited by their disease when they are actually deconditioned. For example, when patients with asthma were asked why they had reduced exercise capacity, they stated that it was because of their asthma. When that same group was subjected to formal exercise testing, their primary limit was cardiovascular deconditioning, not airway reactivity [19]. Patients with COPD, even those with severe airway obstruction (FEV1 < 40% predicted), are often limited

by leg fatigue rather than by poor ventilatory reserve [21]. Dyspnea associated with deconditioning has been characterized as "heavy breathing," "breathing more" [11], or "huffing and puffing."

When questioning a patient with shortness of breath, it is best to inquire about the nature of the "breathing discomfort." This phrase is generic and allows one to elicit specific qualities of a patient's distress without introducing bias toward a particular sensation. At times, it may be helpful to show patients a dyspnea questionnaire and ask them to select up to three phrases that best describe their breathing discomfort. Patients may have different sensations (and different kinds of dyspnea due to different problems) under varying conditions (e.g., a patient with interstitial lung disease and superimposed airway reactivity, or a patient with asthma who also is deconditioned). It is also important to distinguish between dyspnea due to chest wall pain and breathing discomfort, which is a primary sensation. For example, patients with a fractured rib may have severe pain with inspiration and express a sensation of "inability to get a deep breath" or "air hunger" despite the absence of pulmonary or cardiovascular pathology.

Essentials of the History

Timing: Acute versus Chronic Dyspnea

There are relatively few conditions that result in an abrupt onset of breathing discomfort (Table 51.5). These tend to be due to sudden changes in airway resistance, sudden hypoxemia, or sudden increases in pulmonary vascular pressures. With treatment, these conditions often improve as rapidly as they begin. On occasion, dyspnea may develop acutely in a patient with a chronic pulmonary disease and limited pulmonary reserve from a sudden metabolic stress (e.g., a patient with severe COPD who develops an infection with a high fever and metabolic acidosis). The need to increase ventilation in the setting of a sudden metabolic stress to meet the increased demands for oxygen consumption and/or carbon dioxide elimination may result in a combination of increased work of breathing and an increased urge to breathe.

TABLE 51.5
Acute Causes of Dyspnea

Bronchospasm
Acute asthma
Acute interstitial edema
Hypoxemia
Acute mucous plugging of airways
Pulmonary embolism
Pneumothorax
Increases in pulmonary vascular pressures
Myocardial ischemia
Pulmonary embolism
Sudden increased demand for ventilation
Acute metabolic acidosis

Chronic dyspnea tends to develop slowly over the course of weeks or months. Often, patients have difficulty pinpointing the exact onset of symptoms or attribute it to a respiratory infection despite resolution of all systemic infectious symptoms with the exception of chronic breathing discomfort. Not infrequently, the date that a patient gives up cigarette smoking is, in retrospect, consciously or unconsciously related to the onset of dyspnea. Causes of chronic dyspnea include COPD, fibrotic lung disease, pleural effusion, progressive chest wall deformities, chronic CHF, and recurrent pulmonary emboli. The chronicity of these conditions may be masked by lifestyle changes. As walking up stairs becomes progressively difficult, a patient with COPD may move to a building with elevators or to the ground floor. Children are called upon to do the shopping. Deconditioning becomes superimposed on the underlying cardiopulmonary disorder making even routine tasks uncomfortable. Patients may present complaining of seemingly new symptoms over the course of a few weeks. The reality is that the patient has a chronic condition and is only able to avoid recurring dyspnea because of avoidance of physical activity.

Timing: Night versus Day

Nocturnal dyspnea, awakening in the middle of the night with acute respiratory distress, can be an extremely frightening experience for a patient. The majority of cases are due to one or more of three problems: bronchospasm, aspiration, and CHF.

Patients with asthma may have worsening symptoms at night because of a trough in the level of bronchodilator medications, triggering of bronchospasm by gastroesophageal reflux through a reflex mediated by the vagus nerve when acid enters the esophagus, or as a result of exposure to allergens localized to the bedroom. Nocturnal sensations are usually similar to daytime asthma attacks (e.g., chest tightness and increased effort to breathe) although the precipitating factors are generally different. At times, patients may cough without discernible wheezing. The association of the symptoms with changes in the home environment (e.g., new carpeting or a new pet) may give clues to the diagnosis.

Recurrent aspiration causing nocturnal dyspnea can be an elusive diagnosis. Reports of witnessed aspiration or gagging are rare. The presence of partially digested food on a patient's pillow is infrequently reported, but if present is suggestive of regurgitation and aspiration. The diagnosis is usually suspected in a patient with a history of gastroesophageal reflux or hiatal hernia, infiltrates on chest imaging in dependent portions of the lung, and no history of asthma.

Nocturnal dyspnea characterized as a sense of air hunger or a suffocating feeling is most typical of CHF and is termed *paroxysmal nocturnal dyspnea* (PND). Clues to the diagnosis of PND include the presence of peripheral edema and relief of the respiratory discomfort shortly after assuming an upright position. Redistribution of

edema fluid to the central circulation during the night with consequent increases in pulmonary vascular pressures in a patient with compromised left ventricular function is believed to be the pathophysiological basis for this condition. Acute myocardial ischemia at night may mimic PND, but is unlikely to have a recurring pattern, may be associated with chest pain, and is less likely to be relieved by sitting upright.

One cause of dyspnea that never occurs while sleeping is hyperventilation syndrome. The primary clinical manifestation of hyperventilation syndrome is intermittent episodes of tachypnea and subjective discomfort characterized by air hunger or an urge to breathe. Despite taking large tidal volumes, patients perceive that they cannot get a deep breath. Patients with hyperventilation syndrome experience dyspnea during the day, but objective assessment reveals normal spirometry, normal DLCO, and normal chest imaging. While sleeping, these patients have normal breathing patterns and appear quite comfortable.

Position

Dyspnea that occurs with or is relieved by changes in position should prompt a consideration of abnormalities in the ventilatory pump (i.e., the muscles of ventilation and the configuration of the chest wall), focal lung abnormalities that lead to hypoxemia when blood flow is increased to that area, or redistribution of fluid into the central circulation in patients with a history of CHF.

Orthopnea is dyspnea that occurs in the recumbent position. The most common explanation is a redistribution of blood pooled in the dependent veins back into the central circulation, leading to increased pulmonary vascular pressures in the setting of compromised cardiac function. However, given the very rapid onset and resolution of orthopnea with change in position, it is probably secondary to stimulation of intracardiac (possibly the right atrium) or pulmonary vascular receptors rather than the development of interstitial edema. In very obese patients or patients with a distended abdomen due to ascites, the large abdomen reduces chest wall compliance and increases the work of breathing. The complaint that dyspnea is severe when bending over to tie one's shoes is common in these patients. Lying down, which removes gravity as a factor in pulling the abdomen away from the diaphragm, worsens dyspnea in these individuals. Patients with cervical spinal cord injury who lack active intercostal inspiratory muscles may also suffer from orthopnea.

Arteriovenous malformations (AVMs) in the pulmonary circulation lead to shunting of blood from the right to the left side of the heart (i.e., the blood never passes through the pulmonary capillaries and is sent to the systemic circulation with a low oxygen saturation). Any position that increases the gravity-dependent flow of blood through the AVM will lead to worsening hypoxemia and dyspnea. Focal areas of atelectasis or pneumonia will lead to similar gas exchange derangements when the body position is such that blood flow to that region of lung is enhanced. Consequently, the guiding principle in these circumstances is "good lung down" when positioning a patient to maximize gas exchange and minimize dyspnea.

Platypnea describes the development of tachypnea and hyperventilation when the patient is in the upright position. It is a physical finding rather than a symptom, although the patient may also complain of associated breathing discomfort. The exact mechanism of platypnea is unclear, but it probably relates to the presence of pathology at the lung bases with stimulation of pulmonary receptors or worsening gas exchange when blood flow is increased to these areas with the patient upright.

COUGH

Definition and Physiology

A cough is a sudden expiratory maneuver, associated with high intrathoracic pressures, intended to clear secretions and foreign material from the airways. An effective cough starts with a deep breath, which expands the lungs and chest wall to a point of elevated elastic recoil. This elastic recoil works in synchrony with the optimally contracting expiratory muscles to produce high intrathoracic pressures against a closed glottis. The sound of the cough is associated with the sudden opening of the glottis and the subsequent explosive release of pressurized intrathoracic gas with vibration of the vocal cords. Vibration may help to loosen secretions from the larynx.

Impaired inspiratory or expiratory muscle function leads to weakened cough. Patients with vocal cord paralysis or tracheostomy are unable to seal the glottis and cannot generate the high intrathoracic pressure needed to effectively clear secretions. Such patients are at increased risk for lower respiratory infection and may complain of increased chest congestion. The triggers for cough are complex; selected examples are reviewed in Table 51.6.

TABLE 51.6
Selected Causes of Cough Stimulation

Anatomic Location	Mechanism of Cough Stimulation
Larynx	Activation of epithelial irritant receptors
Trachea and large airways	Activation of epithelial irritant receptors
Lung parenchyma	Activation of stretch receptors Activation of C fibers
Pleural space	Activation of irritant receptors
Esophagus	Reflex mechanism in response to reflux of gastric acid
Tympanic membrane	Stimulation of irritant receptors in the external auditory canal

Clinical Causes of Cough

The most common etiologies of cough are outlined in Table 51.7. The differential diagnosis for cough varies whether a patient has an acute, subacute, or chronic cough. The differential diagnosis for chronic cough is further subdivided based on a normal versus abnormal chest x-ray.

Acute Cough

Acute cough is a cough that has been present for less than 3 weeks [22]. The most common cause of acute cough is a respiratory infection and is characterized by sputum production and may be accompanied by a "raw" substernal sensation. Chest congestion may also be present. Fever, malaise, and other systemic symptoms of a viral or bacterial infection are likely to coexist.

Subclinical bronchospasm is another cause of acute (as well as chronic) cough. In patients with mild asthma, wheezing may not be present. Sudden exposures to allergens, cold air, or exercise may result in transient cough. A high index of suspicion, along with appropriate PFTs including spirometry and possibly bronchoprovocation maneuvers, is needed to make this diagnosis.

Inhalation of toxic fumes (e.g., cleaning agents, smoke) can damage the airway epithelium and produce cough. Airway hyperreactivity may also result. As with acute infections, a raw substernal sensation is often present. Dyspnea commonly accompanies inhalational exposures. Foreign body aspiration (e.g., food particle or, in children, a small toy) may not be recalled by the patient. A cough may occur immediately after aspiration, but in some cases can be delayed for hours or days at which point airway inflammation is probably contributing to the cough. A focal wheeze is appreciated on examination of the chest in some cases, and a post-obstructive pneumonia can develop if the foreign material occludes the greater portion of the airway lumen.

TABLE 51.7
Common Clinical Causes of Cough

Acute cough
Respiratory infection, airway inflammation
Bronchospasm
Inhalational injury
Aspiration
Subacute cough
Infectious or postinfectious cough (*Bordetella pertussis*)
Sinus infection/inflammation resulting in postnasal drip
Chronic cough with clear chest x-ray
Upper airway cough syndrome (postnasal drip)
Bronchospasm
Gastroesophageal reflux
Chronic bronchitis
Bronchiectasis
Endobronchial neoplasms
Chronic cough with abnormal chest x-ray
Interstitial lung disease
Recurrent aspiration
Endobronchial neoplasm
Indolent infections (e.g., *Pneumocystis jerovici*, pneumonia, tuberculosis)

Subacute and Chronic Cough with Clear Chest X-Ray

Chronic cough is defined as a cough lasting for more than 8 weeks, while subacute cough lasts 3–8 weeks [22]. There is considerable overlap in the causes of subacute and chronic cough, and they are generally considered together in this section. However, postinfectious etiologies are an important cause of subacute, but not chronic cough. A history of recent airway or sinus infection should be sought in patients with subacute cough. Subacute cough and normal pulmonary exam may be due to sinus infection and inflammation resulting in postnasal drip. In the appropriate clinical scenario, sinus imaging and/or treatment with nasal decongestants and antibiotics for bacterial sinusitis may be warranted [23].

Paroxysms of cough resulting in post-tussive emesis or, less frequently, cough that produces a "whooping" sound, are clues to a potential diagnosis of *Bordetella pertussis* infection. For patients with cough and these symptoms, *B. pertussis* infection should be considered the diagnosis barring clinical evidence of another cause being more likely [22]. Although infants are typically vaccinated against pertussis, immunity wanes over 5–10 years. As such, adolescents and adults are at risk for developing infections from *B. pertussis* [24]. While early antibiotic treatment (macrolides are particularly effective) can reduce the severity and duration of cough due to *B. pertussis*, the efficacy of antibiotics after 2 weeks of symptoms is unclear. General consensus based on the available studies is that after 4 weeks of symptoms, it is not appropriate to provide antibiotics; rather, care should focus on symptom management [22,25].

Chronic cough without significant dyspnea and with a normal chest x-ray is commonly seen both by primary care physicians and by pulmonary specialists. This entity has been well studied [23,26], and the vast majority of patients will have one or a combination of three findings: upper airway cough syndrome (UACS), asthma, and gastroesophageal reflux disease (GERD).

UACS includes the spectrum of rhinosinosal causes of postnasal drip. From perennial rhinitis to the sequela of upper respiratory infections, UACS encompasses the breadth of diseases that result in secretions from the posterior nasopharynx descending to the larynx, causing an irritating feeling or a "tickle" in the throat. Cough due to UACS may be nonproductive or result in small amounts of white sputum. UACS due to chronic sinus infections may result in purulent sputum. Typically, the cough worsens when patients assume a supine position to go to sleep, both because of positional worsening of the nasal drainage and a greater awareness of the "irritation" in the absence of typical distractions one encounters during the day. Not uncommonly, patients will not be aware of a "drip," per se, but when questioned about the source of the cough (i.e., where the cough seems to be

originating), they will localize it to the throat rather than the chest. Frequent "throat clearing" may be a clue suggestive of UACS. Friends or family members may be more aware of frequent throat clearing than the patient. Frequent throat clearing may be observed during the interview. A history of allergies may be suggestive of UACS due to rhinitis, particularly if there is seasonal variation of the frequency or severity of the cough. However, in most cases, patients are unaware of specific allergens, and skin testing may be necessary if symptoms persist despite treatment.

Hyperactive airways without wheezing can present as chronic cough and has been termed *cough-variant asthma* [27]. In a patient without a prior history of asthma, symptoms often follow a respiratory infection. The systemic infectious symptoms will clear over several weeks, but cough persists. In many cases, the cough will resolve spontaneously in 8–12 weeks, but it can continue indefinitely. Typically, the cough will be nonproductive or result in small amounts of clear to white sputum. In contrast to cough due to UACS, patients with cough-variant asthma localize the origin of the cough to the chest. Exposure to cold air, exercise, smoke, and toxic fumes characteristically worsens cough arising from airway reactivity. Spirometry is often normal when patients are seen by their physician, and the diagnosis may be made based on response to a therapeutic trial of bronchodilators or by bronchoprovocation tests. Patients with cough-variant asthma are typically quite responsive to treatment and generally achieve symptom control more easily than patients with classic asthma symptoms [27,28].

GERD completes the triad of common causes of chronic cough. GERD may produce cough on its own or exacerbate cough in a patient with airway reactivity. Cough due to GERD is typically nonproductive and localizes to the chest. A history of heartburn or reflux symptoms is helpful but is frequently absent. In addition to asking about heartburn, one should inquire about "waterbrash," the sudden sensation of a sour taste in the mouth, which is typically associated with reflux of gastric contents. Treatment of cough due to GERD should focus on lifestyle modifications (e.g., raising the head of the bed at night, avoiding foods that dilate the lower esophageal sphincter, and avoiding eating shortly before lying down.) Proton pump inhibitors are no better than placebo in treating cough due to GERD [29].

Other less common causes of chronic cough with a normal chest x-ray include nonasthmatic eosinophilic bronchitis (NAEB), bronchiectasis, chronic bronchitis, and bronchial carcinoid. NAEB causes cough by allergic airway inflammation in response to an environmental stimulus. NAEB is not associated with airway hyperresponsiveness in response to bronchoprovocation maneuvers such as a methacholine challenge, as compared to chronic cough due to asthma. The definitive diagnosis of NAEB requires the presence of eosinophils in sputum or bronchial washings, or bronchial mucosal biopsy demonstrating increased eosinophil concentrations [30]. Given that these diagnostic modalities are not practical for most patients, empiric treatment may be appropriate when NAEB is suspected. The best treatment for NAEB is identification and avoidance of a causative environmental stimulus. When that is not possible or not effective, empiric treatment with glucocorticoids can be tried. Typically, patients with NAEB return to their premorbid baseline after treatment with glucocorticoids or avoidance of causative environmental stimuli.

Patients with bronchiectasis typically have a cough productive of purulent sputum, although upper lobe disease, which tends to drain well throughout the day, may be associated with a dry cough or scant secretions. Sputum may be occasionally streaked with blood. A history of prior pneumonia(s) is suggestive but not diagnostic. Bronchiectasis increases the risk of recurring respiratory infections associated with low-grade fever, worsening cough, and sputum production. Growth of *Pseudomonas aeruginosa* on repeated sputum cultures is very suggestive of this condition. Although the chest x-ray is often normal, focal areas of fibrosis or fibrocystic disease may be present, and chest computerized tomography (CT) scan is quite sensitive in defining the extent of disease.

Chronic bronchitis is defined as a productive cough present for ≥3 months of the year for 2 years. Chronic bronchitis is due to chronic airway inflammation induced by cigarette smoking or other environmental irritants. The cough is typically most pronounced early in the morning and tends to diminish as the day progresses. Patients localize the cough to the chest. Sputum is occasionally mixed with blood. Due to associated obstructive lung disease, these patients can have dyspnea on exertion.

Endobronchial neoplasms in central airways can produce cough and, in the absence of significant airway obstruction leading to focal atelectasis, will usually have a normal chest x-ray. Although bronchogenic carcinoma can present in this manner, bronchial adenomas or carcinoid tumors are more likely in this setting. These tumors, which usually behave as very low-grade malignancies with a small potential for distant metastases, may have a polypoid appearance that in some cases leads to a positional cough due to intermittent positional airway obstruction from the adenoma.

Chronic Cough with an Abnormal Chest X-Ray

Interstitial lung disease typically presents with the gradual onset of dyspnea on exertion, but nonproductive cough may be the prominent (or only) symptom early in the disease. Patients localize the cough to the chest. Chest x-ray findings may be subtle in early disease; later in the clinical course, chest x-ray frequently demonstrates low lung volumes and reticular interstitial changes [31]. For patients with normal chest x-rays but suspected interstitial disease, high-resolution CT scan is a very sensitive tool for confirming the diagnosis [31]. The interview should include questions about the occupational history (e.g., exposure to inorganic or organic dusts), joint symptoms or peripheral skin nodules suggesting collagen-vascular disease (e.g., rheumatoid arthritis, systemic lupus erythematosus), and eye symptoms or lower extremity joint pain suggesting sarcoidosis. Patients with symptomatic interstitial fibrosis typically have a restrictive defect on spirometry and lung volume testing.

Bronchogenic carcinomas in the central airways may cause partial or complete obstruction of a segmental or lobar bronchus leading to focal atelectasis on chest x-ray and chronic cough. The cough is typically nonproductive but may be associated with intermittent hemoptysis.

Although cough due to lower respiratory infections usually presents acutely, there are indolent infections that can present with a chronic cough and minimal systemic symptoms. Pneumocystis jerovici pneumonia in patients with acquired immunodeficiency syndrome due to human immunodeficiency virus is characterized by a nonproductive cough and dyspnea on exertion over weeks to months. Similarly, early reactivation of *Mycobacterium tuberculosis* can present with cough, fatigue, and mild weight loss. Chest x-ray usually provides evidence of the infection.

HEMOPTYSIS

Definition and Physiology

Hemoptysis refers to the coughing or expectoration of blood or blood-tinged sputum. As a general principle, the term is reserved for blood that originates in the lower respiratory tract (i.e., below the larynx). However, it may be difficult to determine whether blood is coming from the lungs versus the posterior nasopharynx or the gastrointestinal tract, especially if vomiting is associated with a paroxysm of cough. It is worth noting that the normal tracheobronchial tree should not bleed even in the presence of a coagulopathy. Thus, hemoptysis in the setting of anticoagulation should be considered as a potentially pathologic finding.

The four major sources of blood in the lower respiratory tract are airways, pulmonary parenchyma, pulmonary circulation, and bronchial circulation. Inflammation or irritation of airway epithelium (e.g., with acute pulmonary infections, chronic bronchitis, or foreign body aspiration) usually results in small-volume hemoptysis, often mixed in with sputum. Bleeding from the pulmonary parenchyma occurs with pulmonary infarction or contusion. In the presence of pulmonary AVMs or greatly elevated pulmonary vascular pressures (e.g., from mitral stenosis), bleeding may occur as well. Finally, the bronchial circulation may result in hemoptysis in patients with bronchiectasis or large intrapulmonary cavities.

Massive hemoptysis is generally defined as production of $\geq$600 mL of blood in 24 h. Patients commonly overestimate the amount of blood they have expectorated because of concomitant anxiety. Therefore, it is important to compel the patient to be as explicit as possible when quantifying the amount of blood. One should show the patient, and witnesses to the episode, various-sized containers to assist them in estimating the quantity expectorated. While massive hemoptysis can occur from an endobronchial carcinoma, it is more commonly associated with erosions of bronchial vessels in large intrapulmonary cavities or with bronchiectasis [32].

Etiology

There are six etiologic categories to be considered when evaluating a patient with hemoptysis (Table 51.8). Determining the reason for a patient's hemoptysis depends on the presence or absence of additional symptoms beyond hemoptysis itself.

Lower respiratory tract infections cause airway inflammation, which can result in bleeding. This is most common with bacterial tracheobronchitis, but can also occur with bacterial pneumonias. Typically, hemoptysis in the setting of an acute infection is small in volume (<50 mL) and resolution of hemoptysis is coincident with improvement in the other associated symptoms (e.g., cough, fever, malaise). Bronchiectasis and chronic bronchitis predispose patients to acute infections and are associated with occasional episodes of blood-streaked sputum, typically in the presence of an acute infection. Bronchiectasis infrequently leads to massive hemoptysis.

Lung cancers, most commonly bronchogenic carcinoma, are a common cause of hemoptysis. Lung cancer should be especially considered in patients over age 40 with a significant smoking history and more than 10 days of hemoptysis [33]. Patients with an extrathoracic malignancy that can metastasize to the lungs (e.g., breast carcinoma or sarcoma) are at increased risk of hemoptysis due to cancer. Bleeding due to cancer usually occurs in the absence of other symptoms and presents as frank blood without sputum.

Hemoptysis in association with joint symptoms, rashes, dyspnea, and/or renal dysfunction suggests collagen-vascular disease as an etiology. Pulmonary–renal syndromes (e.g., systemic lupus erythematosus, Wegener's granulomatosis, and Goodpasture's syndrome) may present with hemoptysis as part of the symptom complex. In most cases, hemoptysis is not an isolated finding.

AVMs, pulmonary emboli, pulmonary edema, and mitral stenosis are cardiovascular causes of hemoptysis. Pulmonary edema classically produces pink sputum, and lung biopsy reveals hemosiderin-laden macrophages consistent with pulmonary hemorrhage. Gross blood is uncommon in CHF without concomitant coagulopathy. Bleeding may occur as the first symptom of an AVM, and massive hemoptysis has been reported [34]. Hemoptysis from pulmonary emboli or mitral stenosis usually occurs with other symptoms such as dyspnea and chest discomfort.

Foreign body aspiration can lead to hemoptysis either by causing direct airway trauma or local inflammation.

TABLE 51.8
Etiologic Categories for Hemoptysis

Pulmonary infections
Neoplasms
Collagen-vascular and immunologic lung diseases
Cardiovascular diseases (including pulmonary vascular and valvular diseases)
Aspiration of foreign bodies
Chest trauma with pulmonary contusion

Pulmonary contusions result most commonly from blunt chest trauma and are associated with other trauma such as rib fractures, pneumothorax, and cardiac contusion. Hemoptysis in these settings is usually small in quantity.

WHEEZING

Definition and Physiology

Wheezing is a sound that emanates from lower airways (i.e., below the larynx), resulting from turbulent air flow. It is a "continuous" sound, as compared to the intermittent or staccato sounds that accompany chest congestion with mucus in the airways. Wheezing may occur during expiration, inspiration, or throughout the respiratory cycle. It is both a symptom, a sound that patients report hearing with breathing, and a physical finding appreciated when one examines a patient.

The sound is produced by turbulent flow through narrowed airways and in some cases may reflect the rapid oscillation of the airway walls [35]. There are multiple causes of airway narrowing (Table 51.9). Wheezing, a sound originating in the airways, should be distinguished from stridor, a primarily inspiratory sound. Stridor is qualitatively similar to wheezing, but it arises from the larynx and upper airways. During inspiration, transmural pressure across the *intrathoracic* airways favors expansion (due to negative pleural pressures). As such, inspiratory wheezing is relatively uncommon. In contrast, atmospheric pressure surrounding *extrathoracic* airways is greater than the negative pressure inside of them; consequently, the extrathoracic airways tend to collapse during inspiration. Collapse of extrathoracic airways during inspiration accentuates any preexisting airway narrowing. Thus, wheezing that worsens during inspiration is likely due to an obstruction in the extrathoracic airways (transmural pressure in the extrathoracic airway, i.e., the trachea and larynx, during inspiration favors narrowing of the airway), whereas wheezing that is more pronounced on expiration likely originates in the intrathoracic airways. When the intensity of wheezing is constant throughout the respiratory cycle, a fixed obstruction is likely.

Etiology

The most common cause of wheezing is asthma, although asthma may occur in the absence of wheeze. Historical data suggestive of asthma include wheezing associated with exposure to inhaled allergens or irritants, cold air, and exercise. Decreased wheezing in response to inhaled bronchodilators also suggests asthma. Physical examination reveals diffuse expiratory wheezing when a patient is suffering from acute asthmatic symptoms and is usually normal in the absence of symptoms. With acute symptoms, PFTs demonstrate an obstructive ventilatory defect with a decreased FEV1 and a reduced FEV1/FVC. In the absence of symptoms, between asthma exacerbations, PFTs are typically normal. Airway hyperresponsiveness can be elicited by performing bronchoprovocation maneuvers such as a methacholine challenge, which is sensitive but not specific for a diagnosis of asthma.

Mucous hypersecretion due to infections and/or airway inflammation may also cause wheezing. Since lower respiratory tract infections can also produce transient airway hyperreactivity, it may be difficult to distinguish wheezing from infection and/or inflammation from asthma. Rapid improvement of wheezing after cough or bronchopulmonary hygiene, however, is more suggestive of mucous hypersecretion than asthma.

"Cardiac asthma," wheezing in association with increased pulmonary capillary pressures and interstitial edema, is another common cause of wheezing. Generally, there is other evidence of CHF in the history (orthopnea, PND) and physical examination (distended jugular veins, S_3 gallop, peripheral edema). However, acute CHF secondary to myocardial ischemia may be difficult to distinguish from asthma in a patient with a history of airway reactivity.

Partial endobronchial obstruction can lead to focal or localized wheezing. The patient may not recognize the focal origin of the sound nor be able to localize any internal sensations associated with the wheeze. Bronchogenic neoplasms, either carcinomas or adenomas, and aspirated foreign bodies can cause focal wheezing.

Expiratory wheezing may originate from the upper airways when laryngospasm is present. Termed paradoxical vocal cord dysfunction (PVD), this condition is due to adduction of the vocal cords during expiration; expiratory wheezing originating from the upper airways can be extremely difficult to distinguish from asthma by history alone. Frequently, PVD occurs in young women, often with a history of emotional and/or psychiatric difficulties. PVD is commonly treated as asthma for months or years before the diagnosis is recognized [36]. Clues to the diagnosis are a very rapid symptom onset, an association of psychological stress with wheezing, and inconsistent bronchodilator response. Fiber-optic laryngoscopy during an attack can confirm the diagnosis by directly visualizing adduction of the vocal cords during expiration. Treatment is speech therapy and psychological counseling to assist patients in understanding the cause and nature of their symptoms and to teach techniques to develop better vocal cord control.

Vocal cord swelling from infection, allergic reaction, or chemical or smoke inhalation narrows the upper airway, increases turbulent flow, and may lead to stridor. As inhalational injuries can damage both upper and lower airways, laryngeal edema and inspiratory wheezing may be associated with intrathoracic airway hyperresponsiveness and classical expiratory wheezing. Allergic reactions causing laryngeal

TABLE 51.9
Common Causes of Wheezing

Primary airway reactivity (e.g., asthma)
Interstitial edema
Airway inflammation and mucous hypersecretion
Endobronchial obstruction (e.g., neoplasm or foreign body)
Vocal cord dysfunction

edema can be differentiated from inhalational injuries both from the history and from an association with urticaria and angioedema.

NOCTURNAL RESPIRATORY SYMPTOMS: SNORING AND APNEA

Definition and Physiology

The prevalence, clinical importance, and societal impact of nocturnal respiratory symptoms have increased markedly over the past decade. The primary cause of the increased frequency and severity of nocturnal respiratory symptoms is the marked increase in obesity in the general population. Over one billion people in the world are overweight or obese [37]. In the United States, the National Health and Nutrition Examination Surveys have demonstrated progressive increases in obesity (defined as a body mass index of $\geq 30\,kg/m^2$) since the 1960s. Even over the short period from 2000 to 2006, the prevalence of obesity in adult men has increased from 27.5% (1999–2000) to 33.3% (2005–2006) [38].

Snoring is defined as noisy breathing during sleep. The prevalence of snoring varies between studies, ranging from 10% to 60% [39]. Loud snoring is more commonly reported by men than women [40]. The prevalence of snoring increases with age up to 50–60 years of age, after which time prevalence decreases [41]. Snoring occurs due to vibration of the soft palate and faucial pillars. The likelihood that snoring will occur is dependent upon the size of the airway, the tone of the soft tissue structures in the airway, and one's body position.

The clinical significance of snoring is uncertain. Generally, in the absence of observed or measured apneic episodes, snoring is considered to be benign. However, the decrease in the prevalence of snoring that occurs with advancing age (>50–60 years of age) may indicate a survivorship phenomenon [39]. It is unknown whether snoring indicates pathologically narrowed airways causing comorbid conditions and death, or whether snoring is simply a marker of comorbid conditions that ultimately cause morbidity and death. Regardless, when a patient (or a patient's bed-partner) complains of snoring, a history of signs or symptoms of the obstructive sleep apnea (OSA) syndrome should be performed.

Nocturnal apneas are defined as a cessation of airflow during sleep. The term apnea specifically describes a cessation of airflow for ≥10 s; hypopnea is a transient reduction in airflow (a reduction in the respiratory rate and/or tidal volume) that lasts for ≥10 s and is associated with a ≥4% decrease in oxygen saturation. Frequent nocturnal apneas and hypopneas may result in hypoventilation. The diagnostic criteria for clinically significant OSA is an average of >5 apneas and/or hypopneas per hour of sleep (the "apnea–hypopnea index" [AHI]). Polysomnography (i.e., a "sleep study") must be performed to accurately measure one's AHI.

The clinical syndrome of OSA is the combination of an AHI of ≥5 with daytime symptoms due to chronic nocturnal hypoventilation. Daytime symptoms associated with the OSA syndrome include fatigue, somnolence, and morning headache. These symptoms are common even in patients without nocturnal hypoventilation, but clinical suspicion of the OSA syndrome is increased in patients with concomitant obesity, snoring, and/or comorbid conditions such as hypertension, coronary artery disease, and cerebrovascular disease. Cognitive issues (specifically difficulty concentrating), erectile dysfunction, enuresis, and depression may also be associated with the OSA syndrome, due to end-organ damage from the systemic consequences of chronic nocturnal hypoventilation and cyclical hypoxemia.

The severity of daytime somnolence can be assessed and quantified by the Epworth Sleepiness Scale (ESS) [42]. The ESS asks patients to rank their sleepiness in eight scenarios, such as "sitting quietly after a lunch without alcohol" or "in a car, while stopped for a few minutes in traffic" (see Table 51.10) [42]. Patients with a high score (≥9) have increased daytime sleepiness, but the ESS has not been validated as an independent predictor of the OSA syndrome.

There are multiple pathophysiological mechanisms in the OSA syndrome that account for the epidemiologic association between OSA and cardio- and cerebrovascular diseases (see Table 51.11). Essential hypertension occurs in at least 50% of patients with the OSA syndrome [43]. CHF, arrhythmias, coronary artery disease, myocardial infarction and

TABLE 51.10
Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

0 = would *never* doze
1 = *slight* chance of dozing
2 = *moderate* chance of dozing
3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g., a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

TABLE 51.11
Mechanisms of End-Organ Damage in the OSA Syndrome

Pathophysiological Mechanism	Systemic Effects	End-Organ Consequences
Increased sympathetic tone due to apneas/hypopneas	Increased systemic vascular resistance	Hypertension Cardiovascular disease Cerebrovascular disease
Increased systemic inflammation due to intermittent hypoxemia	Accelerated atherosclerosis	Coronary artery disease Cerebrovascular disease Peripheral vascular disease
Systemic oxidative stress due to cyclical hypoxemia and reoxygenation	Atherosclerotic changes Tissue ischemia	Cardiovascular disease Cerebrovascular disease
Endothelial dysfunction (uncertain mechanism)	Increased thrombogenesis	Coronary artery disease Cerebrovascular disease

Chronic nocturnal hypoventilation results in increased sympathetic tone during airway obstruction, which leads to increased systemic vascular resistance and hypertension. Intermittent hypoxemia results in increased systemic inflammation, which accelerates vascular atherosclerotic changes and increases the risk cerebrovascular and/or coronary artery disease [38]. Systemic oxidative stress is increased due to the nightly cycle of hypoxemia and reoxygenation [43]. Endothelial dysfunction occurs, resulting in increased thrombosis, although the mechanism is speculative.

cerebrovascular disease, including stroke, are all associated with and likely due to systemic physiological derangements caused by OSA [44].

The "obesity-hypoventilation syndrome" (OHS) is the constellation of chronic hypoventilation with chronic hypercapnia and obesity. Right ventricular dysfunction, due to elevated pulmonary arterial pressures and left heart dysfunction, is commonly present in patients with OHS.

Of note, certain cerebral pathologies, particularly abnormalities involving areas of nonvoluntary respiratory control, may result in a rare condition called central sleep apnea syndrome. Central sleep apnea is not associated with obesity, while OSA and obesity are clearly directly correlated.

Etiology

While snoring can be a normal finding, it may be associated with the OSA syndrome. As noted previously, the extrathoracic airways, including the hypopharynx, are prone to collapse during inspiration due to the combination of positive atmospheric pressure outside the airway and negative intraluminal pressure during inspiration. Snoring is more likely to occur in obese patients, as the hypopharynx is already narrowed from increased soft tissue fat. Conditions that reduce the muscle tone of the surrounding tissue (e.g., alcohol, sedative agents) further increase the risk of hypopharyngeal obstruction and snoring. Rapid eye movement sleep is associated with decreased muscle tone, and snoring occurs most commonly during this phase of sleep.

The tongue is a major component of the anterior wall of the hypopharynx, and movement of the tongue can contribute to upper airway obstruction. When the tongue falls posteriorly, obstruction is worsened. Given the lack of bony support to maintain patency of the hypopharynx, intact glossal and pharyngeal muscle tone is necessary to keep the airway from collapsing. Patients who sleep in the supine position are more likely to have snoring or more severe obstruction because of the propensity of the tongue to be pulled posteriorly by gravity.

Children with large tonsils or adenoids may present with snoring although significant airway obstruction is unusual in this clinical setting.

Essentials of the History

Snoring, unlike many symptoms, is less likely to be reported by patients than by bed-partners. It may be valuable to distinguish between nasal and mouth snoring, as nasal snoring is generally not considered indicative of a pathologic process. If possible, the physician should ascertain whether the patient has been observed to experience apneas, either central (when there is no evidence of airflow or chest wall movement) or obstructive (no airflow but preserved chest wall motion). The presence of loud snoring or loud snorts (which may occur at the end of the obstructive episode) is an indicator of intermittent airway obstructions. Additional questions are focused on the daytime symptoms of the OSA syndrome as outlined earlier.

The chronicity of snoring, changes in weight, and/or drug and alcohol use are also important components of the history. For example, a middle-aged, nonobese woman whose snoring dates back to adolescence and who has otherwise been well is likely to have a benign condition. Alternatively, a middle-aged man with a 20-lb weight gain over the last year and 6 months of snoring should be questioned about symptoms of the OSA syndrome.

Definitive diagnosis of OSA requires the presence of associated daytime symptoms and an AHI of ≥ 5. AHI can only be measured by formal polysomnography, which requires a patient to spend a night in a sleep laboratory. There is no role for PFTs or chest imaging in diagnosing OSA, although these studies may be helpful in searching for associated conditions.

SUMMARY

Respiratory symptoms are extremely common in clinical practice. As the lungs and upper airways have fairly limited ways to respond to pathologic changes, the challenge for clinicians is to understand the nuances of the descriptions of the sensations and the sounds that patients report, and to ask probing questions that elicit these subtle distinctions.

An understanding of the physiology underlying respiratory symptoms can help a physician perform a focused yet thorough history, determine what further testing is needed, and recommend targeted and effective interventions. And, perhaps equally important, having a better understanding of the physiology of respiratory symptoms augments one's intellectual enjoyment when assessing and managing patients with these symptoms.

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52 Chronic Obstructive Pulmonary Disease

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CONTENTS

Introduction 651
Definition 652
Clinical Features and Diagnosis 652
History 652
Risk Factors 652
Physical Examination 653
Imaging 653
Pulmonary Function Testing 653
Spirometry 653
Lung Volumes and Diffusing Capacity 653
Blood Testing 653
Differential Diagnosis 654
Pathophysiology 654
Staging and Prognosis 654
Management of Stable COPD 654
Smoking Cessation 654
Pharmacotherapy 655
Bronchodilators 655
Inhaled Glucocorticoids 656
Systemic Glucocorticoids 656
Mucolytics 656
Oxygen Therapy 656
Nutrition 656
Pulmonary Rehabilitation 656
Treatment of Obstructive Sleep Apnea 656
Vaccinations 656
Education 656
Advanced Treatments 657
Management of Acute Exacerbations 657
Summary 657
References 657

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide. COPD is the fourth leading cause of death in the United States, causing more than 120,000 deaths/year. It is estimated that by the year 2020, COPD will be the third leading cause of death worldwide.[1] The overall prevalence of COPD is 4%–10% worldwide and approximately 7% in the United States, which translates to approximately 16–20 million people living with the disease.[2] The high prevalence of COPD creates an economic burden on our health care system that approaches $50 billion in costs for 2010.[3] Chronic medication use, frequent emergency department and office visits, as well as frequent hospitalizations for acute exacerbations all contribute to this economic impact.

It is important to recognize the symptoms of COPD and to diagnose the disease early. With proper pharmacologic and non-pharmacologic treatment, patients can have a decrease in their symptoms, exacerbation rates, and mortality. Also, lifestyle modifications such as smoking cessation and proper diet and exercise are of paramount importance in the treatment of COPD.

This chapter will focus on the diagnosis of COPD as well as management of stable disease and acute exacerbations. More importantly, issues such as smoking cessation as well as nutrition and exercise will be discussed.

DEFINITION

The hallmark characteristic of COPD is progressive airflow limitation that is not fully reversible. The overwhelming majority of cases occur in former or current smokers, though exposure to occupational dusts, chemicals, and indoor air pollution may also contribute to the disease.[4] Traditionally, COPD was divided into the two subgroups of chronic bronchitis and emphysema. Chronic bronchitis is defined as a chronic productive cough for at least 3 months occurring in each of two successive years. Chronic bronchitis may or may not be associated with significant airflow limitation. Emphysema is defined as destruction of airspace walls distal to the terminal bronchioles, without evidence of obvious fibrosis. This is often associated with severe airflow limitation as well as hyperinflation. The most current definition by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), a comprehensive and widely accepted report by the World Health Organization and the National Heart, Lung, and Blood Institute, does not include the terms chronic bronchitis and emphysema. The GOLD definition of COPD is as follows.

COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[5]

COPD is commonly associated with risk factors such as smoking and can lead to multiple comorbidities as well as extra-pulmonary manifestations.

CLINICAL FEATURES AND DIAGNOSIS

History

COPD usually occurs in patients over the age of 40 years with a history of prior or current smoking of tobacco products. Genetic factors as well as exposure to occupational dusts (i.e., coal miners) also play a role in the development of COPD.[6] The classic symptoms of COPD are chronic cough, sputum production, and/or dyspnea. The cough may not be productive and may be intermittent. Patients will often initially complain of dyspnea on exertion that may progress to dyspnea at rest as lung function continues to decline. Any patient who presents with progressive or persistent dyspnea, chronic cough, or sputum production with a history of smoking or environmental exposures should be evaluated for COPD with spirometry. Important measurements of spirometry are the forced expiratory volume in 1 s (FEV_1) and the forced vital capacity (FVC). The characteristic findings on spirometry are a reduced FEV_1 and FEV_1/FVC ratio (see Pulmonary Function Testing section). Other symptoms may include wheezing, weight loss, muscle weakness, and fatigue. Symptoms such as morning sputum production should also increase clinical suspicion for COPD. COPD is a disease that often goes unrecognized by both the patient and his or her medical provider. These patients will often unknowingly limit their own activity and lead an increasingly sedentary lifestyle.[7] Therefore, it is important to carefully investigate subtle symptoms in patients at risk for developing COPD.

Risk Factors

The normal lung continues to grow through adolescence and peaks at approximately age 20. With further aging, lung function decreases secondary to a decrease in elastic recoil of the lung tissue, loss of respiratory muscle power, as well as a decrease in chest wall compliance. These changes lead to an average decrease in $FEV_1$of approximately 27 mL/year in men and 22 mL/year in women. Smoking and presumably other risk factors associated with developing COPD accelerate this rate of decrease in lung function. For example, heavy smoking (>20 pack years) can lead to an annual decrease in FEV_1 up to nine times that of a lifelong nonsmoker.[8] Over time, this leads to a substantial reduction in lung function that eventually leads to symptomatic disease.

The risk for developing COPD is dependent upon the interaction between both external as well as host factors. The most important modifiable risk factor is cigarette smoking. Smoking appears to be the responsible cause in up to 85% of COPD cases worldwide. In a retrospective cohort study of 8045 smokers, at least 25% will develop clinically significant COPD after 25 years.[9] Cigar and pipe smoking appear to also increase the risk of developing COPD, though not as much as cigarette smoking. Passive smoke exposure (second hand smoke) may also increase the risk of developing COPD.[10] The risk of developing COPD is also greater in individuals with first degree relatives who developed COPD.[11] This is consistent with the belief that host factors leading to an increase in susceptibility to tobacco smoke also play a role. The fact that not all smokers demonstrate a rapid decline in lung function supports that hypothesis.

There are many other possible external risk factors that can lead to the development of COPD. Both coal and gold miners are exposed to occupational dusts that can lead to clinically significant COPD in nonsmokers. The risk appears to be dose related and much higher for gold workers when compared to nonsmoking coal miners.[12] In developing countries, the use of biomass fuels (wood, crop residue, etc.) is an extremely common source of energy. It is estimated that biomass fuels are used in up to 50% of households worldwide. Exposure to biomass smoke has been linked to an increased risk of developing COPD in both smokers and nonsmokers.[13] A history of pulmonary tuberculosis also appears to increase the risk of obstructive lung disease independent of prior history of smoking or exposure to biomass fuels.[14]

Though there are many possible genetic factors that can increase the risk of developing COPD, alpha-1 antitrypsin (AAT) deficiency is the most well known and studied. AAT is serum protease inhibitor that is made in the liver and is responsible for inactivating specific enzymes such as neutrophil elastase. Neutrophil elastase, if left unchecked by AAT, can lead to destruction of lung connective tissue and eventual obstructive disease. Though a complete review of AAT deficiency is beyond the scope of this chapter, a few points should be noted regarding this deficiency. AAT is coded on a single gene but its effectiveness is determined by the expression of two independent alleles. Patients who are at the highest risk of developing

COPD are those with homozygous deficiency of both alleles (termed PiZZ) and who also smoke. Characteristics that should increase the index of suspicion for AAT deficiency are the development of COPD at a young age (<45 years old), COPD in a nonsmoker, or a patient that is found to have predominantly bilateral lower lobe emphysema on an imaging study. For a comprehensive review of the diagnosis and treatment of AAT deficiency, please see the American Thoracic Society/European Respiratory Society consensus statement.[15]

Physical Examination

The value of physical examination in aiding in the diagnosis of COPD is uncertain. For patients with early or mild COPD, examination of the chest may be normal. As lung function declines, signs of increased obstruction can become more apparent. Physical examination may demonstrate signs of hyperinflation with an increase in anteroposterior chest diameter and depression of the diaphragm. Diminished breath sounds as well as wheezing and prolonged, slow exhalation become more prominent.[16] Other common findings are distant heart sounds, accessory respiratory muscle use, and pursed lip breathing. Signs of cor pulmonale include pedal edema, enlarged liver, and distended neck veins. Severe COPD can lead to hypoxemia and cyanosis as well as asterixis from severe hypercapnia.

Imaging

Chest radiography and computed tomography studies are not required to make the diagnosis of COPD. In early COPD, chest radiographs may be normal. If there is prominent hyperinflation, a chest radiograph will demonstrate flattened hemidiaphragms, a narrow cardiac silhouette, and an increase in retrosternal airspace. Radiolucent areas corresponding with bullous disease may also be noted. Chest computed tomography, especially high resolution, has a much better sensitivity and specificity for detecting emphysematous changes compared to standard chest radiographs.[17] Though imaging studies may not be helpful in making the diagnosis of COPD, they are invaluable in ruling out alternative causes of respiratory failure, dyspnea, and cough as well as planning for possible lung volume reduction surgery (see the following section).

Pulmonary Function Testing

Pulmonary function studies are extremely important for diagnosing COPD, determining a patient's stage of disease, and for stratifying risk. Though routine screening of asymptomatic patients at risk for developing COPD is not currently recommended, all patients who exhibit symptoms of COPD with an appropriate risk factor should undergo pulmonary function testing.[18]

Spirometry

Spirometry is used to diagnose airway obstruction and to determine its severity. Airflow obstruction is determined by measuring the FEV_1 and FVC, and examining the ratio of the two (FEV_1/FVC ratio). If the FEV_1/FVC ratio is below the lower limit of normal (<0.70), then airway obstruction is present.[19] The percent predicted for the FEV_1 then determines the severity of the airway obstruction.[20] An FEV_1% predicted greater than 70% corresponds to a mild degree of airway obstruction; 60%–69% moderate; 50%–59% moderately severe; 35%–49% severe; and less than 35% very severe. Assuming alternative reasons for airway obstruction are ruled out (e.g., vocal cord dysfunction, tracheal stenosis, and asthma), a diagnosis of COPD can be made in a patient that has risk factors, symptoms, and spirometric evidence of obstruction. As FEV_1 decreases, morbidity and mortality increases. This value is often used in combination with symptoms and other physiologic factors in the staging of COPD and to guide therapy (see Staging and Prognosis section). Spirometry can sometimes be useful in distinguishing asthma from COPD. In patients with asthma, there is usually a brisk response to short-acting bronchodilators with an increase in FEV_1 and or FVC of >200 mL and 12%. Asthmatic patients will also demonstrate evidence of bronchoconstriction when exposed to a stimulus such as methacholine. COPD patients, on the other hand, often have an insignificant response to inhaled bronchodilators and are less likely to demonstrate hyperresponsiveness to methacholine. This does not hold true in all patients, however, as up to 42% of patients with COPD can be responsive to inhaled bronchodilators.[21] Differentiating asthma and COPD is discussed later in this chapter.

Lung Volumes and Diffusing Capacity

Measurement of lung volumes and the single breath carbon monoxide diffusing capacity (DLCO; diffusion limitation of carbon monoxide) are not required in making the diagnosis of COPD. However, lung volume measurements may demonstrate a decrease in inspiratory capacity and an increase in total lung capacity and residual volume, all findings consistent with airtrapping and hyperinflation. DLCO has been shown to decrease as the severity of emphysema increases. A decreased DLCO in conjunction with spirometric data may be helpful in differentiating COPD from other obstructive disease processes, such as asthma.

Blood Testing

Arterial blood gas sampling is often used to guide therapy both in stable patients (oxygen therapy) and those having an acute exacerbation. Hypoxemia is often the initial abnormality seen. Hypercapnia may develop when the FEV_1 falls below 1 L. During an acute exacerbation, the patient may develop severe hypoxemia, hypercapnia, and acidosis. Arterial blood gas measurement is often used to guide the need for mechanical ventilation and assess the response to treatment.

Brain natriuretic peptide (BNP) is a blood test that can often be helpful in distinguishing the cause of dyspnea in an acutely ill patient. BNP is a hormone that is predominantly secreted by the cardiac ventricles and is used to regulate vascular tone and extracellular volume. In patients with

congestive heart failure (CHF), BNP values are elevated. Though mild elevations can be seen in patients with COPD, these values do not approach the elevations seen in CHF.[22]

Differential Diagnosis

The major differential diagnosis for COPD includes asthma, CHF, and bronchiectasis. Infections such as tuberculosis as well as some interstitial lung diseases can also present similarly to COPD.

Asthma usually presents at a younger age (<35 years) than COPD and symptoms often vary from day to day as opposed to being slowly progressive. Airway obstruction caused by asthma is largely reversible on post bronchodilator spirometric testing. There is often a family history of asthma as well as a history of atopy. Symptoms of chronic productive cough are usually absent.[23]

Heart failure can be distinguished from COPD by physical exam and chest radiograph. Though patients with CHF can have wheezing, the most common finding is fine crackles on auscultation of the chest. Chest radiograph often demonstrates pulmonary edema, cardiomegaly, and pleural effusions. Serum BNP levels are often extremely elevated.

Bronchiectasis is a disease that is characterized by voluminous production of purulent sputum as well as dilatation and thickening of bronchial walls on chest imaging. Infectious etiologies such as tuberculosis can be diagnosed by history of exposure, symptoms, as well as abnormalities seen on chest radiography.

PATHOPHYSIOLOGY

The pathophysiology of COPD is complex and not yet fully elucidated. COPD is thought to be an inflammatory disease triggered by an external irritant such as cigarette smoking. Multiple inflammatory cells are involved including neutrophils, macrophages, lymphocytes, and fibroblasts. These cells release various proteinases and inflammatory mediators and increase mucous production. There is also an increase in oxidative stress that leads to the destruction of large and small airways as well as the lung parenchyma. These destructive changes lead to emphysema, airway obstruction, and hyperinflation as well as an increase in sputum production. Inflammatory mediators are also thought to be responsible for the systemic manifestations of COPD such as weight loss and muscle wasting.

STAGING AND PROGNOSIS

The natural history and prognosis of COPD is variable and dependent on many factors, including rate of FEV_1 decline, genetic factors, continued environmental exposure, and comorbid conditions. Most patients with the disease remain relatively asymptomatic for decades until their lung function gradually decreases to a symptomatic level. Though there are different clinical guidelines related to staging and prognosis of COPD, the two most commonly used are the GOLD staging system and the BODE index. The GOLD (http://www.goldcopd.org) system uses FEV_1 values as the major determinant of severity of COPD. This system, however, does not take into account the importance of extra pulmonary manifestations of COPD in predicting outcome. The BODE index takes into account the patient's body mass index, airway obstruction (FEV_1), as well as dyspnea and exercise capacity. A patient's dyspnea is assessed using the Medical Research Council dyspnea score (ranging from 0 when asymptomatic to 4 when breathless while dressing) and exercise capacity is assessed using 6 min walk distance.[25] The BODE index appears to be superior in predicting both mortality as well as risk of hospitalization when compared to using FEV_1 alone.[26] Other predictors of increased mortality in patients with COPD are advanced age (>70), continued cigarette smoking, HIV infection, and evidence of pulmonary emphysema on chest CTstudies.[27–29]

MANAGEMENT OF STABLE COPD

The major goals of therapy for stable COPD are to slow the progression of disease, improve quality of life, provide symptom management and relief, as well as reduce the rate of hospitalizations, acute exacerbations, and mortality. A comprehensive approach should be used when managing these patients, utilizing both pharmacologic as well as nonpharmacologic therapy.

Smoking Cessation

Cigarette smoking is the world's leading preventable cause of death and the most important modifiable risk factor for the development of COPD.[30] Abstinence from cigarette smoking can lead to a sustained decrease in the rate of lung function decline and, therefore, delay the onset or progression of respiratory symptoms in patients with COPD. Though the majority of smokers surveyed state that they want to quit, only 5%–7% of smokers remain abstinent after 1 year if their quit attempt is unaided. With optimal treatment, however, the 1 year abstinence rate can be as high as 30%.[31] Therefore, it is imperative for health care providers to identify patients who are actively using tobacco and to assist them in quitting.

The two most important barriers to smoking cessation are addiction to nicotine and the conditioning to certain triggers that patients associate with the effects of tobacco. Therefore, physician-delivered intervention should focus not only on the pharmacologic aspects of nicotine withdrawal, but also should provide intensive psychosocial counseling.

A variety of behavioral counseling techniques have been studied. These include in-person counseling, telephone counseling, group programs, computer programs, and clinician directed counseling. Virtually all of these modalities have been shown to increase the rate of successful abstinence. The cornerstones of behavioral counseling are to identify patients that are ready to quit, to pick a specific quit date, to educate on the effects of nicotine withdrawal, and to have a predetermined plan to deal with nicotine cravings. Close follow-up, whether by practitioner-mediated

telephone calls, office visits, or group meetings, is extremely important in the days following the quit date.

Pharmacotherapy is used to aid in the prevention of nicotine withdrawal. Unless medically contraindicated, all smokers should be offered some form of pharmacotherapy when they are trying to quit. The combination of behavioral counseling plus pharmacotherapy leads to much higher success rates than either modality alone.[49]

The choice of therapy will vary with each patient and a treatment plan should be tailored to the individual. Alternate treatments may be selected if a patient has a history of an underlying psychiatric illness or has failed a certain treatment in the past. The three major pharmacologic treatments are nicotine replacement therapy, bupropion, and varenicline.

Nicotine replacement therapy provides nicotine to the patient and helps relieve withdrawal symptoms. These products come in various forms such as transdermal, gum, lozenges, nasal spray, and inhalers. The nicotine patch is often selected as a first line agent as it is long acting, and compliance with the patch. The other forms of nicotine replacement are shorter acting, have a more rapid onset, and are often used in conjunction with the patch to control cravings.

Bupropion is an antidepressant that enhances noradrenergic and dopaminergic release in the central nervous system. The use of bupropion doubles the likelihood of successful smoking cessation.[32] The addition of the nicotine patch plus a nicotine inhaler, appears to increase the success rate as well.[33] Currently, the drug is used at a dosage of 150–300 mg/day for up to 12 weeks. However, it can be continued for up to 6 months to prevent relapse. Side effects are usually mild (insomnia, dry mouth, and headache). The major contraindication to the use of bupropion is that it lowers the seizure threshold and therefore should not be used in patients with an underlying seizure disorder. Along with varenicline, there is a possible association with an increase in suicidal events when using this medication even in patients with no prior history of psychiatric disease. Therefore, close follow-up after initiating therapy is necessary. Patients and families should be aware of this possibility and the patient should be instructed to discontinue the medication if there is any change in behavior or mood.

Varenicline is thought to be a partial agonist of the nicotinic receptor. Multiple studies have demonstrated the efficacy of varenicline. There is ongoing controversy as to whether varenicline is superior to bupropion and nicotine replacement therapy. As with bupropion, the most serious side effect is the increase in suicidal behavior and close monitoring after initiation of therapy is necessary.

There are currently no consensus guidelines for the form of pharmacotherapy that should be initiated first. The choice should be made depending on patient preference, co-morbid medical conditions, as well as previous experience with a medication.[34]

Pharmacotherapy

Medications are used to decrease symptoms, improve exercise capacity, and reduce the frequency of exacerbations. The most common medications used are short-acting bronchodilators, long-acting bronchodilators, and inhaled glucocorticoids. The medications are often added in a stepwise fashion to control patient symptoms and decrease exacerbations. Antidepressants are used to treat depression that is commonly associated with COPD and to assist in smoking cessation.

Bronchodilators

Bronchodilators form the cornerstone of treatment of COPD. Short- and long-acting medications most commonly prescribed are the beta adrenergic agonists and anticholinergics. All bronchodilators have been shown to decrease symptoms and increase exercise capacity. They are most commonly administered either via metered dose inhaler (MDI) or by nebulizer. The inhalation route is preferred as it maximizes the bronchodilator's effect on the airways while minimizing systemic effects. When used correctly and in equivalent doses the efficacy of the metered dose inhaler administered with a spacer device is equivalent to that of a nebulizer. All patients with COPD should be prescribed a short-acting bronchodilator to use as needed for shortness of breath.

Short-acting beta agonists like albuterol have a rapid onset of action with a duration of approximately 4–6 h. They are usually prescribed to use three to four times per day as needed. With greater doses, there is an increase in side effects such as tremor, tachycardia, and, in extreme cases, hypokalemia. They have been shown to improve symptoms as well as lung function.[35]

Short-acting anticholinergic agents (ipratropium) have also been shown to decrease symptoms and improve lung function including FEV_1, FVC, and dyspnea scores.[36] The duration of action is similar to that of albuterol. They are associated with minimal side effects such as dry mouth.

When compared to each other, both medications appear to improve symptoms and lung function to a similar degree. When combined treatment is used, the degree of bronchodilation achieved appears to be additive.[37] Beta adrenergic agonists and cholinergic antagonists each function through different mechanisms and have different side effect profiles so the combination treatment is well tolerated. Many experts recommend prescribing combination therapy because of these reasons.

Long-acting beta agonists such as salmeterol have been shown to decrease exacerbation rates, improve lung function, and improve quality of life when compared to placebo.[38] They have a longer duration of effect than the short-acting beta agonists and are therefore used twice per day. They are generally well tolerated with minimal side effects.

The long-acting anticholinergic medication tiotropium has also been shown to improve lung function as well as decrease dyspnea and exacerbations. Tiotropium is longer acting than the other anticholinergic antagonists and is therefore used only once per day. There has been some concern regarding the possible increase in adverse cardiovascular effects with its use, but there are recent data supporting the safety of its use.[39]

For patients with COPD that is not well controlled with short-acting bronchodilators, a long-acting bronchodilator

should be added. Many experts recommend the addition of tiotropium over salmeterol as it has a more convenient dosing schedule and may induce a greater improvement of lung function.

Theophylline is an oral medication from the xanthine family of drugs (similar to caffeine) that has multiple effects. It relaxes bronchial smooth muscle, increases heart rate and contractility as well as blood pressure. Due to its narrow therapeutic window and significant side effects and toxicities (including seizures, cardiac arrhythmias), it is now rarely used in the treatment of COPD.

Inhaled Glucocorticoids

Inhaled corticosteroids may reduce inflammation of the airways in COPD. Though they do not appear to affect lung function or mortality when used alone, when used in combination with a long-acting beta agonist they appear to improve lung function and decrease exacerbation rates when compared to placebo or bronchodilators alone. The combination also may decrease mortality.[38] The addition of an inhaled glucocorticoid to a long-acting beta agonist is recommended for patients that are poorly controlled or who have frequent exacerbations with a long-acting bronchodilator. For patients with advanced COPD, the combination of long-acting beta agonist, anticholinergic, and inhaled corticosteroid is often used.

Systemic Glucocorticoids

Systemic corticosteroids are frequently used for acute exacerbations of COPD (see the following). Chronic therapy with systemic corticosteroids is not recommended as there is no evidence of long-term improvement in lung function to offset the significant side effects.[40]

Mucolytics

Mucolytic agents such as acetylcysteine have not shown any benefit in the treatment of COPD. When given by inhalation, N-acetylcysteine may induce severe bronchospasm in some patients. Mucolytics are not currently recommended in the treatment of COPD.

Oxygen Therapy

Current Medicare guidelines recommend that oxygen should be prescribed for COPD patients if the arterial PaO_2 is <55 mm Hg or the arterial oxygen saturation is <88%. For patients with electrocardiogram evidence of P pulmonale, pedal edema, or erythrocytosis, oxygen is recommended if the PaO_2 is <59 mm Hg. These recommendations are based on two studies that demonstrated a mortality benefit as well as improvement in quality of life measures when oxygen was used for >15 h/day.[41–42] Oxygen is often prescribed for patients who desaturate with exercise and while sleeping. Supplemental oxygen during exertion may improve dyspnea and increase exercise tolerance, but no mortality benefit has been demonstrated.[43] There may be, however, improvements in health-related quality of life.[44]

When prescribing oxygen for a patient, the goal for arterial oxygen saturation should be approximately 90%. Patients should be instructed in the care of their oxygen devices, as well as important safety measures. Patients must be instructed to never smoke while wearing their oxygen nor should they allow others to smoke near them. They should also avoid using open flame appliances while cooking. If the patient plans on traveling by airplane, the flow of their oxygen should be increased (usually ~2 L/min), as passenger planes are not pressurized to sea level.

Nutrition

Many patients with severe COPD develop protein-calorie malnutrition. A BMI < 21 is associated with increased mortality, increased fatigue, and impaired respiratory muscle function. Unfortunately, there are currently no clinical trials that demonstrate long-term benefit of instituting dietary supplements or appetite stimulants. Patients may also complain of increasing dyspnea while they are eating. For these patients, it may be helpful if they eat more frequent, smaller meals. Nutrition or dietary consultation is often helpful in managing these patients.

Pulmonary Rehabilitation

Pulmonary rehabilitation programs have been shown to improve exercise capacity as well as improve quality of life and should therefore be considered for all patients with advanced COPD. A comprehensive review of pulmonary rehabilitation is provided in Chapter 54.

Treatment of Obstructive Sleep Apnea

Hypoxemia and hypercapnia may worsen at night in patients with severe COPD. However, it is now recognized that up to 20% of patients with COPD also have coexisting obstructive sleep apnea.[45] For patients that complain of daytime somnolence or have witnessed apneas, a full laboratory polysomnogram should be obtained.

Vaccinations

It is recommended that patients with COPD receive the pneumococcal vaccine as well as an annual influenza vaccine.

Education

One of the most important aspects of management of COPD is education and communication between the health care team and the patient. Adherence to a treatment plan improves when there is better overall communication between the patient and his or her providers.[46] Patients should be educated about their disease, the proper use of their medication, and instructed in self-management. Practitioners should address concerns regarding cost of medications, polypharmacy, and the patient's psychosocial well-being.

Advanced Treatments

There are currently many advanced bronchoscopic and surgical techniques being used to treat severe COPD. These include endobronchial valve placement, bronchial thermoplasty, lung volume reduction surgery, and lung transplant. Most of these should be provided only in the context of a well-designed clinical trial. Discussion of these treatments is beyond the scope of this chapter.

MANAGEMENT OF ACUTE EXACERBATIONS

An acute exacerbation of COPD is variably defined in the medical literature. Most consensus panels agree that it involves an acute increase in symptoms such as cough, dyspnea, or sputum production above the patient's baseline. Patients may also present with increased wheezing, tachypnea, and tachycardia. The most common precipitating factors are bacterial and viral respiratory tract infections, though up to a third of cases of acute exacerbation are from an unclear etiology.

The severity of an exacerbation can vary from mild to severe with impending respiratory failure and death. All patients should be evaluated and triaged to treatment as outpatient, acute care inpatient, or intensive care unit settings. The American Thoracic Society/European Respiratory Society proposed some criteria for hospitalization that includes changes in mental status, worsening hypoxemia or hypercapnia, high risk co-morbidities, significant increase in dyspnea, inadequate response to outpatient management, and acute respiratory acidosis.[47] Patients should be evaluated for potential alternative diagnoses such as heart failure, pulmonary embolism, and pneumonia.[48]

Treatment should focus on the precipitating cause, improvement of symptoms, and assuring adequate oxygenation. Specific therapies include supplemental oxygen to maintain a saturation of approximately 92%, short-acting bronchodilator medication, systemic corticosteroids, and antibiotics. Short-acting bronchodilators are usually given via nebulizer as it is often difficult for a patient with an acute exacerbation to coordinate the use of a metered dose inhaler. Usually, both a beta adrenergic agonist and anticholinergic are given.

The use of systemic corticosteroids has been shown to improve symptoms, reduce hospital length of stay, and reduce the rate of treatment failure.[49] The current optimal dose and duration of steroid treatment is not known. However, we agree with the current GOLD guidelines that the majority of patients can be treated with an equivalent dose of prednisone 30–40 mg/day for 7–10 days. For patients with severe exacerbations, especially those requiring an intensive care unit, this dose can be increased and is often given intravenously (methylprednisolone) until the patient is stable enough to take medication orally. Of note, concerns for possible adrenal suppression are unwarranted in patients who receive steroids for a duration of less than 3 weeks.

Antibiotics are typically given to patients with moderate to severe COPD exacerbations demonstrating increased dyspnea, sputum production, and purulence, especially those requiring mechanical ventilation. The use of antibiotics for mild COPD exacerbations is controversial; however, there does appear to be a decrease in the risk of developing a new exacerbation.

For patients who develop severe respiratory acidosis, increase work of breathing, and impending respiratory failure, the use of noninvasive positive pressure ventilation (NIPPV) should be considered prior to intubation. Numerous studies have demonstrated a decreased need for invasive mechanical ventilation and a reduction in hospital mortality.[50] NIPPV is contraindicated in patients that have facial trauma or burns, are unable to cooperate due to poor mental status, have cardiac instability such as hypotension or acute myocardial infarction, or have respiratory arrest.

Unfortunately, patients who are admitted to the hospital with an acute COPD exacerbation have an estimated 14% predicted mortality within the next 3 months.[51] Patients who are admitted with an elevated $PaCO_2$ have an even poorer prognosis.

SUMMARY

Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide and the prevalence of the disease is increasing. Early recognition, diagnosis, and treatment can lead to a decrease in hospitalizations as well as improvement in quality of life. Smoking cessation is the most important modifiable risk factor associated with this disease.

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53 Asthma

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CONTENTS

Clinical Features 659
Pathogenesis 660
Monitoring Disease Activity 661
Therapy of Asthma 662
Environmental Control 662
Pharmacologic Therapy 663
Chronic Controllers 664
Quick-Relief Medications 665
Management of Asthma according to Severity and Control Classification 665
Other Issues in Long-Term Asthma Management 668
Patient Medication Adherence and Inhaler Technique 668
Review of Comorbid Conditions 668
Asthma Complications 669
Skin Testing and Immunotherapy 669
Exercise and Asthma 670
Occupational Asthma 671
Stress 672
Food Hypersensitivity 672
Medication-Induced Asthma 672
Gastrointestinal Reflux 673
Pregnancy and Asthma 673
References 673

Asthma is an inflammatory disease of the airways characterized by intermittent symptoms, including chest congestion, cough, and wheezing. These symptoms are associated with airway responsiveness and variable airflow obstruction.

Approximately 22 million individuals in the United States have asthma [1]. Therefore, the prevalence of asthma is approximately 5%–7%. Despite the constant development of new medications to treat asthma over the last decade, there has been a rising hospitalization rate, and it remains a frequent cause of absenteeism from both school and work. Most concerning is that approximately 3500 deaths in the United States occurred in 2007 due to asthma (CDC Vital Signs, May 2011).

The prevention and treatment of disease are highly dependent upon a variety of interventions, both pharmacologic and non-pharmacologic. The daily habits and activities of patients with asthma play an important role in disease management and prevention. Minor alterations in lifestyle practices can make substantial differences in the long-term health of the asthmatic patient.

This chapter focuses on the traditional asthma topics of pathogenesis, diagnosis, and treatment. More importantly, the environmental issues important to asthma are discussed. Asthma symptom prevention and enhanced control of disease are stressed, and the effect of exercise, occupation, stress, and pregnancy on asthma is discussed.

CLINICAL FEATURES

Clinical symptoms of asthma are dyspnea, cough, chest congestion and tightness, and noticeable wheezing. Milder cases of asthma may only be recognized by a cough that is worse at night, or dyspnea during or following exertion. In more severe attacks, some or all of the symptoms have been occurring over several days before the patient seeks medical help; however, a minority of patients have a rapid onset of severe symptoms over just a few minutes or hours. Very severe attacks may lead to respiratory failure requiring tracheal intubation and mechanical ventilation.

An asthma patient may be able to identify a certain trigger that destabilizes his or her asthma. Often symptoms occur during exercise, viral infections, exposure to furry or feathered animals, or exposure to environments laden with dust, mold, smoke, or other noxious fumes or chemicals.

Changes of weather, emotions such as laughing or crying, and menses may destabilize the asthmatic patient. There are certain patients who have attacks following the ingestion of aspirin or other medications. Eczema, hay fever, rose fever, or a family history of asthma is often associated with asthma, but their presence is not required for its diagnosis.

The patient will often have a normal physical examination when asthma is not active. However, in patients who are having asthma symptoms, the physical examination often reveals an increase in respiratory rate with a prolonged expiratory time and wheezing. Wheezing becomes accentuated on forced expiration and coughing generally occurs. With more severe asthma, the use of the accessory muscles of ventilation occurs, the chest appears to be hyperinflated, and the patient may be diaphoretic and not able to speak in full sentences. These clinical features of asthma have been used to develop a clinical classification of asthma severity based on frequency of these symptoms and nighttime awakenings, interference with activities, lung function impairment, and their frequency of exacerbations (Figure 53.1) [1].

PATHOGENESIS

Airway narrowing leading to increased airway resistance and airflow obstruction occurs through three major mechanisms:

Airway smooth muscle contraction
Increased airway lumen debris
Airway wall thickens from inflammation, edema. With long-standing asthma, airway fibrosis also plays a role [1].

Damaged epithelial cells detach from the mucosal surface of asthmatic airways. Airway wall thickening occurs in patients with persistent asthma as a result of the unimpeded inflammatory process. The effects of inflammation accumulate over time, leading to smooth muscle hypertrophy, epithelial basement membrane thickening, connective tissue deposition, and proliferation and hypertrophy of mucus-producing glands. All of these factors contribute to progressive airflow obstruction, which is further compromised by the presence of thick tenacious mucus, ineffective mucociliary clearance, and edema in the walls of the bronchi, especially during an acute asthma exacerbation.

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications					
Components of severity		Classification of asthma severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 y 85% 20–39 y 80% 40–59 y 75% 60–80 y 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 >60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. → Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended step for initiating treatment (See "Stepwise Approach for Managing Asthma" for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5 and consider short course of oral systemic corticosteroids
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

FIGURE 53.1 Classification of asthma severity. (Adapted from National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, *J. Allergy Clin. Immunol*., 120, S94, 2007.)

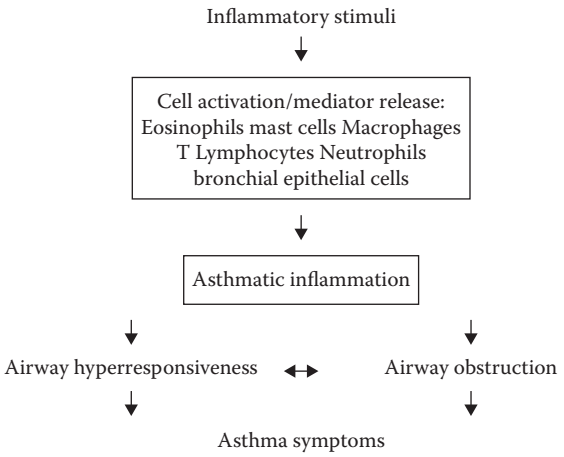


FIGURE 53.2 Steps involved in the asthmatic inflammatory cascade. These include the introduction of inflammatory stimuli to cell activation and mediator release, to asthmatic inflammation and bronchial hyperresponsiveness, and finally clinical asthma.

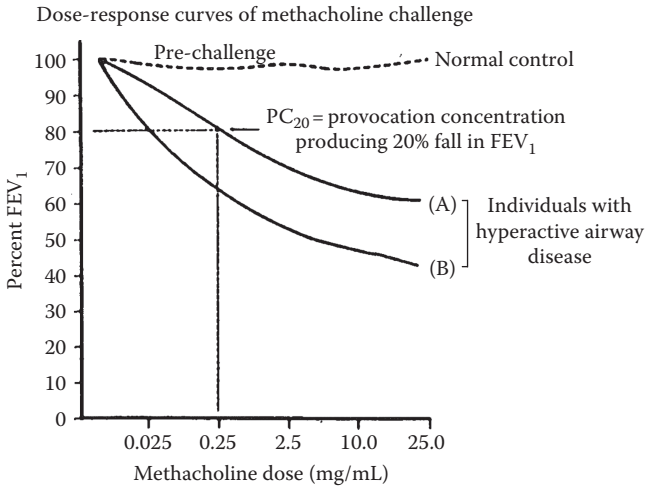


FIGURE 53.3 Asthmatics have hyperresponsive airways that are overly sensitive to immunologic or non-immunologic stimuli. Bronchial provocation testing can serve as a useful tool to measure the severity of bronchial hyperresponsiveness and is helpful to confirm the diagnosis of asthma.

Finally, episodic smooth muscle contraction further leads to the variability of symptoms in asthma.

Multiple mechanisms produce airway inflammation, and they involve a variety of interactions between pro-inflammatory and inflammatory mediators. The asthmatic inflammatory cell matrix is made up of mast cells, macrophages, eosinophils, and activated lymphocytes (Figure 53.2). Both immune and nonimmune factors can activate the disease process. When an asthmatic is exposed to a specific activating antigen, the release of a variety of mediators occurs via high-affinity immunoglobulin E (IgE) receptors, which are found on bronchial mast cells, and low-affinity IgE receptors on macrophages and eosinophils. Lymphocytes control these processes. Both antibody-mediated and cell-mediated immune systems are involved. The chemical mediators from these activated cells can directly contract airway smooth muscle, stimulate mucus secretion, enhance vascular permeability, and result in airway edema, all of which contribute to airflow obstruction. Furthermore, some mediators actually attract other inflammatory cells and activate them, and these activated cells further damage the airway. Part of the inflammatory reaction causes a disruption of airway epithelial cell wall integrity, which allows increased permeability to inhaled allergens and other triggering substances and decreases mucociliary clearance of airway debris, enhances cholinergic-mediated airway hyperreactivity, and predisposes asthma patients to bacterial and viral infections.

Inflammation can be acute or chronic. The acute inflammatory response involves early recruitment of cells to the airway. This is followed by an evolving inflammatory reaction, as recruited and resident cells are activated and produce a complex pattern of inflammation. Chronic inflammation can lead to permanent airway damage.

Airway hyperresponsiveness is a hallmark of asthma. Airway inflammation induces hyperresponsiveness (Figure 53.2). This hyperresponsiveness, along with the inflammatory changes of the airways, contributes further to airflow obstruction. Certain triggers may not only activate but also propagate inflammation and drive airway responsiveness to a more severe state. The magnitude of airway hyperresponsiveness seems to correlate with the activity of airway inflammation. Furthermore, airway hyperresponsiveness seems to correlate with the clinical symptoms and signs of asthma.

Hyperresponsiveness is assessed by measuring airflow before and after the inhalation of increasing doses of inhaled methacholine or histamine (Figure 53.3) [2]. Hyperresponsive airways will develop obstruction at lower cumulative doses of these chemicals than normal airways. This increased "twitchiness" of the airways is thought to protect the lungs from the detrimental effects of irritating inhalants. Airway hyperresponsiveness is not unique to asthma. Hyperresponsive airways are found in other airway inflammatory diseases, like chronic bronchitis and sarcoidosis. The treatment of asthma does diminish, but may not eradicate airway responsiveness, suggesting that additional factors are involved.

Monitoring Disease Activity

The goals of asthma therapy are as follows: (1) prevent symptoms and help the patient achieve normal lung function and activity, especially during exercise; (2) prevent exacerbation of asthma, no matter how mild; (3) minimize the need for emergency department visits or hospitalizations; (4) meet patient and family expectations for asthma care; and (5) provide optimal pharmacotherapy with minimal adversity [1].

In order to ensure that these goals are met, periodic assessment and ongoing monitoring of asthma are recommended [1]. If the patient has minimal signs and symptoms, with optimal airflow during exertion and sleep, then overall patient-perceived quality of life improves. Physician assessment and patient self-assessment are part of the asthma monitoring process.

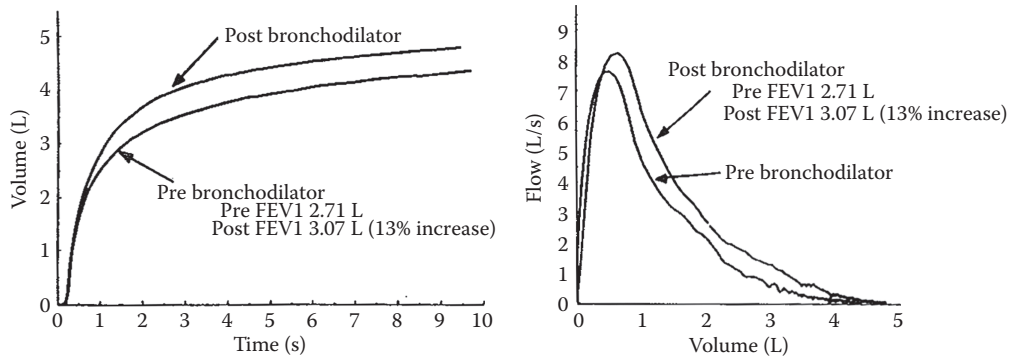


FIGURE 53.4 Spirometry pre/post-bronchodilator in the asthmatic. Administration of an inhaled bronchodilator improves airflow significantly. The left panel depicts the volume–time curve and shows improvement in FEV_1. The right panel shows the flow–volume curve and improvement in PEFR over exhaled lung volume. The dependent portion of the curve is also curvilinear (not straight) consistent with airflow obstruction. (From National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 2, Guidelines for the diagnosis and management of asthma, Full Report 1997.)

Spirometry is recommended at the time of initial assessment, during treatment, and when changes in symptoms or home monitoring of peak expiratory flow (PEFR) have occurred [1,3]. A spirometer is a simple device used to measure certain lung volumes and airflows [4,5]. The patient takes a deep breath and forcefully exhales air from the lungs until all airflow has ceased (Figure 53.4). Airflow obstruction is shown by a decrease in the forced expiratory volumes, the forced vital capacity (FVC), and the forced expiratory volume in 1 s (FEV1) and a decreased FEV1/FVC ratio. The FEV1 is the most important airflow measurement, and usually the asthmatic has a reduction in the FEV1. These measurements are generally taken before and after a bronchodilator. The asthmatic typically shows significant improvement in these airflows following a beta-2 agonist treatment, indicating reversible airways disease. This is determined by an increase in either FVC or FEV1 by 12% or more with a minimum absolute change of 200 mL pre/post-bronchodilator. The asthmatic can also measure airflow at home on a daily basis, using a handheld device made of durable plastic to measure PEFR rates.

The airflow obstruction of asthma waxes and wanes with variations in the degree of inflammation and smooth muscle constriction. With these changes, there are alterations in FEV1 and PEFR (Figure 53.4). There are variable needs for the use of medication to relieve symptoms. As the asthmatic becomes better controlled with therapeutic interventions, overall airflow improves, variability in airflow decreases, and the need for short-acting beta-2 agonist medication to relieve symptoms substantially decreases. As all of these factors change, overall quality of life improves. This translates into better sleep at night and improved resistance to asthma exacerbation during exposure to environmental challenges. It is important to teach patients to recognize symptom patterns that indicate inadequate asthma control. The NAEPP 2007 Guidelines recommend a written asthma action plan for all asthmatics based on signs and symptoms, changes in PEFR, or both. Written asthma action plans may be particularly helpful for those with poorly controlled asthma, moderate or persistent asthma, or a history of severe exacerbations. The more chronic and severe the asthma, the greater is the importance of a written asthma action plan.

THERAPY OF ASTHMA

Environmental Control

Environmental control measures, such as allergen avoidance, should always be included in asthma management strategies [1]. A comprehensive approach to control of allergen or irritant exposure is needed since single measures for avoidance of allergens is not effective. Exposure of asthma patients to certain irritants or allergens increases asthma symptoms and often precipitates exacerbations. As a team, the physician and the patient should do everything possible to identify those allergens and irritants causing asthma symptoms. The common inhalant allergens that are known to cause asthma exacerbations are animal allergens; house dust mites; cockroaches; indoor and outdoor fungi; and outdoor plant allergens such as tree, grass, and weed pollens. The NAEPP guidelines 2007 have a questionnaire to help determine environmental factors and other factors that worsen asthma symptoms [1,6]. A history of likely sensitivity to seasonal allergens from the questionnaire and positive skin testing or in vitro IgE blood testing to assess the sensitivity to perennial allergens can be helpful in identifying these sensitivities [6]. Generally, seasonal allergens in early spring are trees; late spring, grasses; late summer to autumn, weeds; summer and fall, Alternaria, Cladosporium, mites; and cold months in temperate climates, animal dander [1]. Allergy skin or blood testing is the only way to determine sensitivity accurately to year-round indoor allergens.

Certain environmental exposure rules should be followed. If an asthmatic knows what irritants or allergens destabilize his or her disease, everything should be done to avoid these exposures. Exposure to tobacco smoke should be avoided [7,8]. Asthmatic patients should avoid beta-blocker therapies: if possible [9,10] or foods that contain sulfites [11], preservatives that often exacerbate the asthmatic condition. Aspirin and other nonsteroidal anti-inflammatory agents should be avoided [12,13], especially in patients who have nasal polyps.

Finally, rhinosinusitis [14] and gastroesophageal (GE) reflux [15], which have been implicated as asthma destabilizers, should be controlled.

The most important step in controlling allergen-induced asthma is to reduce exposure to relevant indoor and outdoor allergens. Major indoor allergens are animal dander, dust mites, mold, and cockroaches. All warm-blooded pets can cause allergic reactions. If there are pets in the patient's home and the patient is sensitive to that animal, then the most effective measure is to remove the animal from the house [1]. At a minimum, the animal should be kept out of the patient's bedroom by keeping the bedroom door closed and remove any carpets and cloth-covered furniture from the home. It should be kept clean [16], and all air ducts that lead into the bedroom should be covered with a filter.

House dust mite allergen is a major environmental factor in asthma [1]. House dust mites are universal in areas of high humidity, which includes most of the United States. In addition to high humidity, mites depend upon human dander for survival. Dust mites thrive in mattresses, pillows, carpets, upholstered furniture, and soft toys. In patients who are house dust mite sensitive and demonstrate a clinical picture consistent with allergy to the mite allergens, there are a variety of desirable control measures that should be considered [17]. Mattresses and pillows should be encased in an allergen-impermeable cover. The sheets and blankets on the patient's bed should be washed weekly in hot water, which must be >130°F to kill mites. Indoor humidity should be maintained at less than 50%, and carpets, upholstered furniture, and stuffed animals should be removed from the area. Although there are a variety of chemical agents available for killing mites and denaturing the antigens, they are not as effective as the measures described earlier.

Molds are fungi, which proliferate in humid environments, especially homes that have dampness problems. Creating a drier environment by fixing old water leaks and eliminating water sources reduces mold growth. Reducing indoor humidity to less than 50% substantially limits mold growth.

If cockroach infestation is present in the home, it is very important to institute chemical control measures to reduce this antigen load [1]. Asthma severity seems to increase with increasing levels of cockroach antigen. Food should be kept out of bedrooms and food and garbage should be kept in closed containers. When chemical agents are used to control infestation, the home should be well ventilated and the patient should not return to the home until the odor has substantially dissipated.

A variety of measures can be taken to reduce allergen in the home by modifying indoor air. Vacuuming carpets twice a week, preferably with a cleaner loaded with a high-efficiency particulate air filter, can reduce house dust accumulation, but the patient should not be in the room when the vacuuming is occurring. Air conditioning and the use of a dehumidifier are helpful. Humidifiers and evaporative coolers are not recommended for use around dust mite-sensitive patients with asthma. Indoor air cleaning devices should not substitute for the measures previously described. High-particulate air filters and electrostatic precipitating filters have been shown to reduce certain animal dander, mold spores, and the particulate from tobacco smoke. However, these devices do not have an impact on house dust mite and cockroach allergens, which are heavy particulates and do not remain airborne, and thus are not effected by air filtering.

A variety of tree, grass, and weed pollens and seasonal spores contribute to the outdoor allergen loads that affect many asthmatic patients. By staying indoors with windows closed, generally in an air-conditioned environment, patients with outdoor allergen problems can be relatively protected. Pollen and spore counts are highest during the midday and afternoon, at periods of brightest sunlight. For the asthmatic who has a significant outdoor allergen problem, conducting outdoor activity shortly after sunrise or before sunset can result in a reduced pollen exposure.

Allergen immunotherapy can be helpful in certain asthmatic patients [1,18,19]. According to the NAEPP Expert Panel Report 3, subcutaneous immunotherapy should be considered for patients that have allergies and have mild-to-moderate persistent asthma (steps 2–4) [1]. However, it is preferable to have clear evidence of a relationship between asthma symptoms and exposure to the allergen in question. Finally, symptoms should be nearly perennial and difficult to control with pharmacotherapy alone. The whole concept of allergen immunotherapy is under constant debate, in terms of long-term benefit. If allergen immunotherapy is started, it should be given under the careful guidance of a well-trained physician immunotherapist who is capable of treating any life-threatening reaction that may occur [20]. The immunotherapy should be directed at a single or only a very few antigens. There is a paucity of data support for use of multiple-allergen mixes. Finally, the course of allergen therapy is typically 3–5 years in duration, but a recognizable favorable improvement in asthma should occur early in treatment.

Pharmacologic Therapy

The pharmacologic treatment of asthma includes two broad categories of drugs: bronchodilators that relax airway smooth and anti-inflammatory drugs that reduce the influx of inflammatory cells and the release and/or effects of a large variety of chemical mediators from these cells.

Bronchodilators include short- and long-acting beta-2 receptor agonists (beta agonists), methylxanthines, and anticholinergics. Anti-inflammatory agents include glucocorticoids, cromones (cromolyn and nedocromil), omalizumab, and leukotriene blockers.

In the chronic management of asthma, pharmacologic therapy is given by the oral or inhalation route, but inhalation therapy seems to be preferred because of the higher concentration of medication directly delivered to the lungs, often with greater efficacy and lower risk of adverse effects [21]. The inhalation of medication can be performed through a small-volume nebulizer or a metered-dose inhaler. An inhaler is sometimes attached to a tube spacer device, in order to

TABLE 53.1
Controller and Quick-Relief Therapies for Asthma

Controllers	Quick Relief
Inhaled corticosteroids	Short-acting beta-2 agonists
Cromolyn	Systemic corticosteroids
Nedocromil	Ipratropium bromide
Leukotriene modifiers	
Long-acting bronchodilators	
Systemic corticosteroids	
Omalizumab	

reduce certain oropharyngeal adverse effects and, for some patients, enhance aerosol drug delivery into the lungs.

Medications are characterized into two general treatment classes: long-term controller medications, which are used to achieve and maintain control of chronic asthma, and quick-relief medications, or relievers, which treat acute symptoms during an asthma exacerbation (Table 53.1) [1]. The most effective medications for long-term controller therapy are those that have clearly demonstrated anti-inflammatory effects.

Chronic Controllers

Corticosteroids are the most potent and effective anti-inflammatory medications available for the management of asthma. The inhaled form of medication from a metered-dose inhaler, often attached to a spacer device, is used for the long-term control of asthma. Systemic corticosteroids administered orally are used to gain control of asthma following a period of destabilization and are avoided for long-term control. However, some patients with severe chronic disease may require systemic corticosteroid therapy on a regular basis. Corticosteroids reduce airway inflammation and airway hyperresponsiveness. Glucocorticoids also prevent asthma exacerbations and bronchial wall remodeling, which is known to occur with chronic inflammation and is responsible for the development of fixed airflow obstruction later in life [22–25].

There are many different products and delivery devices for the administration of inhaled corticosteroids, and their per-inhalation doses vary [1]. The lowest daily dose of an inhaled corticosteroid should be used in order to control disease.

Cromolyn and nedocromil sodium are nonsteroidal, anti-inflammatory inhaled medications used in the chronic management of mild and moderate asthma. The mechanisms of action of these medications are not fully understood [1]. These medications prevent bronchospasm caused by an inhaled allergen and have been shown to decrease nonspecific bronchial hyperreactivity, decrease asthma symptoms, and improve airflow obstruction [23,26]. These therapies are used as initial long-term controller medication for children and adolescents, but their response is less predictable than that of inhaled corticosteroid therapy.

Another group of anti-inflammatory agents is the leukotriene receptor blockers and synthesis inhibitors. These are oral therapies that block or inhibit the production of leukotrienes, which are by-products of the arachidonic acid-metabolic pathways and are potent bronchoconstrictors and inflammatory stimulants in humans [23]. Leukotrienes are released from a variety of inflammatory cells, such as lymphocytes, eosinophils, and mast cells, and not only induce bronchoconstriction but increase vascular permeability, mucous secretion, and other inflammatory cells. When these additional cells enter the airway, they are activated and release other powerful chemicals that propagate the inflammatory state even further [23]. There are three agents currently being used in the United States and include zafirlukast and montelukast, which are leukotriene receptor blockers and zileuton, a 5-lipoxygenase inhibitor. Zileuton acts earlier in the arachidonic acid/leukotriene pathway and potentially could have greater effects. Zileuton is taken twice a day and requires liver function monitoring. Leukotriene-pathway agents improve lung function, diminish asthma symptoms, and reduce the need for the rescue use of short-acting inhaled beta agonists [24,25,27]. Their efficacy has been shown in patients with mild-to-moderate asthma, and the improvements seen are modest when compared to inhaled corticosteroid therapy [28] but some studies show no difference [29]. These agents have also been shown to reduce bronchoconstriction caused by exercise [30], aspirin [31,32], and inhaled allergen exposure [33,34].

Omalizumab is a subcutaneously injected recombinant humanized monoclonal IgG antibody that binds to IgE antibody that has been used for the treatment of patients with moderate to severe persistent allergic asthma [35–38]. Other controller medications do not inhibit IgE production. Recommendations from the NAEPP 2007 guidelines consider it for allergen-associated severe persistent asthmatics (age 12 years or older), in steps 5 (inadequately controlled on high-dose inhaled corticosteroids and LABAs) or 6 (requiring oral corticosteroids on a daily or alternate-day basis) [1]. Omalizumab prevents IgE binding to high-affinity receptors on mast cells, basophils, and other cells and leads to decreased mediator release from these cells [1]. Patients on omalizumab have been able to reduce the dose of their inhaled steroids and frequency of exacerbations [39–43] including those requiring hospitalization [35,44–46]. However, in patients already on therapy for asthma, omalizumab does not improve spirometry, that is, FEV1 [36,44]. There is also little to no effect on bronchial hyperresponsiveness [47], but it does decrease some airway inflammatory markers [40,41,47,48].

Omalizumab is an expensive medication even in the lowest doses, determined by both body weight and IgE levels, and may require once or twice a month injections. Treatment will also affect the accuracy of most allergen-specific assays. The drug is not recommended for use in pregnant women. In rare circumstances, it has been used in occupational asthma with beneficial effects [49,50]. It can have adverse effects including anaphylaxis [51], local reactions such as

injection-site reactions, and others [51]. Anaphylaxis associated with omalizumab has been reported as any combination of bronchospasm, angioedema of throat or tongue, hypotension, syncope, and/or urticaria [51]. Anaphylaxis may occur at a rate of less than 1 in 500 patients [51]. Most patients (61%) who develop anaphylaxis will develop it within the first three injections [52] and within 2 h after a dose, but some patients may not develop symptoms for more than 12 h after a dose [51]. Overall, 75% of the reactions would be seen if monitored for a period of 2 h for the first three doses and 30 min for subsequent omalizumab injections. In our experience, anaphylaxis has been less common than reported. The Omalizumab Joint Task Force Report on omalizumab-associated anaphylaxis in 2007 has made safety and management recommendations for patients being prescribed omalizumab. Those recommendations are summarized elsewhere [52].

Theophylline, a methylxanthine compound, acts as a modest bronchodilator and may also improve asthma through certain anti-inflammatory effects and reductions in bronchial reactivity [53,54]. When theophylline is administered in a sustained-release oral therapy form, it has a long duration of action and can further control asthma when used in combination with inhaled corticosteroid therapy [55,56]. Theophylline should be considered as an alternative controller therapy to that of inhaled corticosteroids [1]. Theophylline's narrow therapeutic margin of safety, multiple medication interactions, and weak bronchodilating effect have placed it as a third-line controller therapy for chronic asthma. It is often used in patients with moderate to severe asthma after inhaled corticosteroid therapy has been optimized and a second-line controller therapy, such as a leukotriene blocker or an inhaled long-acting beta agonist, has been employed. Some patients may adhere better to an oral regimen than an inhaler-administered regimen. For each patient, the dose must be titrated to optimize efficacy and minimize the potential for drug toxicity. The target level for theophylline is recommended to be approximately 5–15 mg/L [1,57,58]. It is well known that the theophylline level may be affected by a number of factors. These include conditions that decrease the level (e.g., smoking), conditions that increase the level (e.g., heart failure, cor pulmonale, cirrhosis, hypoxia, hypothyroidism, fever, pregnancy), and drugs that increase or inhibit metabolism. Theophylline itself decreases the effect of certain sedative benzodiazepines such as lorazepam and midazolam and levels of certain antidepressants such as lithium. Seizure medications such as carbamazepine, phenytoin, and phenobarbital can also affect theophylline levels. After the patient is on a stable dose of theophylline, drug levels should be checked at least once a year as long as the patient remains stable and has no changes in health or other medications. It has also been used as additional therapy in the ICU for a patient not responding to conventional therapy for status asthmaticus.

Sustained-release oral beta-agonist tablets and a long-acting inhaled beta agonist may be used as controller therapy in addition to anti-inflammatory therapy. Patients with moderate and severe asthma generally require at least two or three controller medications to optimize their pharmacologic therapy [1]. Inhaled beta agonists that are more selective for the beta-2 receptor are preferred. Long-acting beta-agonist inhalers and tablets can have a duration of action at least of 12 h, far longer than that of the short-acting beta agonists that are needed by inhalation for the acute control of symptoms [59].

Quick-Relief Medications

In order to achieve immediate relief of bronchoconstriction and the discomforting symptoms associated with asthma, quick-relief medications such as fast-onset short-acting beta-2 agonists and anticholinergics are used. Short-acting beta-2 agonists relax airway smooth muscle within minutes and improve airflow. These agents are the drugs of choice for treating asthma exacerbations [1]. They are also used for preventing exercise-induced bronchospasm [1]. Inhaled anticholinergic therapy, such as ipratropium bromide, can also be used as a bronchodilator in this setting, but a beta agonist should be used first. Ipratropium bromide may provide some additional benefit during a moderate to severe asthma exacerbation and may also be considered as an alternative for those who absolutely cannot tolerate beta agonists [1].

Systemic corticosteroid therapy can speed the resolution of airflow obstruction and reduce the rate of relapse of severe asthma [1]. Therefore, systemic corticosteroid therapy is used in more serious asthma exacerbations, as part of the quick-relief medical plan.

Because short-acting beta-2-agonist therapies like albuterol should only be used for the symptomatic relief of asthma, the use of this medication can also serve as a marker of asthma stability. The more albuterol necessary to control symptoms, the greater the airway inflammation that is present and the stronger is the need for optimization of inhaled anti-inflammatory therapy. Using a short-acting beta-2-agonist inhaler at the rate of one or more canisters per month has been associated with an increase in asthma morbidity and mortality [60]. The majority of chronic asthma patients in this country should be able to be controlled to a level of mild episodic asthma. Mild episodic asthmatics have two or less mild asthmatic attacks a week. Therefore, if more than four puffs of a short-acting beta agonist are used weekly, then enhanced asthma control is necessary. A well-controlled asthmatic should only need one or two canisters of a short-acting beta-2 agonist per year, not counting the therapy that would be used to prevent exercise-induced bronchospasm. This should be the case for 70%–80% of asthmatics.

MANAGEMENT OF ASTHMA ACCORDING TO SEVERITY AND CONTROL CLASSIFICATION

A stepwise approach has been proposed for the pharmacologic therapy of asthma [1] (Figure 53.5). The amount and frequency of medication is dictated by asthma severity in those patients not currently on medication (Figures 53.1 and 53.5).

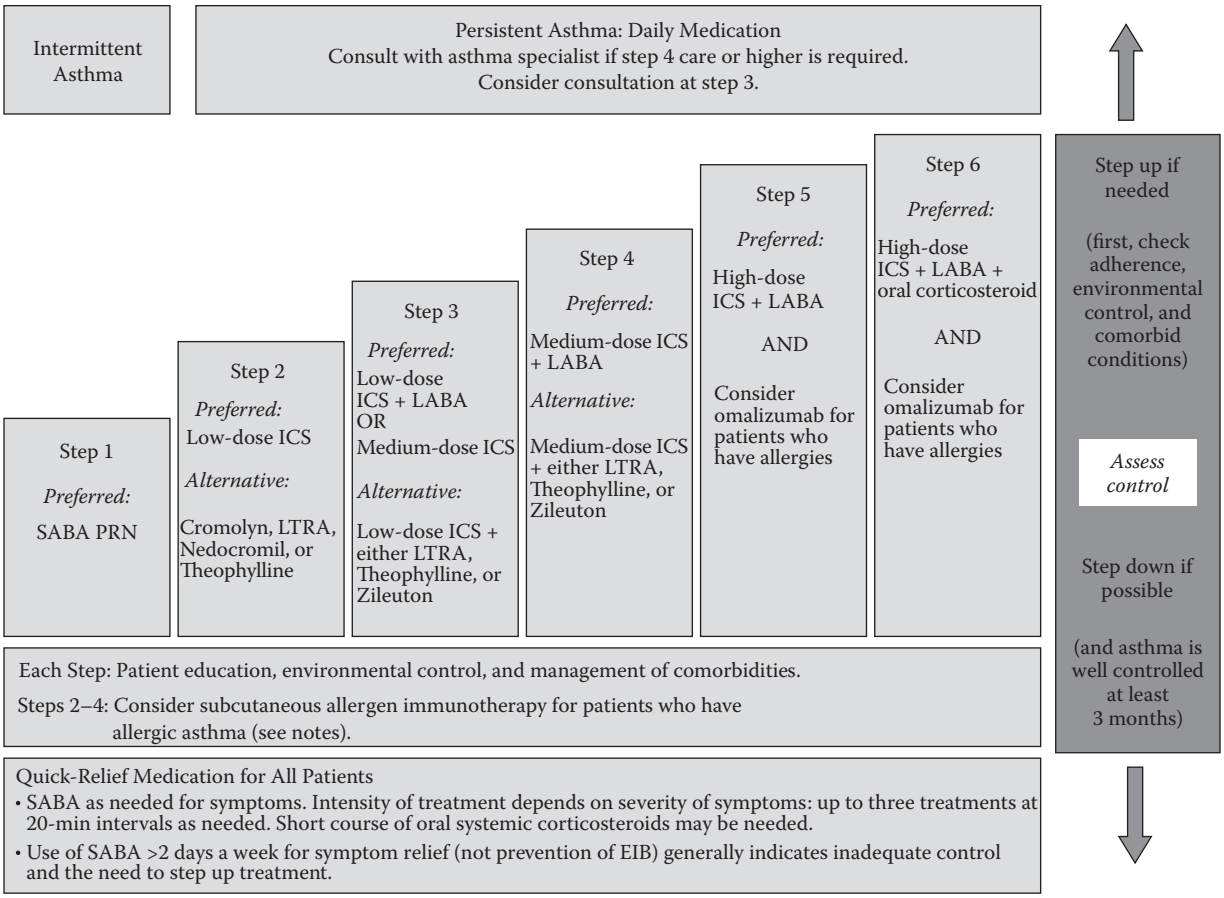


FIGURE 53.5 Stepwise approach for managing asthma. (From National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, *J. Allergy Clin. Immunol*., 120, S94, 2007.)

The level of severity is determined by assessment of both impairment and risk components [1]. According to the Expert Panel 3, the level of severity is based on the most severe impairment or risk category. The components of impairment include symptom frequency, medication use (short-acting beta agonist), and lung function measurement by spirometry. The risk assessment includes frequency of exacerbations of asthma requiring systemic corticosteroids over the last year. However, there is not enough information to correlate the frequency (specific number of exacerbations) and severity of exacerbations with the various step classification levels of asthma severity. The guidelines suggest that patients with a risk component of two or more exacerbations per year would be considered as having persistent asthma despite impairment levels that would not indicate this degree of severity. Once the severity level is assessed, the suggested step level of therapy can be determined (Figure 53.5). Therapy is directed toward treating airway inflammation. Therefore, controller therapies are emphasized, with anti-inflammatory therapy considered the mainstay. Controller therapies are often initiated at a higher level than the patient's step of severity at the onset in order to gain immediate control of disease.

Patients should be evaluated within at least 2–6 weeks after starting therapy. Once the patient returns for follow-up appointment or for a patient already on long-term controller therapy, the asthma control is assessed to adjust the current therapy (Figure 53.6). Determination or measurement of asthma control is based on impairment and risk components [1]. According to the NAEPP guidelines Expert Panel Report 3, the level of control is based on the most severe impairment or risk category. The components of impairment include symptom frequency, medication use (short-acting beta agonist), and lung function measurement by either FEV1 or peak flow. The impairment component is based on the last 2–4 weeks. If a longer period is being evaluated, it is recommended to use an overall assessment by the patient as to whether their asthma is better or worse. There are also validated questionnaires that can be used to assess impairment, but these do not assess the lung function component or even risk category. The three validated questionnaires include the Asthma Therapy Assessment Questionnaire, the Asthma Control Questionnaire, and the Asthma Control Test (ACT). The ACT can be administered quickly, and the score is based on the answers to five questions assessing symptoms, interference with activities, and beta-agonist use over the past 4 weeks [61]. Based on these parameters, asthma control is determined to be well controlled, not well controlled, or very poorly controlled.

After control has been achieved, then therapy is reduced or stepped down. Step-down therapy (Figure 53.5) is essential if

Components of control		Classification of asthma control (≥12 years of age)		
		Well Controlled	Not well controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60-80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires			
	ATAQ	0	1–2	3–4
	ACQ	≤0.75*	≥1.5	N/A
	ACT	≥20	16–19	≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see notes)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term follow-up care.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended action for treatment (See "Stepwise Approach for Managing Asthma" for treatment steps.)		• Maintain current step. • Regular follow-up at every 1–6 months to maintain control. • Consider step down if well controlled for at least 3 months.	• Step up 1 step. • Re-evaluate in 2–6 weeks. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids. • Step up 1–2 steps. • Re-evaluate in 2 weeks. • For side effects, consider alternative treatment options.

FIGURE 53.6 Classification of asthma control. (From National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, *J. Allergy Clin. Immunol*., 120, S94, 2007.)

one is to identity the minimum medication necessary to maintain disease control. During this process, it is helpful that airflow is monitored and correlated with asthma symptoms and signs and the intermittent use of inhaled short-acting beta-2 agonist. Patients may relapse if inhaled corticosteroids are completely discontinued.

Patients with intermittent symptoms are treated with a beta-2 agonist, which has a quick onset and short duration of action. Albuterol by metered-dose inhaler or nebulizer, used on as-needed basis, is the quick-relief therapy of choice, but other medications can also be used [1]. However, when any one of these medications is being used on more than two times per week for the relief of asthma, then the patient no longer has episodic asthma and must be classified as having a more persistent form of asthma. Persistent asthma is most effectively controlled with the daily long-term use of a controller medication. Inhaled glucocorticoid therapy is most often used and should be added to the beta-agonist therapy, which still should be on an as-needed basis [1].

The clinician must treat each individual patient, paying attention to the needs and circumstances of the patient in his or her stepwise treatment process. In order to initially gain disease control, it is often necessary to initiate anti-inflammatory therapy at a more aggressive level than that required in the long run by the patient's actual clinical disease severity [1]. Therapy can be then reduced. Many times, a short course of systemic corticosteroid therapy is used to gain control, along with a reasonable, perhaps more intermediate, daily dose of inhaled corticosteroids. Once asthma is controlled, oral therapy is quickly reduced and stopped. Within a brief period of time, inhaled corticosteroid may even be reduced to a lower daily dose. With reduced inflammation, asthma symptoms and signs should improve, PEFR should increase, variability of airflow over each 24-h time period should decrease, and finally the dependency on the use of inhaled albuterol for rescue should decrease. Enhanced control should eliminate nocturnal awakenings and activity limitation.

Most patients with moderate and severe chronic asthma require not only a higher daily dose of inhaled corticosteroid therapy but a second- or third-line controller medication. These medications include the preferred long-acting inhaled beta agonist like salmeterol or formoterol, or alternatively a leukotriene blocker therapy or perhaps a sustained-release

theophylline. However, before going to daily doses of an oral corticosteroid at step 6, you may consider a trial of high-dose inhaled corticosteroids, a long-acting beta-2 agonist, and either a leukotriene modifier or theophylline to enhance disease control, thereby improving the asthma patient's overall quality of life. Long-acting beta-2 agonist or theophylline may be especially helpful in controlling nocturnal breakthrough symptoms [62]. For patients with perennial allergen sensitivity at step 5 or 6, we would also consider omalizumab.

The most severe persistent asthmatic population requires high daily doses of an inhaled corticosteroid in addition to other controller therapies in an effort to reduce the need for daily, every-other-day, or frequent bolus-taper courses of systemic corticosteroid therapy. This group of patients should see an asthma specialist on a regular basis.

With regular follow-up visits, the clinician may be able to reduce inhaled corticosteroid therapy by 25% every 3 months, until an optimal daily dose is achieved and disease control is maintained. A chronic asthmatic who is completely withdrawn from inhaled corticosteroid therapy often relapses [63]. Therefore, there should be an excellent reason why inhaled corticosteroid therapy or other anti-inflammatory controller therapy is completely discontinued.

This discussion has focused on inhaled corticosteroid therapy as the anti-inflammatory medication of first choice. However, other anti-inflammatory therapies can be used in the first-line management of persistent asthma. These medications include inhaled cromolyn and nedocromil sodium and oral leukotriene blocker therapy [1]. This point is particularly important for children and other patients who are unable to use inhaled corticosteroid therapy on a regular basis, perhaps because of the occurrence of bothersome local adverse effects such as dysphonia and thrush. If there is difficulty in gaining control or maintaining control with reasonable doses of controller therapy, then an asthma specialist should be consulted (Table 53.2) [1]. If the asthma is not well controlled, then the following factors must be considered before increasing therapy:

TABLE 53.2
Referral to Asthma Specialist for Consultation or Comanagement

1. Patient has had a life-threatening asthma exacerbation
2. Patient has needed more than two bursts of oral corticosteroids in 1 year or required hospitalization
3. Patient is not meeting the goals of asthma therapy after 3–6 months of treatment or is unresponsive to therapy
4. Diagnosis unclear
5. Conditions complicating asthma or its diagnosis (e.g., sinusitis, nasal polyps, aspergillosis, severe rhinitis, VCD, GERD, COPD, psychosocial problems)
6. Further diagnostic testing is needed (e.g., allergy skin testing, rhinoscopy, complete pulmonary function studies, provocative challenge, bronchoscopy)
7. Consideration for immunotherapy
8. Patient requires step 4 care or higher or even consider referral for step 3 care
9. Patient education and guidance on complications of therapy, problems with adherence, or allergen avoidance
10. Confirmation of possible occupational or environmental inhalant or ingested substance contributing to asthma

Source: Adapted from National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, *J. Allergy Clin. Immunol*., 120, S94, 2007.

Other Issues in Long-Term Asthma Management

Patient Medication Adherence and Inhaler Technique

Examination of inhaler technique is often forgotten by the busy clinician but needs to be checked when prescribing either a dry powder or metered-dose inhaler for asthma. This is very important as the patient frequently may be taking the medication but ineffectively delivering the medication to the lungs. The patient may believe that the drug does not work and discontinue it. It should be checked on the initial clinic visit and then periodically depending on their inhaler skill.

Educating the patient on the roles of the medications, especially the short-acting beta-2 agonist and the inhaled corticosteroids, is paramount. Moreover, the role of the anti-inflammatory medication especially the inhaled corticosteroids should be emphasized. It is not infrequent that patients will stop their inhaled corticosteroid because they do not notice an immediate effect. Patients must understand the type of therapeutic benefit and the time of onset of the benefit. These should be reiterated during clinic visits.

To enhance compliance with anti-inflammatory medication, it is often helpful to the patient to try and integrate the medication frequency in with their lifestyle or their ability to adhere to the regimen. For patients who are uncontrolled or even controlled on their current regimen, it is important to determine if the patient is taking their medication as prescribed, especially inhaled corticosteroids, because it is not uncommon to find that patients dosed on a twice-daily regimen will remember their morning dose but tend to forget their evening dose. This may also depend on their work schedule whether they work days, evenings, or nights. To improve patient adherence to their inhaled corticosteroid dose regimen, it may be better to determine if it is easier for the patient to take the medication (e.g., inhaled corticosteroids) all in the morning or evening instead of two divided doses.

Review of Comorbid Conditions

Moreover, in the not well-controlled asthmatic, the physician should also evaluate for other comorbid conditions: allergic bronchopulmonary aspergillosis, GE reflux, smoking, obstructive sleep apnea, rhinosinusitis, paradoxical vocal cord dysfunction, and chronic stress or depression.

Asthma Complications

Complications from asthma can occur acutely or chronically. An acute asthmatic attack is associated with a variety of complications, including pneumothorax, pneumomediastinum, a variety of cardiac arrhythmias, lung atelectasis, and respiratory failure. Rarely, death can occur. The young and the elderly are at particular risk for death because the severity of their disease is either not appreciated or is ignored. Asthma death can be sudden in onset, possibly associated with laryngospasm. However, most asthmatic deaths are slow in evolution to the point at which respiratory failure occurs as a multitude of metabolic problems develop [64]. Table 53.3 shows the factors that have been implicated in asthma exacerbation and mortality.

With poorly controlled asthma over a long period of time, irreversible airflow obstruction develops [65,66]. Recurrent airway infection is associated with fixed airflow obstruction [67]. In a few patients, allergic bronchopulmonary aspergillosis occurs, often with mucoid airway impaction and secondary bacterial infection. Allergic bronchopulmonary aspergillosis associated with asthma is characterized by episodes of severe recurrent asthmatic exacerbations [68]. Fever can be associated with this condition, as can chest pain; mucous impaction causes transient infiltrates to develop on the chest x-ray, usually in the upper lung fields. Associated blood eosinophilia and an increased serum IgE level are associated with allergic bronchopulmonary aspergillosis, but a positive skin prick test and serum precipitating antibodies to the fungus *Aspergillus fumigatus* are confirmatory for this particular form of chronic asthma. This condition generally requires high doses of inhaled corticosteroids each day, often with oral corticosteroid therapy.

Skin Testing and Immunotherapy

The discovery of IgE as the antibody responsible for allergic reactions has led to the development of certain blood tests, which can measure the amount of IgE in response to certain allergens. This form of in vitro testing is commonly an immunoassay [6]. Skin testing is less expensive and more sensitive than in vitro tests, often providing results within 1 h. There are two types of skin tests. The epicutaneous test is often referred to as the scratch or prick technique. Also there is an intracutaneous or intradermal test. These skin tests are generally easy to perform and cause little patient discomfort. When the skin test is positive, the patient can see the positive skin test, which encourages the patient to enhance their compliance with environmental control measures. Immunoassay require expertise in technique, there is no risk of an allergic systemic reaction, and it can be performed on patients who are taking medications that often suppress the skin test reaction (antihistamines, prednisone, singulair, tricyclic antidepressants).

When a positive result is found with skin testing or immunoassay, the clinician is obliged to look for clinical significance of the positive allergy test in the context of the patient's medical history. If this relationship is clear and the allergen cannot be avoided and it is difficult to control symptoms with pharmacologic therapy (mild-to-severe persistent asthma, steps 2–4), then immunotherapy should be considered [1]. Evidence is strongest for house dust mites, animal danders, and pollens [1]. However, immunotherapy should not be used until environmental control has been maximized. Allergen immunotherapy should be administered by a physician in the office or the hospital where facilities are available to treat the serious adverse reactions that can occur as a result of this form of therapy [69]. It is better to use immunotherapy for a single allergen—the more allergens that are being treated for, the higher is the incidence of failure [1]. Although multiple-allergen mixes are used for immunotherapy, only a few studies clearly support this practice [70]. Allergy immunotherapy is typically administered for 3–5 years.

There are controlled studies and a meta-analysis that support the use of immunotherapy in the treatment of asthma, which do show some benefit for asthma symptoms, bronchial reactivity, and reduced medication use [1,19,71,72]. Immunotherapy is felt to reduce not only the frequency of symptoms but also the extent of symptoms and to minimize the need for bronchodilator medications. Immunotherapy is most effective for some types of seasonal pollens (tree, grass, weed) and house dust mites with some success in pet allergy, particularly cat, in controlled studies [19,71,72]. Immunotherapy is not a cure, but may reduce asthma and allergic rhinitis symptoms and signs. The success of immunotherapy is dependent upon identifying the correct potential allergens.

There are certain risks associated with immunotherapy [69]. The most common reaction to an allergy shot is swelling, erythema, and pruritus at the site of the injection. This type of a reaction is usually short-lived and can be minimized by using topical anti-inflammatory therapy in the form of a cream or an oral antihistamine. The most serious reaction from an allergy shot is anaphylaxis. Anaphylaxis can occur quickly after the injection. Therefore, immunotherapy should be performed in the presence of a physician experienced in treating anaphylaxis. Sufficient time should be allowed for

TABLE 53.3
Factors Associated with Increased Risk of Asthma Exacerbations or Mortality

1. Severe airflow obstruction, as detected by spirometry
2. Two or more ED visits or hospitalizations for asthma in the past year; past intubation or ICU admission, especially in past 5 years
3. Patients feeling in danger or frightened by their asthma
4. Patient characteristics: female, nonwhite, nonuse of ICS therapy, and current smoking
5. Psychosocial factors: depression, increased stress, socioeconomic factors
6. Attitudes and beliefs about taking medications

Source: Adapted from National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, *J. Allergy Clin. Immunol.*, 120, S94, 2007.

the reaction to occur, so patients should remain at the physician's office for 15–30 min after each injection. Less serious reactions include nasal congestion and sneezing, asthma itself, difficulty swallowing and talking because of a swollen tongue or larynx, and light-headedness. With these reactions, there is often an increase in heart rate and perhaps even a slight change in blood pressure.

Exercise and Asthma

Exercise-induced asthma (EIA) or bronchoconstriction (EIB) is typically a transient airway narrowing and airflow obstruction that occurs during or after exercise [2,73]. Nearly 90% of persistent asthmatics have EIB, and patients with allergic rhinitis and even normal relatives of asthmatics can demonstrate this phenomenon. The most common symptoms are cough, wheezing, chest tightness, shortness of breath, and what the patient describes as an inability to take in a full breath of air during or following exercise. Symptoms start several minutes after exercise has stopped and usually improve within 1 h, even without medication. The typical fall in airflow is seen between 5 and 20 min after exercise and resolves in about 60 min (Figure 53.7). EIB can seriously and adversely affect athletic performance if not recognized and controlled.

EIB is thought to be associated with the exchange of heat and water that occurs in the airways during exercise in which minute ventilation is increased. The main factors affecting the severity of EIB during exercise are the amount of minute ventilation attained and sustained as well as the inspired air water content and temperature. Because of the high minute ventilation, there is a cooling and drying effect on the airway that somehow influences airway inflammation in a way that expresses itself more intensely [2,73]. During exercise, the airways cool down as minute ventilation increases. This cooling and drying effect of the airways sets the stage also for rapid rewarming of the airways that occurs with resting. The high flow ventilation may dry the surfaces of the airways and cause an increase in osmolarity, which may trigger the release of inflammatory mediators. Well-controlled chronic asthma should not exacerbate following exercise. It is realistic to expect that if chronic asthma is controlled, patients can participate in athletic activities at a reasonable level to maintain body conditioning and enjoy themselves. This is important because the lifestyle changes of reduced exercise may increase the risk for asthma [74]. There are interventions that should be followed to control exercise-induced bronchospasm.

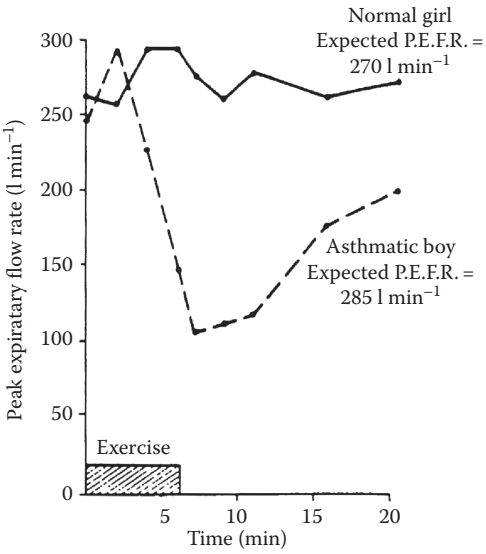


FIGURE 53.7 Response to exercise of a boy with asthma and a healthy girl whose resting peak expiratory flows were within the normal range. The boy with asthma developed a typical attack of exercise-induced bronchospasm.

Exercise-induced bronchospasm can be diagnosed simply for the majority of patients. We have had the experience of measuring PEFRs prior to exercise. After an exercise challenge, airflow is measured sequentially at 5, 15, and 30 min. The patient with EIA often has a drop in airflow within this time period. When airflow falls, especially when associated with symptoms consistent with asthma, the diagnosis can be made. This evaluation process can be done by a physician or under the guidance of a physician by instructed individuals such as trainers or coaches. Patients that are known to have asthma should be screened for EIB breakthrough. Also individuals that may be at high risk for EIB should be screened. We have found that as many as 14% of high-performance athletes will have bronchial hyperresponsiveness, including bronchoconstriction associated with exertion. There is also a substantial rate of unrecognized EIB among urban varsity athletes. In one study, we have found that during screening for asthma and EIB, approximately 10% of 238 students had a history of treated asthma and another 9% had unrecognized EIB. This suggests that active screening for EIB, especially for students residing in poverty areas, may be indicated [75].

The prevention and control of EIB can be accomplished by both non-pharmacologic and pharmacologic approaches. For some athletes, it is important to choose a sport that does not require sustained exercise, such as baseball, golf, or weight lifting. When the exercise is performed, it is preferable to avoid cold, dry environments. However, in cases when exercise is performed in colder environments, a mask or scarf covering the mouth may help reduce exercise-induced bronchospasm [76]. A warm (but not too warm) and moist environment can often be helpful in minimizing EIB. Finally, it is not only the type of sport that one plays but the position selected. For example, a football lineman is at less risk than a running back.

The use of an extended warm-up session and special breathing techniques that help minimize hyperventilation and also promote relaxation can be helpful. There is some literature that reports a warm-up period before exercise results in a refractory period or reduction in EIB for less than an hour [77,78]. The athlete should begin warming up slowly to loosen the muscles and elevate the heart rate. With the beginning of a light sweat, the athlete can perform the exercise at or close to his or her maximum exertion for up to 5 min and then take a rest. More accomplished athletes can continue this warm-up process recurrently for 30–40 min. Another strategy is to do brief bouts of exercise for 2–3 min followed

by 3–5 min of rest. These repetitive exertional challenges should occur over a 30- or 40-min period. It is important for the individual athlete to find out which warm-up protocol works best for him or her. Some athletes require a warm-up period of as long as an hour.

Just as important as warming up appropriately is concentrating on breathing maneuvers during and following exercise. Symptoms can be reduced by breathing warm, humid air rather than cold, dry air. Therefore, swimmers are likely to tolerate their disease better than football players. Certain athletes have learned to breathe through their nose instead of their mouth. This is a difficult technique to master. When athletes breathe through their nose, especially during periods where heavy breathing is unnecessary, the air that is brought into their lungs is humidified and heated. By breathing deeper and more slowly, the cooling and drying effect of the hyperventilation of exercise can be minimized.

The postexercise period is also very important. The cooldown phase after a workout or competition should resolve taking deep, slow breaths. Cooling down in a warmer but not too warm environment can be helpful.

Often, drug therapy is necessary to prevent EIB. There are numerous inhaled beta-agonist medications that can be used shortly before exercise and even during and after exercise to prevent or relieve asthma symptoms [1]. Beta agonists administered by inhalation will prevent EIB in more than 80% of patients. Administering a short-acting inhaled beta agonist such as albuterol approximately 15–30 min before exercise provides protection for 2–3 h. When asthma breaks through, these medications can be safely administered by a metered-dose inhaler. The inhaled long-acting beta-2 agonists (formoterol, salmeterol) can be helpful for controlling frequent need for short-acting or daily need for short-acting beta-2 agonists. Salmeterol has been shown to prevent EIB for 10–20 h [79] and is valuable for prolonged prevention when the athlete will reexpose himself or herself to the exercise challenge over this time period. Long-acting beta-2 agonists should not be used alone as daily prophylaxis of EIB as the duration of effect may be masking less suboptimally controlled asthma [1]. Other therapies can be used in addition to the beta agonist. Inhaled cromolyn or nedocromil, although less effective than short-acting beta-2 agonists, can be taken approximately 30 min to 1 h prior to exercise, often in addition to the pre-exercise use of the short-acting inhaled beta agonist for further control in those patients who fail single preventative therapy [80]. Administered in a single-dose pretreatment manner, the leukotriene receptor antagonists can decrease EIB in approximately half of patients within hours of administration [1,81].

Most EIB occurs in the chronic asthmatic, making control of chronic asthma with the therapies described earlier crucial. Inhaled corticosteroids can decrease airway responsiveness over the long term and decrease EIB. When chronic asthma is controlled, the frequency and severity of EIB are reduced [82].

Occupational Asthma

It has been estimated that occupational factors account for approximately 9%–15% of cases of asthma in adults of working age, including new onset or recurrent disease [83]. A variety of substances in the workplace have been implicated in the development of asthma, including a large variety of animal proteins, flour and grain dust, wood dust, cotton dust, chemical compounds such as isocyanates and hydrides, metal salts, and even pharmaceuticals [83]. The workers most commonly reported for occupational asthma include paint sprayers, bakers and pastry makers, animal handlers, nurses, chemical workers, welders, food processing workers, and timber workers [83].

The causes of occupational asthma can be grouped into immunologic and non-immunologic causative agents. Up to 90% of cases have been of the immunologic type. Some causative agents can produce occupational asthma through both immunologic and non-immunologic mechanisms. The immunologic agents can be divided into high- and low-molecular-weight substances (Table 53.4). The high-molecular-weight agents are complete sensitizing agents while the low-molecular-weight agents need to combine with a protein to form a sensitizing agent. The high-molecular-weight agents are usually mediated through IgE. There is a time delay between exposure to the offending agent and the development of symptoms of occupational asthma.

It is important to recognize occupational asthma as soon as possible, because the likelihood of complete resolution of symptoms decreases over time [1]. Occupational asthma is suspected when either the patient or the clinician realizes that there is a relationship between asthma symptoms and work exposure. Many times, the patient will improve on the days that he or she is away from the workplace, particularly during vacations. Sometimes coworkers have similar symptoms, and

TABLE 53.4
Select Causes of Allergic and Nonallergic Occupational Asthma

Allergic	
High-Molecular-Weight Substance	*Occupations*
Animal protein	Laboratory workers
Papain	Brewers, lens workers
Wheat flour	Bakers, millers
Trypsin	Plastic/pharmaceutical workers
Soybean dust	Farmers, food workers
Vegetable gums	Printers, food workers
Low-molecular-weight substance	
Platinum	Jewelers, refiners
Trimellitic anhydride	Plastic and epoxy resin workers
Phthalic anhydride	Plastic and epoxy resin workers
Nonallergic	
Isocyanates	Spray painters, foundry workers
Polyvinylchloride	Meat wrappers
Western red cedar	Carpenters

sometimes asthma can occur during the night. Serial peak flow measurements at work and away from work can help diagnose occupational asthma [83]. There are some allergens available, which are not well standardized, for skin prick testing and blood tests for specific IgE for high-molecular-weight agents but only a few for low-molecular-weight agents. Occupational asthma can usually be diagnosed without using specific bronchial provocation testing, although occasionally a specific bronchial provocation challenge done in a specialized laboratory with a suspected allergen or irritant from the workplace can be helpful [83].

The management of occupational asthma can be difficult, and the patient may have to be referred to an occupational asthma specialist. Diagnosing patients early and avoiding further exposure to the causative agent will give the worker the best opportunity for a complete recovery. Often, the employee must avoid the triggering substance. If impossible, then the employee should be moved to an area of low or occasional exposure with increased monitoring. The use of respiratory protection by wearing a ventilator mask can be helpful. Many times the patient must completely avoid exposure to the irritating agent; therefore, a new job position may be necessary. The outcome of any intervention for patients with confirmed occupational asthma depends on factors such as age and the type of agent [83]. Unfortunately, some patients will have persistent asthma despite removal of the inciting substance. A variety of chemicals, dust, and other particulates can sensitize the airways and actually induce chronic asthma [84]. This is different than allergen- or irritant-induced asthma, in which these substances aggravate preexisting asthma but do not actually initiate the disease process. A single high-intensity exposure to a non-immunologic irritant can produce the syndrome known as reactive airways dysfunction syndrome, in which symptoms occur in minutes and may last for years.

Stress

Asthma is not a psychosomatic illness. However, there is emerging evidence that stress plays an important role in precipitating asthma exacerbation and may act as a risk factor for the increased prevalence of this disease [85]. Since emotional upset does contribute to the asthma symptom picture, a variety of psychological interventions may be necessary to enhance overall asthma care. Stress exacerbation of asthma may involve enhanced generation of pro-inflammatory cytokines, but more importantly, psychosocial factors associated with stress influence the asthmatic's personal sphere and often lead to a poor outcome [86]. Conflict that develops between the patient, the family, and the medical staff often interferes with appropriate asthma care. It is true that the poorly controlled chronic asthmatic can despair, and his or her disease can have a significant negative effect on personal relationships, family life, and self-image. Enhanced asthma control and careful discussion of these issues with the patient and family can help the overall asthma care process. The asthmatic who needs psychosocial assistance should take the advantage of appropriate professional counseling with a psychologist, psychiatrist, social worker, or other licensed practitioner [1]. There are a variety of psychologically oriented approaches to asthma care that can be helpful, including family counseling, educational seminars, and psychotherapy. Ignoring one's asthma symptoms and neglecting to use medication can adversely affect asthma control. Asthma education has been associated with enhanced confidence in the patient's management of chronic asthma [1].

Food Hypersensitivity

Food allergy may rarely precipitate asthma symptoms alone. (The diagnosis and management of food allergy is discussed in Chapter 55.)

Medication-Induced Asthma

The ingestion of aspirin in sensitive individuals may result in nasal congestion, eye irritation, facial flushing, and asthma exacerbation, which usually occurs rapidly after ingestion, often within 30 min [87]. Approximately 4%–20% of asthmatics are sensitive to aspirin and related compounds [88], especially nonsteroidal anti-inflammatory agents. Severe and even fatal asthma exacerbations have been associated with aspirin ingestion. Adult patients with severe persistent asthma who have nasal polyps should be carefully instructed not to use any aspirin or aspirin-like medication. Some safe alternatives to aspirin to consider include salsalate, acetaminophen, and celecoxib [89], but highly sensitive patients may even react to these [1,12]. Nasal polyposis and chronic rhinosinusitis occur in nearly 90% of the patients with aspirin sensitivity (Samter's syndrome) [90]. The prevalence of aspirin sensitivity increases with age and the severity of the asthma. There is no known familial predilection to aspirin sensitivity. It is not known to be associated with atopy. Medications that interfere with leukotriene synthesis or leukotriene receptor antagonists are helpful in the management of aspirin-induced asthma. Patients are treated according to asthma guidelines but usually include a leukotriene-modifying agent [31,32,91]. The treatment of aspirin-exacerbated asthma also includes avoiding all NSAIDs that inhibit COX-1 enzyme. An alternative to complete avoidance is aspirin desensitization and daily aspirin therapy [1].

Tartrazine or yellow food dye No. 5 can induce asthma symptoms in some individuals. This food coloring is found in a number of foods and in some medications.

Beta-blockers, including a variety of eyedrop preparations, can induce asthma symptoms and should be avoided in asthmatic patients [1,9,10]. The more cardioselective may be better tolerated by the asthmatic [92], but in order to be safe, an asthmatic should avoid beta-blocker therapy, unless this form of medication is unavoidable for the cardiac or eye condition. The NAEPP Asthma Guidelines 2007 suggest avoiding nonselective beta-blockers [1]. However, patients who have mild-to-moderate airflow obstruction are often able to tolerate selective beta-blockers, and we recommend using

them if needed after careful consideration in patients with appropriate cardiac disorders [1].

Gastrointestinal Reflux

GE reflux results when some of the liquid contents of the stomach regurgitate into the esophagus. The GE reflux material does not have to be aspirated into the lungs to induce asthma. Reflux of the acidic fluid into the esophagus likely destabilizes asthma either by enhancing the cholinergic autonomic nervous system influence or by microaspiration or both. GE reflux should be suspected in patients with poorly controlled asthma, particularly those who have nocturnal symptom breakthroughs [1]. Reflux symptoms do not have to be present, which makes the diagnosis difficult. However, when GE reflux is symptomatic, patients usually complain of "heartburn" or sometimes note food regurgitated into the throat [1]. A patient who has a hiatal hernia is at particular risk for GE reflux.

Treatment of patients with symptomatic GE reflux has been associated with improvement in some aspects of their asthma [93,94]. Patients with nocturnal symptoms and/or regurgitation are more likely to show improvement in their asthma with treatment [1,95]. However, a recent study indicated that treatment of asthmatics without GE reflux symptoms did not improve their asthma [96]. If GE reflux symptoms are present, medical management includes the following: (1) avoidance of eating food and drinking liquids within 3 h prior to bedtime; (2) sleeping with the head of the bed elevated by using 6–8 in. blocks; (3) eating smaller, and if necessary more frequent, meals; (4) pharmacologic therapy with H_2 receptor blockers or proton pump inhibitors; and (5) cessation of alcohol, cigarettes, and caffeinated foods [1]. Also theophylline can reduce the lower esophageal sphincter tone and predispose the asthmatic to GE reflux.

If the medical management as described earlier fails or the patient has other disturbing symptoms, then further evaluation by a gastroenterologist and other treatment options should be considered. Some patients may have to be referred to a surgeon for evaluation.

Pregnancy and Asthma

Asthma is the most common medical condition during pregnancy, occurring in 4%–8% of pregnant women [97]. The risk of asthma exacerbation during pregnancy is higher for woman who had asthma before becoming pregnant. For the patient who has had asthma and is now pregnant, there is a chance that the asthma will remain the same, improve, or worsen [1]. Whatever way the asthma changes during the first pregnancy, it is likely that similar symptoms will occur with subsequent pregnancies. Patients with more severe and difficult-to-control asthma generally have worse symptoms during pregnancy. As a general rule, one-third of all pregnant asthma patients improve, one-third remain the same, and one-third have worsening disease during pregnancy [1]. It is important for every asthma patient who becomes pregnant to be carefully managed medically during the pregnancy.

Asthma may also have an effect on pregnancy complications [98]. Uncontrolled asthma itself is a risk for the fetus. One large study showed that asthmatic patients had an increased risk of infant mortality, preterm birth, and low-birth-weight infants compared to non-asthmatics [98]. Those with more severe asthma have a higher risk of complications [98]. However, this study did not find an increased risk of congenital defects [98]. A mother whose asthma is well controlled and free of complications imposes no additional risk on the fetus.

The goals of asthma treatment during pregnancy are to prevent acute exacerbations and to optimize lung function with medications shown to have the lowest potential adverse effect on the fetus. This should provide maximum benefit to the health of the mother and the fetus [1,99]. The majority of asthma medications that are used in practice present little to no risk during pregnancy although prospective well-designed and well-controlled clinical trials do not exist for most medications. The U.S. Food and Drug Administration has classified medications into five categories (A through D and X) related to their potential for adverse effects on pregnancy. These classifications are based on animal and human data and also risk–benefit. The safest is category A, but there are no asthma medications in this group. Both systemic and inhaled corticosteroids can be used during pregnancy. The inhaled steroid, budesonide, has long been listed as category B and preferred [1] during pregnancy because of the large amount of safety data obtained from the medical birth registry in Sweden [1]. However, patients that are doing well on other inhaled corticosteroids could be continued. Inhaled beta-agonist therapy with albuterol, which has the most safety data during human pregnancy [1], should be used for symptom breakthrough. During pregnancy, the leukotriene inhibitors, montelukast and zafirlukast, are not the preferred therapy for mild persistent asthma. Allergy immunotherapy can be continued through pregnancy but should not be started or altered during this period.

Inhaled therapy should be selected over systemic therapies during pregnancy. Over-the-counter medications should be avoided. The obstetrician and the primary care physicians should work together to create the safest treatment regimen for the pregnant asthmatic patient. When questions arise, the local asthma expert, generally an allergist or pulmonary specialist, should be consulted.

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54 Pulmonary Rehabilitation

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CONTENTS

Definition 677
History and Development 677
Development of Measurement Tools 677
Impact of Pulmonary Rehabilitation 678
Effects on Dyspnea, Exercise Capacity, and Quality of Life 678
Impact on Health Care Utilization 678
Physiologic Basis of Pulmonary Rehabilitation 679
Current Practice of Pulmonary Rehabilitation 680
Patient Selection 680
Exercise Training 681
Educational Component 682
Psychosocial Component 682
Nutrition 683
Ongoing Controversies 683
Maintenance of Benefits 683
Optimal Duration 684
Mortality Benefit 684
Pulmonary Rehabilitation in Other Chronic Respiratory Conditions 684
Summary 684
References 685

DEFINITION

The American Thoracic Society (ATS) and European Respiratory Society (ERS) have defined pulmonary rehabilitation as follows:

> … an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease. [1]

History and Development

Until the 1950s, patients with COPD were advised to minimize physical exertion to avoid dyspnea [2]. Dr. Alvin Barach suggested that emphysema patients could obtain a training benefit from exercise that was similar to the exercise benefits seen in healthy people [2,3]. Barach suggested that exercise-based rehabilitation would lead to increased capacity for physical exertion [4].

Pulmonary rehabilitation took a significant step forward with Dr. Thomas Petty's concept of a "comprehensive care program" that he developed and refined in the 1960s. In his formulation of this program, patients with chronic airway obstruction received outpatient-based, individualized educational sessions about bronchial hygiene and breathing techniques in addition to exercise sessions and optimization of pharmacologic therapy. In 1969, he published the seminal paper that outlines many of the concepts still used in pulmonary rehabilitation programs today [5]. Petty demonstrated that patients who completed the program had improved exercise capacity and reduced hospitalization. Other benefits included a "return to gainful employment" in some patients [5].

Broad acceptance of pulmonary rehabilitation as a valid option for COPD treatment was hampered by the fact that pulmonary rehabilitation did not improve spirometry, which was the main parameter that defined the severity of COPD [6]. As of the mid- to late 1980s, there was still debate about the true benefit of pulmonary rehabilitation in COPD [7]. That skepticism also stemmed from the belief that patients with significant airway obstruction would have a ventilatory limitation to exercise and that this impairment would prevent them from achieving work rates high enough to produce a training effect on the muscles [8].

Development of Measurement Tools

The introduction of other clinical outcome measures for investigation facilitated the development and growth of

pulmonary rehabilitation. The principle of the minimally clinically important difference (MCID) is an essential concept to properly understand the results of these measures. The MCID is the smallest difference in a measure that a patient would perceive as beneficial. This is the amount of change needed to indicate a change in treatment, in the absence of side effects or extreme cost [9].

The Baseline Dyspnea Index (BDI) and Transitional Dyspnea Index (TDI) [10], Chronic Respiratory Disease Questionnaire (CRDQ) [11], and St. George's Respiratory Questionnaire (SGRQ) [12] are tools designed to examine changes in dyspnea and health-related quality of life (HRQOL). The BDI consists of three components: functional impairment, magnitude of task, and magnitude of effort. Each component is scored from 0 to 4. The TDI measures the changes from BDI and is scored anywhere from +3 to –3 for each component. One unit change is generally accepted as the MCID [13]. The CRDQ is a 20-item interviewer-administered questionnaire that looks at respiratory illness-related quality of life. It is comprised of four domains and is scored using a 7-point numerical scale. Higher scores indicate better quality of life. A change of 0.5 on the 7-point scale is the minimum clinically significant change [9]. SGRQ is a 76-item questionnaire that was developed for patients with fixed and reversible airway obstruction. The SGRQ had three domains—symptoms, activity, and impacts. Scores are from 0 to 100 with higher scores indicating poorer health status. A change of four units is clinically significant [12]. Measures to quantify exercise capacity, such as the 6-minute walk test (6MWT), were also developed [14]. The test is conducted by asking a patient to simply walk as far as he can within 6 min in a premeasured hallway or corridor. Normal subjects can travel anywhere from 400 to 700 m [15]. A change of 54 m is commonly accepted as the minimal clinically significant difference in patients with COPD [16].

IMPACT OF PULMONARY REHABILITATION

Effects on Dyspnea, Exercise Capacity, and Quality of Life

The use of these measurement tools facilitated the demonstration of benefits of Pulmonary Rehabilitation. In 1991, Casaburi published a landmark paper that proposed a physiologic mechanism for the increase in exercise capacity seen after pulmonary rehabilitation [17]. In that study, 19 patients with COPD participated in an inpatient 8 week pulmonary rehabilitation program consisting of exercise and education. Participants were randomly divided into two groups—a high work-rate group (exercise intensity of 90% of the anaerobic threshold work rate or 80% of maximally tolerated work rate as determined by a prior exercise test) and a low work-rate group (work rate of 60% of the difference between the anaerobic threshold and VO_2 max work rate or 50% of the maximally tolerated work rate). After pulmonary rehabilitation, the high work-rate group lactate threshold increased by 24%. Also, for a given level of exercise, blood lactate decreased by 38% and minute ventilation decreased by 12%. CO_2 production was also decreased. The changes in these parameters in the low work-rate group were significantly less. The authors concluded that high-intensity exercise leads to superior physiologic outcomes and that the basis for the benefit of pulmonary rehabilitation is a lower production of lactic acid during exercise. This leads to less ventilatory demand for a given level of exercise in muscles that achieved a training effect.

Reardon investigated 20 COPD patients who were randomized to receive either a 6 week outpatient pulmonary rehabilitation program with educational sessions or a control group that did not undergo pulmonary rehabilitation [18]. The target intensity for the exercise component was a heart rate or dyspnea severity of 70%–85% of that seen during maximal exercise testing. In the pulmonary rehabilitation group, dyspnea at maximum workload decreased from 74% to 50% while there was no change in the control group. The rehabilitation group also had higher TDI scores, indicative of decreased dyspnea. Two physiologic parameters, dyspnea at maximum workload divided by VE_{max} and dyspnea at maximum workload divided by VO_2 max, were also improved in the rehabilitation group. This was the first randomized clinical trial demonstrating the benefit of pulmonary rehabilitation in COPD patients.

Ries published a large randomized controlled trial of 119 patients randomized to 8 weeks of pulmonary rehabilitation program or an education only program [19]. The exercise goal was "steady-state exercise consisting of continuous walking at the highest tolerated symptom limited level for as long as 30 minutes." The pulmonary rehabilitation group had significantly greater improvements in exercise endurance, perceived breathlessness during exercise, and dyspnea with daily activities when compared to the control group. Other studies showed similar gains in exercise capacity and health-related quality of life after pulmonary rehabilitation [20–22].

Ries et al. published a large study looking at 1218 patients selected from the National Emphysema Treatment Trial (NETT) [23]. These patients underwent a comprehensive pulmonary rehabilitation program prior to being randomized into the lung volume reduction surgery (LVRS) arm or medical management arm. Selected patients had a mean FEV_1 of 26.9%. After completing the rehabilitation program, patients had improved dyspnea, health-related quality of life, and exercise capacity. Patients who had no prior pulmonary rehabilitation experience had a larger improvement compared to those patients who had prior rehabilitation.

Lacasse et al. reviewed the literature on pulmonary rehabilitation in a meta-analysis in 1996 [24] as well as a Cochrane review in 2009 [25]. The 2009 Cochrane review included 31 randomized clinical trials. Significant improvements were seen in health-related quality of life. 6MWT improvement was near, but did not exceed, the MCID of 54 m.

IMPACT ON HEALTH CARE UTILIZATION

Clinical data suggest that patients who complete a pulmonary rehabilitation program utilize fewer health care resources. The patients reported in Petty's original paper

spent fewer days in hospital in the first year after participation in the program [5]. Ries et al. demonstrated a decrease in hospitalization in the pulmonary rehabilitation group of 2.4 days per patient per year versus an increase of 1.3 days per patient per year in the control group in the year after pulmonary rehabilitation [19]. Griffiths et al. calculated that pulmonary rehabilitation has a probability of 0.645 that it will result in a negative cost per quality adjusted life year (QALY) gained [21]. This is comparable to other interventions such as hip replacement, coronary artery bypass grafting, and insulin treatment in type 2 diabetes. Bourbeau published a multicenter clinical trial that randomized COPD patients to an intervention program consisting of daily home educational sessions and an individualized action plan versus usual care [26]. The patients were given an exercise prescription that consisted of a typical pulmonary rehabilitation session—warm-up/stretching activities and then either stationary biking, walking, or stair climbing. In the intervention group, there were significant decreases in hospitalizations for COPD exacerbations, emergency department visits, and unscheduled doctor visits. Hospital admissions for non-COPD issues were diminished as well. Other studies also documented reductions in hospitalization rates, length of hospital stay, hospital readmissions, and interval to readmissions [27,28]. A large study of more than 600 patients participating in 9 pulmonary rehabilitation centers in California [29] demonstrated that program participants had fewer physician visits, phone calls to health care providers and hospital days at 3, 6, 12, and 18 months when compared to the 3 months prior to joining pulmonary rehabilitation.

An observational study looked at how the BODE index changes with pulmonary rehabilitation [30]. The index has four components, the *B*MI, severity of *O*bstruction as measured by FEV_1, *D*yspnea as measured by the Medical Research Council score, and *E*xercise capacity as measured by timed walking distance [31]. Each of these parameters separately have been shown to impact mortality and combined together predict mortality better than spirometry alone [31–36]. The rehabilitation group had diminished length of hospital stay and hospitalization when compared to the non-rehabilitation group [30]. Hospital length of stay decreased by approximately 20% in those patients who completed pulmonary rehabilitation. A larger improvement in the BODE index was associated with a larger decrease in hospital length of stay.

Currently, pulmonary rehabilitation is considered the standard of care in symptomatic patients with COPD. In the latest ACCP/AACVPR clinical practice guidelines [37], pulmonary rehabilitation was given the strongest possible recommendation (1A) as a modality for improving dyspnea and health-related quality of life. In fact, in comparison with the known treatment benefit of inhaled therapies for COPD such as salmeterol [38] and tiotropium [39], pulmonary rehabilitation demonstrates similar efficacy in improving health-related quality of life.

PHYSIOLOGIC BASIS OF PULMONARY REHABILITATION

Pulmonary rehabilitation programs improve exercise capacity without any significant changes in lung function such as FEV_1 [17] or oxygenation [40]. If spirometry and oxygenation does not improve with pulmonary rehabilitation, what is the mechanism of benefit?

It had been previously postulated that the benefits seen in pulmonary rehabilitation may be due to other factors such as dyspnea desensitization (due to the reassuring presence of health care personnel during exercise training) and anxiety reduction [41], or improved muscle function. Of these potential explanations, it now appears that improved muscle function is the most important factor.

A vital concept in the practice of pulmonary rehabilitation is the "dyspnea spiral" or the "fear-dyspnea cycle" [6,42]. This describes a situation where a patient with a chronic respiratory disease gradually limits physical activity to avoid the unpleasant sensation of dyspnea. Consequently, the patient becomes increasingly more sedentary and deconditioned such that progressively lower levels of physical exertion lead to breathlessness. The exercise component of pulmonary rehabilitation is designed to break this cycle and improve a patient's exercise capacity.

It has been demonstrated that exercise limitation in patients with COPD may not always be due to a ventilatory or gas exchange limitation but can also be due to leg fatigue and muscle weakness [43,44]. Saey et al. reported a small group of COPD patients who completed cycling exercises until the onset of quadriceps contractile fatigue [45]. In the group who developed muscle exhaustion, there was evidence of a ventilatory limitation to exercise as well. However, when these patients were pretreated with ipratropium such that their FEV_1 increased by 11%, endurance time did not increase. This suggests that lower extremity weakness is an important factor that limits exercise capacity in patients with COPD. This muscle weakness may simply be due to deconditioning and muscle wasting as COPD patients tend to be progressively more sedentary or due to a more specific "COPD myopathy."

There are increasing data supporting the concept of COPD as a systemic disease not limited to pulmonary symptoms and manifestations [46–49]. Increased systemic levels of inflammatory markers such as CRP, fibrinogen, leukocytes, TNF-α, IL-6, and IL-8 have been found in patients with COPD [50]. It has been suggested that systemic inflammation occurs when inflammatory mediators from COPD do not remain localized within the lung and leaks out into the systemic circulation [48,51,52]. These inflammatory mediators then can cause extrapulmonary manifestations. Among the proposed extrapulmonary consequences are the following: osteoporosis, anemia, coronary artery disease, diabetes, and muscle abnormalities [46,53–58].

Skeletal muscle dysfunction is the change that has the most significance to pulmonary rehabilitation. Patients with COPD have distinct skeletal muscle pathologies in addition to a decrease in skeletal muscle mass in the lower extremities.

Patients with COPD have less muscle capillarity. In a study by Jobin involving biopsies of the vastus lateralis muscle, COPD patients had a significantly lower number of capillaries per square millimeter as well as a reduced capillary to fiber ratio when compared to nonsmoking, non-exercising controls [59]. Furthermore, vastus lateralis biopsies of patients with COPD has shown reduced type I fibers and increased type IIb fibers [59,60]. Type I fibers are slow twitch fibers and are more resistant to fatigue; type IIb fibers are fast-twitch fibers and are more prone to fatigue as they use anaerobic glycolysis [61]. Agusti demonstrated that quadriceps femoris biopsies from COPD patients with low BMI have increased apoptosis when compared to healthy subjects and sedentary patients [62]. In subjects with COPD, body mass index (BMI) was inversely related to degree of apoptosis. Apoptosis was also associated with lower exercise capacity given similar lung function. Muscle apoptosis may be partially responsible for the weight loss frequently seen in patients with COPD.

In 1996, Maltais et al. published a paper investigating the skeletal muscle oxidative capacity of COPD patients [63]. They measured the activity of two oxidative enzymes: citrate synthase (CS) and 3-hydroxyacyl-CoA dehydrogenase (HADH). They found that oxidative enzyme activity was lower in COPD patients and that the rate of increase in lactic acid concentration with exercise was steeper in COPD patients as well. It was postulated that the early rise in lactic acid may be due to this impaired muscle oxidative capacity. The same investigators also demonstrated that CS activity decreased in tandem with decreasing functional status and that CS activity correlated with exercise capacity independent of lung function [64]. The net result of this muscle dysfunction is that lactic acidosis occurs at a lower level of exertion which results in exercise limitation. Lactic acidosis may also indirectly lead to the sensation of breathlessness, as it serves as a stimulus for increased ventilation which patients with a ventilatory limitation are unable to meet.

The cross-sectional area of type I and II muscle fibers increase after participation in rehabilitation [60]. More importantly, Maltais et al. demonstrated that after a 12 week exercise program, exercise lactate threshold increases and levels of oxidative enzymes citrate synthase (CS) and 3-hydroxyacyl-CoA dehydrogenase (HADH) increase as well [63]. The logical and prevailing hypothesis is that the decrease in lactic acid production is due to increased skeletal muscle oxidative capacity resulting from higher oxidative enzyme activity.

CURRENT PRACTICE OF PULMONARY REHABILITATION

Patient Selection

Pulmonary rehabilitation is typically done as an outpatient hospital-based program (Figure 54.1) although several other models exist—inpatient, home-based, or inpatient initially and continued as outpatient [28,40,65,66]. Any patient with a chronic respiratory disease with exercise limitation or significant limitations of activities of daily living (ADLs) can be considered for the program. There are no specific spirometric or pulmonary function test cutoff points as patients may have significant exercise limitation despite mild impairment in tests. The most recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) statement [67] recommends pulmonary rehabilitation for all stages of COPD.



FIGURE 54.1 An outpatient, hospital-based setting for pulmonary rehabilitation.

Pulmonary rehabilitation programs are best implemented by a multidisciplinary team. At a minimum, a pulmonary rehabilitation team should consist of a medical director, program coordinator, and rehabilitation specialist [68]. Other health care professionals such as nutritionists, psychiatrists, and occupational therapists may participate and provide valuable patient services. Before being accepted to the program, a patient is first screened by the medical director to ensure that pulmonary rehabilitation is an appropriate intervention for the patient. Contraindications to pulmonary rehabilitation would include those conditions that would preclude a patient from doing exercise testing safely such as active myocardial ischemia, serious arrhythmias, dissecting aneurysm, and severe aortic stenosis [69]. Other conditions such as severe psychiatric disorders, disruptive behavior, poor cognitive function, severe orthopedic problems, or unwillingness to engage in the program would also prevent a patient from effectively participating in the other components of pulmonary rehabilitation such as educational sessions and psychosocial interventions. If the patient is considered appropriate, he or she meets with other members of the team for psychosocial assessment, nutritional assessment, goal development, and evaluation of rehabilitation potential. The patient's current level of physical activity and ADL limitations are also evaluated. Baseline measures of HRQOL such as the SGRQ and CRDQ are obtained. A pre-rehabilitation exercise test is done to rule out potentially serious cardiovascular issues that may hinder exercise training as well as to establish baseline exercise capacity. The need for supplemental oxygen is also assessed and documented.

Exercise Training

Once a patient is accepted into the program, an individualized exercise prescription is developed based on the patient's existing level of functioning, desired goals, and pre-rehabilitation exercise test results. The exercise prescription will be modified in the course of the rehabilitation program, as the patient's exercise capacity may increase during the course of the program. Pulmonary rehabilitation programs are typically anywhere from 6 to 12 weeks in duration, meeting 3–5 times a week, with each session lasting 2–4 h. Typically, the bulk of each session is dedicated to exercise training with the remaining time for educational, psychosocial, or nutritional counseling.

Exercise is typically done with activities designed to increase the endurance of the lower extremities as they are the main muscles of ambulation. Activities may consist of walking, using the treadmill or elliptical machine, and stationary biking. High-intensity regimens may be superior to low-intensity prescriptions. High-intensity training yields a more demonstrable training effect when compared to low-intensity training [17]. Other papers have confirmed the benefits of high-intensity training on the level of dyspnea at rest, submaximal exercise lactate level, peak VO_2, anaerobic threshold, and 12 min walk distance [70].

On the other hand, there are data showing that low-intensity aerobic exercise may also lead to increased exercise capacity and endurance [71]. Clark et al. showed that low-level exercises targeting peripheral muscle groups in isolation, without high-intensity aerobic activities, can still improve endurance in patients with COPD [72]. Furthermore, there are studies that suggest that a physiologic improvement in exercise capacity is not always necessary to improve health-related quality of life. Puente-Maestu et al. published a study where they looked at 41 COPD patients who were randomized to self-monitored walking for 8 weeks versus supervised treadmill walking for 8 weeks [73]. The goal for self-monitored group was to walk 3–4 miles/day for 4 days a week while the supervised group did physiotherapist-supervised treadmill walking for 60 min a day for 4 days a week. Both groups had similar increases in CRDQ despite a greater increase in physiologic parameters such as the VO_2 max in the supervised group. Normandin et al. demonstrated larger increments in treadmill endurance time, VO_2 max, and dyspnea severity in a high-intensity exercise group when compared to a lower intensity group [74]. Despite this, there was no difference between the improvement seen post-rehabilitation in the health status outcomes as measured by CRDQ and TDI.

Currently, the ideal exercise intensity (or the variable to use to measure intensity) has not been definitively established but several parameters have been used. Among them:

- Target heart rate: (peak heart rate − resting heart rate) × 0.6 [6]
- Target heart rate: 70%–85% found on maximal exercise testing [18]
- Dyspnea: moderate to relatively severe dyspnea on Borg scale [20]
- 75% of peak work rate demonstrated on pre-PR incremental exercise test [75]
- Above anaerobic threshold [76]
- 60%–80% of maximal work attained [69]
- Targeting 20 min on a treadmill [40]
- Borg scale of 3–4 [26]
- Borg score of 4–6 for dyspnea or fatigue [1]

Exercise regimens typically consist of warm-up activities for 5–10 min, aerobic exercise for 25–35 min, and cooldown for 5–10 min. Appropriate rest periods between activities are important. Supplemental oxygen should be used for patients who develop exertional hypoxemia [1] (Figure 54.2). However, there are some data to suggest that prescribing supplemental oxygen during exercise to patients without hypoxemia during exercise may allow patients to exercise at a higher intensity and theoretically obtain a greater training effect. In two separate studies, Casaburi and colleagues demonstrated that patients without hypoxemia exhibited higher work rates and improved exercise endurance when given supplemental oxygen for exercise when compared to similar patients who were not given supplemental oxygen [77,78]. A recent Cochrane analysis concludes that the current clinical evidence "does not provide solid conclusions for oxygen-supplemented exercise training. The evidence at this time indicates that oxygen does little to accentuate the benefit of exercise training" [79]. The latest ACCP/AACVPR guidelines do not recommend routine use of supplemental oxygen during pulmonary rehabilitation in patients without exertional hypoxemia [37].

In addition to lower extremity training, the AACVPR and ATS also recommend upper extremity training (Figure 54.3) targeted to ADL performance and strength training as core components of the exercise prescription [1,37]. Whether inspiratory muscle training during pulmonary rehabilitation is truly beneficial or improves outcomes remains unclear and is not routinely recommended at this point [37].



FIGURE 54.2 Upper extremity exercises are an important part of the exercise component of pulmonary rehabilitation.



FIGURE 54.3 Educational sessions are a core component of pulmonary rehabilitation.



FIGURE 54.4 Supplemental oxygen should be given to patients who have exertional hypoxemia.

Educational Component

The purpose of educational sessions is to increase patient knowledge about their disease, instill self-confidence, and enable as well as empower them through self-management education. Self-management education has been defined as "formalized patient education program aimed at teaching skills needed to carry out medical regimens specific to the disease, guide health behavior change, and provide emotional support for patients to control their disease and live functional lives" [26]. A Cochrane analysis was published in 2009 to objectively assess the value of self-management education programs in COPD [80]. The meta-analysis looked at 14 trials and showed that self-management education reduced the probability of hospital admission and was associated with a small decrease in dyspnea as measured by the Borg scale.

There appears to be no clear benefit of education alone without the exercise component of pulmonary rehabilitation in terms of improving health-related quality of life and exercise capacity. Nevertheless, educational sessions are considered a core component of a comprehensive pulmonary rehabilitation program. These sessions are often done in small groups (4–10 patients) with a pulmonary rehabilitation staff facilitating the session; patient participation is obviously key and very strongly encouraged (Figure 54.4). The topics typically discussed during these sessions may include basic pathophysiology of COPD, proper use of medications and inhalers, how medications and inhalers work, adverse effects of medications, signs of an acute exacerbation and when to seek medical attention (action plan), smoking cessation, breathing strategies, energy conservation, lung irritants and avoidance, normal lung and airway anatomy, vaccinations, end-of-life issues, air travel, secretion clearance, etc. Obviously, this can vary greatly between programs, and should be tailored to suit participant needs. Visual aids such as pictures, slide shows, 3D models of the lungs and airways, and take-home handouts likely facilitate learning.

Psychosocial Component

Psychological disorders, especially anxiety and depression, are fairly common in patients with COPD. It has been reported that the prevalence of depression is anywhere from 10% to 42% while that of anxiety is from 10% to 19% [81]. In a recent retrospective study looking at 35,722 patients with COPD and the same number without COPD, the prevalence of diagnosed depression was higher in the COPD group than in the non-COPD group, 23.1% versus 16.8% [82]. In another study, the prevalence of anxiety (28.2%) and depression (18.8%) in patients with COPD was much higher when compared to healthy subjects [83]. There was no difference in the prevalence of depression and anxiety between patients with mild obstruction and those with very severe obstruction.

A study looking at 121 stable COPD patients showed that 19.8% had moderate to severe depressive symptoms and that the presence of such was a predictor of mortality independent of age, sex, and exercise capacity [84]. Patients with high depressive symptoms had almost twice the risk of dying when compared to low depressive symptoms. In 2007, Paz-Diaz published a small randomized clinical trial looking at 24 patients with severe COPD who were randomized to pulmonary rehabilitation or no pulmonary rehabilitation [85]. The pulmonary rehabilitation sessions were conducted three times per week for 8 weeks. Psychological evaluation was done before and after the study and consisted of the Beck Depression Inventory score and State Trait Anxiety Inventory (STAI) score. In addition to this, dyspnea and health-related quality of life measures were also followed. As expected, patients in the pulmonary rehabilitation group had significant improvements in dyspnea and quality of life. No changes were seen in the control group. Depression and anxiety improved in the pulmonary rehabilitation group but not in the control group. Interestingly, there was no observed correlation between the improvement in dyspnea and improvement in the depression score [85].

Psychosocial intervention includes screening for depression and anxiety, screening for substance abuse, smoking cessation counseling, sessions discussing stress relaxation techniques, encouraging adherence to the prescribed medical regimen, identifying adequate social support and network, and referral to qualified psychiatric professionals if necessary. Working with the patient's family and loved ones and getting them involved will likely lead to better results. In the latest ACCP/AACVPR practice guidelines [37], psychosocial evaluation and support is recommended. As with the educational component of pulmonary rehabilitation, psychosocial support only, without the exercise component, is not recommended and has not been proven to be effective [19].

Nutrition

Poor nutritional status is commonly found in patients with COPD. Sahebjami et al. reported that 23% of their COPD patients were underweight and 24% were overweight [86]. A Spanish study reported that 47% of 177 patients had evidence of muscle wasting [87]. Nutritional depletion is an independent predictor of poor outcome and death [34]. BMI is one of the components of the BODE index, which is a powerful predictor of COPD mortality. Efforts have been made to improve nutritional status in subjects with COPD with the expectation that this will result in improved patient outcomes. A recent Cochrane review by Ferreira et al. evaluated 14 randomized controlled trials that investigated whether caloric supplementation of 2 weeks or more would improve exercise capacity, pulmonary function, and nutritional parameters in patients with COPD. The pooled data show an increase in body weight but no clinically significant improvement in exercise capacity or health-related quality of life [88]. Steiner randomized COPD patients to receive a carbohydrate-rich supplement or a placebo while undergoing a 7 week outpatient pulmonary rehabilitation program [89]. Subjects in both groups had similar improvement in exercise capacity (as measured by shuttle walk tests) and health status (as measured by the CRDQ). In patients with normal nutritional status (BMI > 19 kg/m^2), the increase in the incremental shuttle walk test was greater in the caloric supplementation group than the placebo group.

Nutritional interventions during pulmonary rehabilitation may include educational sessions emphasizing proper diet, maintenance of ideal weight, weight reduction, and formal referral to a nutritionist if a more comprehensive evaluation is deemed necessary. There are insufficient data showing that improving nutritional status with anabolic steroids [90–93], creatine [94], or growth hormone [95] is of benefit.

ONGOING CONTROVERSIES

Maintenance of Benefits

It is well-established that most of the benefits obtained from pulmonary rehabilitation will dissipate with time. For example, Guyatt et al. found that 6 months after a 4–6 week pulmonary rehabilitation program, only 11 of 24 patients had maintained improvements seen in 6MWT and CRDQ [96]. By contrast, patients given a home exercise prescription and access to an exercise therapist maintained 89% of peak exercise capacity [97].

Other studies have had less encouraging results. Ries et al. followed 57 patients who participated in a pulmonary rehabilitation program and reported that the differences between control and intervention groups waned over time [19]. Ketelaars et al. demonstrated that SGRQ scores regressed toward baseline levels 9 months after pulmonary rehabilitation [65]. Vale et al. [98] found that at the mean follow-up time of 11 months, 12 min walk distance declined by 10% and CRDQ worsened by 7%. However, both remained significantly above pre-rehabilitation levels.

Various strategies to maintain benefits accrued from pulmonary rehabilitation have been suggested and include repeat pulmonary rehabilitation, maintenance exercise sessions, home exercise prescriptions, and telephone follow-up/encouragement from rehabilitation personnel. For example, a simple, daily self-monitored walking program after a 7 week pulmonary rehabilitation program was enough to maintain gains in endurance shuttle walk test and SGRQ 6 months after the program but at 12 months a decline in both parameters was already evident [99]. Repeat pulmonary rehabilitation is hampered by the fact that the benefit of the initial program is lost by the time of the repeat program and the gains of subsequent programs are diminished in comparison to the original [100]. The study by Vale et al. [98] mentioned earlier divided the subjects into 19 patients who had post-pulmonary rehabilitation structured maintenance exercise sessions and 32 who did not. The post-pulmonary rehabilitation intervention was a weekly exercise program and was in addition to the prescribed home exercise prescription given to patients after program completion. There was no benefit seen in the

group attending the structured exercise sessions in terms of maintaining the benefits obtained from pulmonary rehabilitation. Ries compared an experimental group that received weekly telephone calls discussing compliance plus a monthly "reinforcement session" consisting of a 60 min educational session, 30 min social session, and a 90 min supervised exercise session compared to referral back to the primary care physician with written instructions for home-based exercise [101]. During the 12 month study period, the experimental group had significantly better 6MWT distance, maximum treadmill workload, and health status as measured by CRDQ while these parameters actually decreased in the nonintervention group. By the second year (2 years after pulmonary rehabilitation and 1 year after the intervention), both groups were close to pre-pulmonary rehabilitation levels. A small randomized controlled study by du Moulin looked at a maintenance program versus usual daily activities [102]. At the end of 6 months, the group receiving the maintenance intervention had superior 6MWT and CRDQ scores.

These studies demonstrate that a specific post-rehabilitation maintenance program that allows patients to maintain the gains from pulmonary rehabilitation beyond 2 years has yet to be developed. However, it appears that potentially successful maintenance programs involve regular contact with clinical staff who provide ongoing education, feedback, and monitoring.

Optimal Duration

The optimal duration of pulmonary rehabilitation is unclear. Programs as short as 3 weeks [102,103] have been shown to improve exercise capacity and health-related quality of life. Sewell published a randomized controlled trial comparing a 4 week program to a 7 week program [104]. In both groups, there were improvements in the incremental shuttle walk test and endurance shuttle walk test as well as the CRDQ at program completion but there was a partial regression toward baseline at 6 months. At 7 weeks and at 6 months, the 7 week pulmonary rehabilitation program did not prove superior in terms of endurance and incremental shuttle walk test results and self-reported CRDQ scores. Rossi compared a 20-session pulmonary rehabilitation program to 10-session program [105]. 6MWT and SGRQ scores were significantly higher in the 20-session group than the 10-session group.

Currently, authorities in the field believe that longer programs are superior to shorter ones. The ACCP and AACVPR state that 6–12 week programs are beneficial (grade 1A recommendation), although programs longer than 12 weeks may result in "greater sustained benefits than shorter programs" (grade 2C recommendation) [37]. The ATS and ERS have made no firm recommendations regarding duration of pulmonary rehabilitation programs but suggest that at least 20 sessions given 3 times/week would be expected to "achieve physiologic benefits" [1]. As with the ACCP/AACVPR guidelines, the ATS/ERS believe that "longer programs yield larger, more endurable training effects" [1].

Mortality Benefit

It is unclear whether the benefit of pulmonary rehabilitation extends to improving mortality in patients with COPD. At this point, there has been no randomized, placebo-controlled clinical trial that has conclusively demonstrated improved mortality with pulmonary rehabilitation. As discussed previously, the BODE index is simple yet powerful prognostic tool for patients with COPD. However, while two of the components of the BODE index are definitely improved with pulmonary rehabilitation (dyspnea and exercise capacity) there has not been conclusive evidence that altering these parameters with pulmonary rehabilitation can actually lead to an extension of life. Currently, given the undeniable alternate benefits of pulmonary rehabilitation, it may be inappropriate to conduct a true prospective, randomized controlled trial with a proper placebo or non-pulmonary rehabilitation arm to further investigate any mortality benefit of pulmonary rehabilitation.

Pulmonary Rehabilitation in Other Chronic Respiratory Conditions

The bulk of the data establishing the efficacy and value of pulmonary rehabilitation has been obtained from patients with COPD. Pulmonary rehabilitation has been used in other chronic lung disorders such as interstitial lung disease [106,107], restrictive lung disease [108], pulmonary arterial hypertension [109–111], lung cancer [112,113], and prior to surgical procedures such as lung cancer resection [114]. The benefits of pulmonary rehabilitation in these disorders are not as well-defined as the benefits seen in patients with COPD.

SUMMARY

Pulmonary rehabilitation has come a long way from being an intervention that was thought to be of dubious efficacy to being one of the standards of care of patients with COPD. The key conceptual breakthrough was rejecting the assumption that patients with COPD could not and should not exercise. This breakthrough was related to the realization that muscle dysfunction is at the very least as important as ventilatory limitation in producing exercise intolerance in COPD patients. There is convincing evidence that patients with COPD have decreased skeletal muscle oxidative capacity and that this abnormality is improved after pulmonary rehabilitation. There are ample scientific and clinical data demonstrating that pulmonary rehabilitation improves exercise capacity, shortness of breath, and health-related quality of life despite not having any beneficial effect on spirometry and oxygenation. Clinical data strongly suggest that health care utilization is decreased in patients who complete pulmonary rehabilitation. Furthermore, comprehensive pulmonary rehabilitation programs address extrapulmonary issues such as poor nutritional status, anxiety, and depression which are common in patients with COPD and have substantial impact on their quality of life. The effect of pulmonary rehabilitation

on mortality is unclear at this point. Although predominantly used for COPD, pulmonary rehabilitation has been used for other chronic respiratory conditions but its benefit in those conditions is less well defined.

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55 Food Allergy and Anaphylaxis

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CONTENTS

Introduction 689
Deciphering Symptoms Related to Food Ingestion 689
Biology of Anaphylaxis 691
Epidemiology of Food Allergy 691
Foods Implicated 692
Natural History of Food Allergy 692
- Cow's Milk Protein Allergy 692
- Egg Allergy 693
- Peanut Allergy 693
- Tree Nut Allergy 693
- Seafood 693
- Soy 693
- Wheat 693

Pollen-Food Syndrome 694
Diagnosis and Management of Food Allergy 694
- Risk Factors 694
- Clinical Symptoms 694
- Brief Testing Overview 694
- Treatment 694
  - Potential Future Therapies 694
  - Prevention of Food Allergy 695
  - Early Life Exposures to Highly Allergenic Foods 695
  - Vitamin D and Food Allergy 695

Conclusion 695
References 695

INTRODUCTION

Food allergy has become an issue of major national and international public health significance. Hospitalizations for food-related anaphylaxis have increased an incredible 350% over the past 10 years [1]. Repercussions of this increasing incidence can be seen almost everywhere. Parents of school-aged children wrestle daily with its implications as they struggle to make "safe" lunches. Schools, restaurants, airlines, food manufacturers, and others have required alterations in their basic functioning in order to cope with the impact of food-related allergies. Public awareness has created exceptional responses to implement protection against food allergies. In many ways, the increasing incidence has impacted lifestyle decisions from infancy through adulthood.

Despite the enormity of the problem, the scientific foundation underlying the understanding of food allergy has not yet provided sufficient support to yield firm diagnostic options and new treatment options. As a result, there is a tremendous amount of erroneous attribution of food allergy risk both by the general public and health care personnel. In addition, without adequate scientific understanding, implemented practices of presumptive avoidance have been widespread.

This chapter discusses the current understanding of food allergy. Initial sections discuss the basic biology of food allergic reactions, focusing on anaphylaxis, the most severe manifestation of food allergy. Diagnosis, management, and prevention are also discussed.

DECIPHERING SYMPTOMS RELATED TO FOOD INGESTION

The prevalence of food allergy has created a heightened awareness regarding food-based reactions. As a result, there is tremendous concern about food allergy and confusion about potential health implications from various experienced food-based symptoms. The term "food allergy" has not been universally defined and has become an umbrella term under which various food-related, though not life-threatening, reactions occur [2].

Self-report of food allergy has grown exponentially over the past decade. One study found self-reported prevalence of

peanut and tree nut allergy to be 1.2% of the U.S. population based on survey data gathered between 1997 and 2002 [3]. A more recent follow-up study found the self-reported incidence of food allergy to be similar among adults. However, a survey performed in 2008 reported that peanut allergy in children more than tripled [4]. While this is an astounding increase, it correlates with similar data from other countries including Canada. A study investigating self-report across more than 10,000 households found incidence of peanut allergy to be around 1% [5]. When combined with the reported rates for other foods, perceived food allergies result in more than 20% of adults and children restricting foods from their diets due to concern for risk of subsequent reactions [6]. This can lead to significant impact on nutrition and wellness. However, when confirmation by allergy testing is implemented, these "prevalence" numbers fall significantly. A recent study demonstrated clear differences between rates of self-reported and confirmed food allergies [5]. Both patients and health care providers often overreported food allergy. The disconnect between perception of and actual food allergies arises for a multitude of reasons.

There are numerous potential effects that can occur after the ingestion of food. Many of these result in uncomfortable symptoms, but do not carry the same severe implications as anaphylaxis. For example, mild food poisoning, lactase deficiency, and reflux can cause uncomfortable symptoms but do not pose a risk for shock. Anaphylaxis is caused by antibody-mediated recognition of food proteins with subsequent activation of immune cells, triggering release of inflammatory mediators. While there are a number of other conditions in the spectrum of food allergy, the remainder of this chapter uses "food allergy" to distinctly reference antibody-mediated reactions potentially giving rise to anaphylaxis. This process is discussed in further detail later in the chapter. Because of this characteristic biologic cascade, the timeline and symptoms of reactions are fairly uniform.

A focused history can quickly provide clear insight into the underlying biologic processes causing a reported reaction. The most critical answer to establish is whether the symptoms portend risk for anaphylaxis with reintroduction of the food. A history of the type of food and the amount ingested should first be ascertained with as much certainty as possible. While this seems obvious, it is often difficult for people to recall specifics. In the case of possible food allergy, specifics are critical [7]. The time course from ingestion of a food to the onset of symptoms must be established. Typically, antibody-mediated reactions occur very quickly—usually within seconds to minutes and, at most, 2 h from ingestion [8]. Food reactions occurring many hours after ingestion suggest other causes. Symptoms of antibody-mediated reactions are very characteristic. Due to a high concentration of causative cells in locations such as the skin, gastrointestinal tracts, and respiratory system, symptoms almost always appear in one or more of these areas. Typical symptoms include flushing, hives, itching/swelling inside the mouth, abdominal cramping, vomiting, diarrhea, wheezing, or other breathing difficulties [8]. Additional systems may be involved, leading to symptoms such as tachycardia, syncope, anxiety, headache, sneezing, congestion, and conjunctival injection [9]. Cutaneous symptoms are exceedingly common in food allergy-related reactions. However, it is important to note that cutaneous symptoms can be absent in 10%–20% of anaphylactic episodes [10]. Anaphylaxis is now "briefly defined" to include two or more of the previously mentioned symptoms documented after allergen exposure. When symptoms are more severe, hypotension can be recorded, providing evidence for shock. This can often be missed in infants and young children [11]. Assessment of blood pressure is crucial as circulatory collapse can occur rapidly, with intravascular volume decreasing by a third within 10 min [12]. For these reasons, it is critical to distinguish allergic reactions from other possibilities.

Emergent treatment is necessary to decrease potential morbidity and mortality. However, allergic symptoms can sometimes be transient, or at other times be overlooked as not being indicative of a systemic reaction. A high index of suspicion must be maintained, especially in a pediatric setting. Only about half of over 450 pediatricians correctly recognized and recommended appropriate treatment for food-induced anaphylaxis in one study [13]. In addition, there can be age-related variation in the presentation of anaphylaxis. In a recent study children under 2 represented the largest proportion of patients presenting to an ED with anaphylaxis over a 6 year period [14]. Symptoms in infants more often included vomiting and hives while wheezing was more commonly seen in older children. This study also found documentation of hypotension in children to be infrequently practiced, which can complicate diagnosis and prevent a diagnosis of anaphylaxis.

Fatal food-induced anaphylaxis is not common, occurring in less than 1% of anaphylactic episodes. There are clear risk factors associated with fatal reactions. Adolescents and young adults represent the majority of fatalities. Peanut and tree nut allergies were the cause of greater than 90% of fatal reactions in one study [15]. Asthma is also a major contributing risk factor. Reactions that were fatal were more commonly associated with respiratory symptoms than with shock [16]. In children and young adults with asthma, food-induced reactions/anaphylaxis may be mistaken for asthma exacerbations. This results in either lack of or delayed use of epinephrine. In one study, only 10% of people who died from food allergy were carrying epinephrine with them [17].

When the history is supportive of food allergy, it is important to conduct appropriate testing to confirm the diagnosis. This allows for identification of specific food allergens, education regarding avoidance, and the prescription of proper medications. Without this evaluation and education, anaphylaxis can occur again, with perhaps more severe repercussions. In addition, given the discrepancies between self-report and actual allergy, investigation of a reaction is necessary to decrease erroneous attribution of food allergy and resultant food removal.

BIOLOGY OF ANAPHYLAXIS

The immune system is designed to provide dynamic, continuously evolving recognition of and responses to potential outside threats. Thus, there is literally continuous surveillance and assessment of various exposures. Antibodies are proteins designed to recognize specific potential danger and act as a bridge between identification and response. Understanding this mechanism is key to understanding the clinical features of food allergy. The distribution of cells involved leads to systemic reactions that occur quickly and diffusely. In addition, the biological mechanism of food allergy that leads to a process of testing can help identify those at risk for possible food induced anaphylaxis.

There are four major categories of antibodies: IgG, IgA, IgM, and IgE. Each one varies in major qualities such as tissue distribution, half-life, and, most importantly, downstream response. IgE is the central antibody in the allergic response. B cells are responsible for generation of antibodies. These B cells can alter the types of antibodies they produce based on external factors allowing them to "switch" from IgG to IgE, for example. External factors promoting this type of switch originate from various other cells including T cells, basophils, and mast cells. Cytokines including IL-4 and IL-13 provide potent induction and amplification of IgE production by B cells [18]. The tendency to shift B cell production toward IgE antibodies results in a higher likelihood for allergy.

Cytokines can have powerful influence over B cells and their increased concentration and resultant signaling produces greater risk for anaphylaxis. Receptors for these cytokines are distributed widely, creating the potential for systemic reactions to allergic stimuli. In a mouse model, increased signaling through the IL-4 receptor can cause both increased specific IgE production to ingested proteins and simultaneously increase the risk of anaphylaxis from the same protein [19]. Thus, high levels of these cytokines predispose the immune system to elevated levels of IgE and resultant escalated risk for allergy. Certain IL-4 genetic polymorphisms have been associated with increased risk of food allergy [20].

As with all antibodies, IgE contains both constant and variable structural components. The variable region confers specificity by recognizing only very specific genetic sequences of a protein. The antibody can bind to these peptides and generate responses entirely as the result of recognition of this food. Thus, the variable portion of the antibody allows diversity in recognition and surveillance. On the other hand, the constant component of the IgE antibody promotes the immune system response after recognition of the allergen. The constant portion of the antibody provides its capability to elicit reactions from other cells. For IgE, its constant portion is recognized by a specific receptor on effector cells such as the mast cell, referred to as the Fcε receptor I or the high-affinity IgE receptor. Given this high affinity, IgE will bind to this receptor at concentrations that are miniscule. This allows a high proportion of IgE to be bound to this receptor, despite very low serum concentrations [21].

Mast cells can be found in numerous tissues throughout the body, but are specifically concentrated in skin, lung alveoli, and the mucosal surfaces of both the intestine and the eye. Their easily identified granules contain preformed mediators responsible for the bulk of symptoms characteristic of allergic reactions [22]. These cells are literally covered with IgE receptors. When multiple IgE antibody-food antigen complexes interact with these receptors, they become "cross linked" and will cluster geographically on the cell surface. This is a critical event required to perpetuate an allergic reaction. The Fcε receptors are tethered to multiple proteins inside the mast cell. When these receptors congregate, the intracellular machinery is dragged along as well, increasing protein interactions, resulting in higher intensity downstream signaling [23]. Early repercussions of this signaling include the hallmark of allergic reactions—release of preformed mediators contained within mast cells. Clinical symptoms occur very quickly in that situation because the mediators being released are preformed.

Histamine is the most important of the preformed mast cell mediators. It strongly promotes vasodilation, increases vascular permeability, bronchial smooth muscle contraction, and bronchoconstriction [24]. These biological responses form the hallmarks of allergic reactions and anaphylaxis. Other preformed mediators include tryptase, platelet-activating factor, and several more than may have various roles in both allergy and other mast cell functions. In summary, IgE antibodies loaded with food-related antigens bind their high affinity IgE receptor on mast cells. The result is an orchestrated intracellular response leading to rapid degranulation of cellular contents with resultant reactions driven largely by histamine. Clinically, this leads to the symptoms previously described in diverse locations such as the eye, nose, skin, airways, and intestines. Shock may occur due to histamine release and decreased intravascular volume.

EPIDEMIOLOGY OF FOOD ALLERGY

The number of people with food allergy seems to be escalating substantially. Determining a true national prevalence is difficult due to several factors including excessive self-reporting and a lack of established definition and criteria for diagnosis of food allergy. Recently, more than 8000 participants from 30 sites across the United States took part in the National Health and Nutrition Examination Survey. Part of the survey was testing for several common food allergies. This study demonstrated an estimated food allergy prevalence of 2.5%. Notably, the prevalence was clearly higher in children under 5 years (4.2%) and decreased with age [25]. This estimate of food allergy closely correlates with other recent findings. The CDC/NCHS published a brief in 2008 suggesting 4 out of 100 children have food allergy. Hospital discharges for children with food allergic reactions were almost four times greater from 2004 to 2006 than from 1998 to 2000 [26].

Food allergy does appear to carry some genetic susceptibility, although this has only been shown for certain foods.

For example, a child with a parent or a sibling with peanut allergy has a sevenfold risk of experiencing the same [27]. Certain polymorphisms have been shown to be correlated with food allergy. Genetic variations have been demonstrated in genes coding for various aspects of the immune response. Typically, the immune system generates a "tolerant" response to most ingested foods. Indeed, the acquisition of tolerance itself is not well studied or understood. Complex interactions within the gastrointestinal tract are likely responsible for inducing food-related tolerance. There are many aspects of these processes that are implicated in development of food allergy. These include a wide spectrum of possibilities including barrier dysfunction, variations in food allergen processing, alterations in immune cells that function to regulate the larger immune response, and many others [28].

The surrounding environment exerts enormous influence over immune system effects. Environmental influences clearly seem to play a role in the development of food allergy. Dr. David Strachan initially proposed the so-called hygiene hypothesis in 1989, based on his study documenting lower incidence of allergic rhinitis with increasing numbers of siblings [29]. In the intervening time, this hypothesis has generated tremendous controversy. However, several studies have demonstrated findings consistent with its general principle. A European study demonstrated variable food allergen sensitization patterns between children who lived on farms compared to those who do not [30]. Studies have generally placed the "hygiene hypothesis" in context with atopic dermatitis. However, several international experts have pointed out that food allergy frequently follows atopic dermatitis. Thus, these results may have some indirect importance relative to the development of food allergy [31].

FOODS IMPLICATED

Geography and culture exert major influences on the inciting foods most often implicated in allergic reactions. Therefore, worldwide variation exists with regard to most common food allergies. In the United States, a group of nine foods is largely responsible for IgE-mediated food allergy. In descending order of incidence, these include milk, egg, peanut, tree nuts, wheat, soy, fish, shellfish, and sesame. While it should be clearly stated that any food protein can cause an allergic reaction, these food proteins seem to be more likely to do so than others. These foods share particular structural characteristics that influence their allergenicity. Most are water soluble glycoproteins, essentially similar in size, and retain stable structure despite potentially degrading exposures including acid, heat, and proteases [32]. The ability to retain 3D structures in the face of these processes has been shown to be a major contributing factor for a food allergen's capacity to elicit reactions [33].

However, there is also evidence that food preparation contributes to increased allergenicity. This provides some explanation to the geographic variation in food allergies for foods eaten worldwide. As mentioned previously, heating of food proteins may generate structural alterations that can either accentuate or mitigate allergenic potential. Antibodies recognize very particular regions called epitopes in any given protein. Certain food protein's ability to bind with IgE antibodies requires a particular 3D arrangement of these epitopes. These are often referred to as "conformational epitopes" given the requirement of the underlying folded structure for antibody binding. Protein folding allows for optimal epitope arrangement which increases antibody-binding efficacy. Processes such as heating that undermine this 3D structure can lead to reduction in allergen potential. For example, ovalbumin, the major egg protein allergen, is quite sensitive to structural changes via heating [34]. In one study, 70% of children with known egg allergy tolerated extensively heated egg [35]. This is in contrast to epitopes that are more sequential and referred to as "linear" epitopes. This essentially literal description suggests that these antigens are much more resistant to various processes that can affect protein degradation. In turn, this has an effect on the allergenicity of the protein. For example, children with IgE antibodies specific for sequential epitopes of the major egg proteins seem to have more persistent allergy [36].

However, heating the major allergen in peanut does not change its ability to bind IgE [37]. In addition, certain forms of heating, such as roasting, lead to specific biochemical changes in the peanut protein that cause it to bind more IgE and, in turn, become more allergenic [38]. This may explain the persistence of peanut allergy over time. It also suggests a basis for the variable geographic predominance of peanut allergy. In China, where peanut allergy is not very common, cooking peanuts is generally done via frying or boiling. Peanut protein cooked via these methods binds much less IgE antibody than roasted peanut, the most common method of preparation in the United States [39].

In the United States, a relatively small group of foods is responsible for the majority of IgE-mediated reactions. These foods are widely consumed and share molecular characteristics making them more likely to elicit allergic responses. However, there are clear differences among these foods in terms of natural history. It is critical to consider this in evaluation of patients.

NATURAL HISTORY OF FOOD ALLERGY

Specific foods seem to exhibit characteristic ages of onset and potential for resolution. These variable features were previously unexplained. However, with improved understanding of food allergy, some of the explanations for these features are being identified.

Cow's Milk Protein Allergy

Milk protein allergy is the most common food allergy in children. It has an incidence of approximately 2.5%. There are various manifestations of milk protein allergy including non-IgE-mediated entities such as food protein-induced enterocolitis. One study found that only half of children with milk protein allergy have IgE-mediated mechanisms responsible

for their symptoms [40]. Milk protein allergy has a very early age of onset. The vast majority of milk protein allergy occurs in the first year of life. Despite this early onset, milk allergy rarely persists. The vast majority of children with this allergy will have resolution by their fifth birthday [41]. However, there does appear to be a trend toward longer persistence of this allergy. In a recent study of more than 800 children with cow's milk allergy, only about 40% had achieved measurable tolerance by age 8 and nearly 80% by age 16. It may be that rising rates of general atopy contribute to this trend [42]. Children with higher IgE levels and other coincident atopic conditions seemed to retain the allergy longer. In addition, children who recovered sooner seemed to have more prevalent "blocking antibodies" that prevented IgE from binding to milk protein allergens [43]. Retesting children with milk allergy is critical in their overall management.

Egg Allergy

Egg protein allergy occurs in about 1.6% of children. However, children with other allergic conditions are much more likely to have egg allergy as well. Like milk allergy, egg allergy is typically outgrown, though the age of resolution seems to be trending later. Children who are diagnosed at a younger age and with less severe presenting symptoms seem to experience egg allergy over a shorter duration [44]. Two major egg allergens—ovalbumin and ovomucoid—respond very differently to heating. Ovalbumin is significantly degraded with high heat while ovomucoid structure is retained in similar conditions, rendering it a more stable allergen (Joo et al. 2006). Due to this stability, children with IgE antibodies to ovomucoid tend to exhibit longer term, "retained" allergy to egg [35].

Peanut Allergy

Peanut allergy has been largely responsible for the sharp increase in public awareness of food allergies in general. Over a very short period of time, the incidence of this allergy seems to have escalated substantially. At the present time, the incidence of peanut allergy is 0.6% of the general population within the United States. However, self-reported peanut allergy in children nearly doubled between 1997 and 2002 [3]. This has had enormous impact on public health measures, perhaps more than any other food.

Reactions to peanuts in people with known peanut allergy constitute the greatest risk for mortality due to food-related anaphylaxis according to one study [17]. Peanut was the identified cause of food-related deaths in 17 out of 32 cases. The vast majority of these people also had coincident asthma. Thus, peanut allergy has received tremendous attention both for its sharp increase in incidence and also for its potential lethality. Even small amounts of peanut protein can cause severe reactions. Exposure to the equivalent of one peanut kernel has resulted in significant symptoms in persons of widely distributed ages [45]. In contrast to both egg and milk allergy, peanut allergy is largely believed to be persistent throughout life. However, it seems that children diagnosed before 2 years of age have nearly a 20% likelihood of outgrowing the allergy [46]. Follow-up testing has a role in children diagnosed early in life.

Tree Nut Allergy

Tree nuts are the second most common food causing food allergy-based mortality [17]. Currently, the incidence of tree nut allergy is approximately 0.5% of the U.S. population. Tree nuts are generally lumped together in one general category. Typical nuts included in this category include almond, Brazil nut, cashew, hazelnut, macadamia, pecan, pine nut, pistachio, and walnut [47]. In general, there seems to be about a 35% cross-reactivity rate among tree nuts [32].

Only approximately 9% of patients with tree nut allergy will experience resolution of symptoms [47]. As with peanut allergy, it is important to consider follow-up testing in patients who have been diagnosed with this allergy.

Seafood

Seafood allergy exhibits a slightly different pattern of onset than the previously mentioned food allergies. In general, seafood allergy is an adult-onset allergy, with an incidence of 0.6% for children compared to nearly 3% in adults [48]. The most common foods implicated are crustaceans including crab, shrimp, and lobster.

It is important to make a distinction between shellfish and finfish because the major allergenic proteins are quite different. The major allergenic protein in most shellfish is tropomyosin, whereas parvalbumin is the major allergen in finfish. There has not been documented cross-reactivity between the allergens in these two groups. Because of this, the term "seafood allergy" should not generally be used as a clinical diagnosis. There may be cross-reactivity between the major groups constituting shellfish, specifically crustaceans and mollusks. Therefore, patients with crustacean allergy may also experience reactions to mussels, squid, clams, scallops, oysters [49]. The incidence of allergies to both groups of seafood may continue to rise as seafood ingestion increases due to its general health benefits [50].

Soy

Soy is one of the more common foods introduced in early childhood. Soy is also a prevalent food additive, making its proteins difficult to avoid [51]. Soy allergy is present in about 0.4% of children. The majority of children with this allergy will become tolerant over time. A retrospective study of 133 children with soy allergy documented a 70% resolution rate by 10 years of age. Higher soy-specific IgE levels at diagnosis correlate with longer lasting allergy [52].

Wheat

IgE-mediated wheat allergy (to be distinguished from gluten sensitivity) is quite common, especially in childhood, occurring in about 0.4%–1.0% of children [53]. In the largest

study published to date of children with wheat allergy, the median age at resolution for wheat allergy was 6½ years of age. Therefore, this seems to be an allergy that is transient, with acquisition of tolerance occurring in most allergic children over time. As with other food allergies, higher IgE levels portend a longer time course to resolution [54].

POLLEN-FOOD SYNDROME

A subgroup of IgE-mediated food reactions results in local symptoms of itching and tingling of the mouth and throat and potential swelling of the lips and tongue [55]. Unlike reactions from the foods mentioned previously, pollen-food syndrome reactions tend not to involve additional systemic symptoms, though almost 2% of people can experience anaphylaxis [56]. Pollen-food syndrome typically occurs in the context of coincident pollen-derived nasal allergies. Allergic rhinitis is caused by IgE antibodies directed against certain pollen proteins resulting in mucosal mast cell degranulation and symptoms consistent with rhinitis. This pollen-directed IgE antibody can also recognize proteins in certain fruits and vegetables because of their genetic similarities to the pollens involved. The result is local symptoms in the oropharyngeal mucosa with ingestion of these foods. Classic cross reactivity occurs between birch pollen and many pitted fruits including apples, cherries, and apricots [55].

DIAGNOSIS AND MANAGEMENT OF FOOD ALLERGY

Risk Factors

The presence of other allergic diseases increases the risk that a particular patient has IgE-mediated food allergy. A detailed family history will often evidence atopy [7]. For example, atopic dermatitis is a major risk factor for development of food allergy, particularly to egg, milk, and peanut. In infancy, IgE to these foods can be demonstrated to be coincident with the presence of atopic dermatitis [57]. In one study, over 80% of children with peanut allergy also had atopic dermatitis [58].

Additional risk factors are important to consider. This includes increased incidence of peanut allergy for children living in homes with high consumption of peanut [59]. Vitamin D deficiency has also been linked to food allergy, thus geographic location may also predispose to food allergies [60].

Clinical Symptoms

The symptoms of food allergy are the symptoms that comprise anaphylaxis. These occur on a spectrum, ranging from mild cutaneous symptoms to overt shock and respiratory failure [7]. The timeline is critical in identifying whether the symptoms correlate with a food exposure because IgE-mediated symptoms occur within minutes to hours after ingestion the food. It is important to distinguish irritant and sensitivity reactions from possible IgE-mediated reactions. Testing is critical in making this distinction.

Brief Testing Overview

A thorough description of food allergy testing is beyond the scope of this chapter. It is briefly reviewed here in an effort to highlight inherent challenges in interpretation. All testing involves identifying the presence of IgE to a particular antigen. This can be done in two ways—skin testing and serum-specific IgE testing. However false-positives occur 50% of the time with both of these tests [61]. Therefore testing must be used in conjunction with a clinically relevant history. In the absence of such a history, the diagnosis becomes more difficult. Age and food variations make the interpretation of serum allergy testing particularly difficult [62].

The gold standard for demonstrating food allergy is an oral food challenge. In a recent pediatric study, over 80% of foods restricted based on IgE testing were able to be reintroduced after negative oral food challenge [63]. These challenges are time consuming and require close observation. They are most appropriately done in a setting where there are personnel trained in the process and management of reactions. There are other tests currently in development that may help increase the specificity of clinic based testing.

Treatment

Restriction of potentially allergenic foods is the most commonly implemented treatment strategy for IgE-mediated food allergy. The efficacy of this strategy has not been proven in randomized controlled studies [2]. Still this approach is sensible given the current shortcomings associated with allergy testing [7]. Patients and their families must be educated about techniques for identifying allergenic foods. This includes reading labels, inquiring about unknown ingredients, and other strategies.

Each patient who has food allergy should have an anaphylaxis action plan. Prescription of injectable epinephrine is critical for patients who may be at risk for anaphylaxis. Delay in epinephrine administration is one of the major contributing factors in food allergy related deaths [17]. A recent study indicated that two doses of epinephrine may be needed to treat food-related anaphylaxis [64]. Therefore patients should be provided with more than one dose to administer in the event of anaphylaxis. Excellent online resources are available for patients, families and providers to be educated about these critical management strategies (Food Allergy and Anaphylaxis Network http://www.faan.org).

Potential Future Therapies

Given the increasing incidence of food allergy, there are diverse potential interventions being pursued for modification of this risk. Food allergies may be treated via introduction of increasing amounts of the allergenic foods over time in a supervised setting. This has been demonstrated to be effective therapy for peanut allergy in recent studies [65].

Several interesting studies have identified a particular Chinese herbal medicine formulation that seems to provide complete protection against food-induced anaphylaxis in animal models [66].

Probiotics have become a potential consideration for treatment of many conditions. At the present time, support for treatment in allergy is conflicting. The literature regarding their usefulness in food allergy is unclear [67]. It is impossible to make strong recommendations regarding the use of these agents because potential probiotics are so vast in number and clinical populations vary much significantly [68].

Prevention of Food Allergy

The prevention of food allergy has received a great deal of attention, but robust evidence to support clear recommendations is lacking. However, there do seem to be some emerging data that allow for lifestyle modifications that may be potentially beneficial.

Early Life Exposures to Highly Allergenic Foods

The recently published expert panel on the management of food allergies does not recommend maternal dietary restrictions during either pregnancy or breastfeeding [7]. Available data are inconclusive with regard to whether early food exposures can either protect against or promote the development of food allergy. One study demonstrated that maternal consumption of peanut during pregnancy correlated with a higher likelihood of peanut specific IgE found in infants [69]. Other studies have shown no relationship between in utero or early exposures to allergenic foods and risk of food allergy [70]. These contradictory results highlight the lack of any consensus upon which to advise families on food allergy prevention.

Our understanding of cutaneous exposure as a risk for food allergy is slightly more clear. It has been shown that topical application of oils containing peanut protein can predispose children to risk of peanut allergy. Eczema is a risk factor for development of food allergy, likely attributable to increased use of emollients generally and perhaps to compromised skin barrier function [71]. One study demonstrated a clear increase in sensitization to peanut among infants living in homes where high levels of peanut protein were consumed [59]. The authors speculated that cutaneous exposure may also occur via accidental topical contact within the household. While the data are not entirely clear at this time, it may be reasonable to counsel complete household restriction of peanuts for families at high risk.

Vitamin D and Food Allergy

Vitamin D deficiency has become another topic of immense public health interest worldwide. There is an unmistakable correlation between the timing of increased incidence of allergic diseases and vitamin D deficiency. With regard to food allergy, it was demonstrated that prescriptions for self-injected epinephrine occurred with a "north-south gradient" in the United States. This relationship endured extensive multivariate analysis. The authors proposed a potential relationship between vitamin D deficiency and food allergy [72]. Subsequent studies have similar findings. Children born during the fall and winter months in Boston were found to have more than 50% higher odds of having food allergy compared to children born in spring or summer [73]. A possible molecular basis for the relationship between allergic disease and vitamin D deficiency was recently published. Calcitriol, the most active form of vitamin D, repressed the production of IgE via regulation at the gene level [74]. A full review of vitamin D and food allergy is beyond the scope of this chapter, but an excellent summary has been published [74].

CONCLUSION

Food allergy is a major public health issue due to a sharply increased incidence and a huge effect on school and business operations. The ramifications of these can be felt from individual homes all the way up to major institutions. Fortunately we now understand the mechanism and pathogenesis of food allergy much better than even a few years ago. While we remain in the early stages of this process, exciting new possibilities will influence diagnosis and management in the future. However the importance of an accurate clinical history remains at the forefront of diagnosing allergic disease. Future research will likely yield improved diagnostic aids to supplement the history and better therapies that improve quality of life for food allergy patients.

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56 Influenza

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CONTENTS

Definition 699
History of Influenza 699
Virology of Influenza Virus 699
Genetic Variation 700
Epidemiology of Influenza 700
Economic Impact 701
Pathophysiology of Influenza 701
Clinical Illness 702
  Seasonal Influenza 702
  Avian Influenza 702
Laboratory Diagnosis of Influenza 703
Prevention 703
  Vaccination 704
  Chemoprophylaxis 704
    Self-Care for Persons with Influenza 704
Antiviral Therapy 705
Summary 706
References 706

DEFINITION

Influenza is a contagious acute illness of the respiratory tract. The etiologic agent is the influenza virus. This common disease is the source of significant illness in the general population and can lead to death, especially in persons at "high risk" for complications of influenza.

HISTORY OF INFLUENZA

The name "influenza" is derived from the Italian, and arose from the notion that the disease was due to the "influence" of the stars. Clinical illness due to influenza virus has had many names over the years, including the "grippe" and epidemic catarrh. Influenza is commonly called "the flu"; however, the term "flu" is also frequently used by the general public for other acute febrile illnesses. Acute gastrointestinal illnesses are often referred to as the "stomach flu" despite the fact that they have no association with the influenza virus. Major influenza epidemics have occurred since at least the middle ages, but may have also occurred in earlier times. The high attack rate, the nature of the epidemic curve, and the characteristic of frequent cough allow the identification of past epidemics. The first influenza epidemic generally agreed upon by medical historians took place in 1580, originating in Asia, spreading across Europe over a period of 6 months and eventually reaching the American continent.[1]

VIROLOGY OF INFLUENZA VIRUS

Influenza viruses are members of the family *Orthomyxoviridae*. There are three types of influenza virus: influenza A, influenza B, and influenza C. Influenza viruses have been divided into these three types on the basis of major antigenic differences in the nucleoprotein (NP) and matrix (M) protein antigens. Influenza A viruses are the most virulent of the three influenza viruses and are the etiologic agents of all known influenza pandemics. Influenza B virus tends to cause milder disease than influenza A.[2] Influenza C virus causes infection in humans only infrequently, and its pattern of infection follows no seasonal variation. All three types of virus exhibit a host-cell-derived lipid envelope and a genome of segmented, negative sense single-stranded RNA. Influenza viral particles are variable in shape, from irregular spheres that measure 80–120 nm in diameter to long filamentous particles. Only influenza A viruses are subtyped. Influenza A is subtyped on the basis of two major surface proteins, neuraminidase (NA) and hemagglutinin (HA). These surface proteins project like spikes, densely covering the surface of the virus, and are important for cell entry. One additional protein, membrane protein M2, is also present in small amounts on the viral envelope. Influenza A viruses are named for their HA and NA surface proteins, for example, a virus called H3N2 will contain HA type 3 and NA type 2. In addition to subtype, influenza A viruses are further characterized on the

basis of the place and time that the virus was first isolated (i.e., A/California/7/2009) (H1N1).

At least 16 antigenically distinct HAs and nine distinct NAs have been described in influenza A viruses. However, viruses that lead to human infection generally contain one of the three most common antigenic subtypes of HA (either H1, H2, or H3) and one of the two most common subtypes of NA (N1 or N2). More recently, H5 and H7 and H9 influenza viruses have been found to infect humans, though sustained human-to-human transmission of these viruses has not been seen.

All influenza viruses are capable of infecting humans. Influenza A viruses are capable of infecting many animal species as well, including swine, horses, marine, mammals, and birds. Wild birds, particularly aquatic birds, are the natural hosts of influenza A virus. Influenza viruses of low pathogenicity do not necessarily lead to clinical illness in the birds they infect, but viruses that cause severe disease and death in birds do exist (e.g., H5N1). The isolation of influenza virus from ferrets in the laboratory took place in 1933 and ferrets continue to be the ideal animal model for the study of influenza. Virus culture in embryonated hen eggs was accomplished in 1936. These advancements allowed the study of virus properties and led to the development of vaccines in the 1940s. Animal cell cultures systems for propagating virus in tissue culture were developed in the 1950s.

GENETIC VARIATION

Influenza viruses are constantly changing their antigenicity. This evolution of influenza viruses is characterized on the basis of the two primary mechanisms by which this genetic variation occurs, antigenic drift and antigenic shift. All influenza viruses (A, B, and C) undergo antigenic drift. Only influenza A virus undergoes antigenic shift. Antigenic drift occurs continuously due to point mutations in the NA gene or (more commonly) the HA gene, both of which code for viral surface proteins. These mutations occur frequently, as the RNA polymerase of the influenza virus has relatively low fidelity and lacks proofreading capacity. Minor changes in the surface proteins occur due to these mutations and lead to what is known as antigenic drift. These antigenic changes lead to virus variants that a previously immune host could now be susceptible to, allowing for new outbreaks of disease. Antigenic shift in influenza A virus occurs in one of two ways. It occurs when reassortment of genome segments takes place between at least two strains of influenza A (usually a human and an animal strain) to produce a new influenza subtype. This reassortment can take place when a cell is infected with two (or more) different strains of influenza virus. Antigenic shift can also occur by direct spread of an animal strain of influenza (usually an avian strain) to a human. An example of this is the H5N1 "bird flu" which continues to cause sporadic human infection in Egypt and Asia.[3] Pandemic influenza can occur after antigenic shift, when a new strain of the flu emerges to which little or no immunity is present in the population.

EPIDEMIOLOGY OF INFLUENZA

It is estimated that 5%–20% of persons in the United States are infected with an influenza virus each year.[4] Influenza constitutes an epidemic when there is an outbreak in a particular location. Outbreaks are detected by monitoring patient visits for influenza like illness, and by surveillance of tests results that are ordered for the specific characterization of influenza like illness. The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have collaborating laboratories for the purpose of influenza surveillance, viral detection, viral isolation, and characterization. Internet search engine queries for influenza have also been shown to be reliable markers of epidemics in a community when they show a rapid increase in frequency.[5] In temperate climates, epidemics of influenza occur most commonly in the winter months. In the Northern Hemisphere, seasonal epidemics of influenza typically occur between late fall and early spring. Influenza epidemics often begin abruptly, reach a peak over several weeks, and last for 2–3 months. In general, 10%–20% of the population will become infected during an outbreak. A major factor in the extent of the population that will become infected in an outbreak is the level of immunity in the population. The major determinant of immunity is the presence of neutralizing antibody to the HA glycoprotein on the surface of the virus. Children have the highest incidence of infection overall. Adults over the age of 65, children younger than 2 years of age, and persons with certain underlying health problems are the most likely to suffer serious consequences of influenza virus infection, including death. Estimates by the CDC suggest that 36,000 people in the United States die each year as a result of influenza virus infection and about a quarter of a million persons are hospitalized.[6]

Pandemics often occur outside the usual influenza season. On average, there have been five pandemics in each century that have been documented in written history. The WHO defines an influenza pandemic as an animal or human-animal reassortant virus causing sustained person-to-person spread which leads to community outbreaks in two or more countries in one WHO region and an outbreak of the same virus in at least one other WHO region. Most pandemic viruses have been due to human-animal reassortant viruses. Well-characterized pandemic influenza viruses from the past century include the 1918 H1N1 "Spanish Flu," H2N2 "Avian Flu" in 1957, the H3N2 "Hong Kong Flu" in 1968, and the latest pandemic, 2009 novel H1N1. The "Spanish Flu" pandemic in 1918–1919 had the largest human impact of any recorded influenza epidemic and is without a doubt one of the more dramatic events of recorded medical history. Although given the name "Spanish Flu," the first known outbreaks of 1918–1919 pandemic influenza were seen in military camps in the United States. This pandemic is estimated to have caused more than 20 million deaths worldwide, more deaths than occurred due to combat in World War I. It is estimated that 25% of people living in the United States and a fifth of the world's population were

infected during this pandemic. The brunt of this excess mortality was dealt to young people, with most deaths occurring in the 20- to 40-year-old age group. In a typical influenza epidemic, 0.1% of individuals who become infected will suffer mortality. The death rate of those who became infected with influenza virus in the 1918–1919 epidemic was 2.5%.[7] It is estimated that half of the deaths among American servicemen in World War I were due to influenza, as compared to deaths due to battle injuries.

The most recent influenza pandemic began in February 2009 with an outbreak in Mexico.[8] In early April 2009 the Mexican government began investigating increased numbers of influenza like illness and informed the Pan American Health Organization of a possible outbreak. Almost simultaneously, ongoing enhanced surveillance for Influenza A viruses that could not be subtyped, being conducted under the auspices of the CDC, identified a novel influenza virus in two patients in southern California.[9] This virus was characterized as a triple reassortant virus containing six genes from previously circulating North American swine viruses as well as two genes of Eurasian avian-like swine virus origin. The two index cases of 2009 H1N1 identified in California were epidemiologically unlinked children, neither of which had had contact with swine. By May 5, 2009, cases of 2009 H1N1 had been identified in 41 states. Many local outbreaks were related to school groups and other travelers returning to the United States from vacation travel to Mexico. By May 25, 2009, this pandemic virus H1N1 had spread to 43 countries, and 12,515 cases had been identified along with 91 deaths. The geographic spread of virus was unprecedented, covering in 6 weeks time what had taken a 6 month period of time in previous pandemics.[10] The CDC estimates that approximately 61 million persons in the United States were infected during this latest pandemic; approximately 265,000 people required hospitalization and 12,000 deaths occurred between April 2009 and February 2010. The virus preferentially infected younger people (i.e., under 25 years of age), most likely due to cross-protective antibodies in older persons who may have been exposed to antigenically related influenza viruses earlier in life.

Although most infections with 2009 H1N1 were mild, severe and fatal respiratory illness occurred in young, otherwise healthy individuals.[11] Medical conditions such as chronic cardiac or pulmonary disease traditionally associated with an increased risk of complications after infection with seasonal influenza were also risk factors for complications from 2009 H1N1 virus infection. Nonetheless, approximately 25%–50% of patients who were hospitalized or died due to infection with 2009 H1N1 had no reported coexisting medical conditions. Ninety percent of deaths due to 2009 H1N1 infection took place in persons less than 65 years of age. Hospitalization rates were highest for children less than 5 years old, and up to 45% of patients hospitalized with 2009 H1N1 were less than 18 years old. Pregnant women were at particularly high risk, accounting for up to 10% of persons who were hospitalized or who died from 2009 H1N1, even though they represent only 1%–2% of the general population. Spontaneous abortion, preterm labor and birth, and fetal distress were also associated with 2009 H1N1 infection. Metabolic syndrome and obesity, which had not been identified as risk factors in previous pandemics or with seasonal influenza, are also associated with the development of severe disease due to 2009 H1N1 virus. Indigenous peoples of North America and the Australasia-Pacific region were also disproportionately affected by 2009 H1N1.

ECONOMIC IMPACT

The CDC has estimated that direct medical costs due to influenza in the United States amount to approximately 10.4 billion dollars annually (2003 values).[12] Direct medical costs only make up a fraction of the economic consequences of influenza though a typical case of influenza is associated with 3 days lost from work or school.[13] Total lost earnings due to illness with influenza virus are estimated to be 16.4 billion dollars yearly. Yearly economic burden of influenza virus to the U.S. economy has been estimated at 87 billion dollars.

PATHOPHYSIOLOGY OF INFLUENZA

The predominant means of spread of influenza virus is from an infected person to a susceptible host at a distance of 6 ft or less.[14] Large (≥5 μm diameter) respiratory droplets are disseminated when an infected person coughs or sneezes. Transmission by aerosolized virus that can travel long distances can occur but is not a common method of viral spread and is not of great clinical significance. Although influenza virus can also be transmitted via hands contaminated with respiratory secretions or by fomites, the virus degrades quickly on human hands (within 5 min) and so this route probably plays a minimal role in spread of infection.[15] Once virus is deposited on respiratory epithelium, it attaches to columnar epithelial cells through interaction of the viral HA glycoprotein with sialic acid residues on host-cell receptors and penetrates via endocytosis. Virus replicates within the cells of the respiratory tract within 4 h. Cell death in infected cells takes place due to both direct necrosis and apoptosis. Dead and dying cells will then release virus that will then infect adjacent cells. The incubation period of influenza is 1–4 days (average 2 days), depending on viral inoculum, with more rapid onset of illness after a heavy viral exposure. Adults infected with influenza virus are able to spread the infection via viral shedding beginning about 1 day prior to the onset of symptoms and for 5–10 days after onset, but the heaviest period of viral shedding is the first 3–4 days of illness. Children may shed virus for a longer period of time, including for several days prior to the onset of illness, probably due to a relative lack of immunity. Among patients infected with the 2009 H1N1 virus viral shedding in intubated patients with viral pneumonia has been detected at higher levels and for longer periods in the lower respiratory in comparison to the upper respiratory tract.[16] Immunocompromised persons can shed virus for months.

CLINICAL ILLNESS

Seasonal Influenza

Influenza virus infection usually presents with the abrupt onset of fever, headache, malaise, myalgias, sore throat, rhinitis, and cough. Illness in children also commonly includes nausea and vomiting along with otitis media, but these had not been seen commonly in adults. However, some reports suggest that infection with 2009 H1N1 may be associated with an increased incidence (up to 25% of infected persons) of nausea, vomiting, and diarrhea, and less rhinorrhea and pharyngitis when compared to seasonal influenza.[16,17] Mild illness without fever, similar to that seen with a common cold, can also occur after influenza virus infection. The incubation period is generally 1–2 days. The duration of illness ranges from 3 to 7 days, though cough may persist for weeks.

Respiratory infection due to influenza virus is difficult to diagnose based on clinical symptoms alone, although systemic symptoms are generally more severe than those found with clinical infection due to other respiratory viruses. The likelihood that a respiratory illness is due to influenza virus will depend in part on whether influenza is currently circulating in the community. On physical examination, the patients may look acutely ill. Although sore throat is common, the pharynx is not usually injected and purulence over the tonsils is uncommon. Mild cervical lymphadenopathy is sometimes found. Lungs are generally clear on auscultation although rhonchi, wheezes, and rales can be found if pneumonia is present.

Pneumonia can occur due to direct viral infection of the lower airway or due to secondary bacterial infection. Viral pneumonia due to seasonal influenza is uncommon but may be quite severe. A common presentation of this entity is the typical onset of clinical disease due to influenza, followed by rapid onset of shortness of breath and cyanosis. Primary viral pneumonia may occur more commonly after infection with 2009 H1N1 virus when compared to infection with seasonal influenza virus. Pulmonary replication of the 2009 H1N1 virus has been noted to occur at higher levels in human bronchial epithelium and in lung tissue when compared to seasonal influenza in animal models. This may explain the propensity of this virus to cause severe viral pneumonia in humans. The principal clinical syndrome leading to hospitalization and the need for intensive care in persons with 2009 H1N1 infections is diffuse viral pneumonitis with severe hypoxia, and ARDS, commonly with association of shock and renal failure.[18] When viral influenza is present viral cultures of the sputum will reveal high titers of influenza virus and bacterial cultures will usually be notable for normal oral flora. The chest x-ray of primary viral pneumonia reveals bilateral infiltrates. Pathologic findings of influenza pneumonia include necrotizing bronchitis, hyaline membranes, alveolar hemorrhage, and edema.

A significant proportion of the mortality associated with influenza virus infection is due to pneumonia caused by secondary bacterial superinfection. The typical clinical picture associated with pneumonia due to bacterial superinfection is that of a typical influenza-like illness, then clinical improvement, followed by worsening with fever, cough productive of sputum and dyspnea. The most common bacterial pathogens leading to secondary infection of influenza are *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae*, and *Streptococcus pyogenes*. With the recent onset of community-acquired MRSA, severe necrotizing staphylococcal pneumonia complicating influenza virus infection has been described particularly in children and young adults.[19,20] Both primary viral pneumonia and pneumonia due to bacterial superinfection occur most commonly in older persons with underlying cardiopulmonary disease, although primary viral pneumonia also has a predilection for pregnant women and young adults. Immunosuppressed individuals, especially those with hematologic malignancies, persons who have had recent solid organ transplantation, and those with HIV and low CD4 counts are at increased risk of severe influenza infection including pneumonia.

Although influenza primarily affects the respiratory tract, involvement of other organ systems have been described including myositis with elevated creatinine phosphokinase, myoglobinuria, and occasionally rhabdomyolysis. Patients with myositis have muscle tenderness that most commonly affects the legs.[21] Myocarditis and pericarditis have been reported but are rare. Guillain–Barre syndrome has been reported after influenza but this may be coincidence rather than etiologic. Transverse myelitis and encephalitis due to influenza are rare.

Reyes's syndrome is seen almost exclusively in children who are taking aspirin. It appears more commonly after influenza B virus infection than with influenza A. Most patients with Reye's syndrome present initially with nausea and vomiting. This is followed by altered mental status manifesting variably as delirium, lethargy, seizures, and progressing at times to coma and respiratory arrest. Most patients will have elevated ALT and AST; bilirubin is generally not elevated. Elevation in serum ammonia level is universal. If a lumbar puncture is performed to evaluate altered mental status, cerebrospinal fluid will be unremarkable. Reye's syndrome has become less common due to warnings to avoid the use of aspirin in children with acute respiratory illnesses. The exact etiology of Reye's syndrome is unclear.

Avian Influenza

Sporadic human infection with influenza A viruses that predominately infect birds has been noted, and involves the H5, H7, and H9 subtypes. Despite concerns of a human pandemic due to avian influenza virus, these sporadic infections have not generally resulted in person-to-person transmission, with the exception of some limited spread between lengthy unprotected close contacts of those infected with H5N1 avian influenza virus. In 1997, the first recognized case of severe human illness with H5N1 avian influenza virus was reported in Hong Kong. At that time "bird flu" emerged resulting in 18 known human infections and

6 deaths. Millions of poultry were slaughtered in order to try and contain the disease. Despite these efforts, H5N1 avian influenza reemerged in humans and birds in Asia in 2003 and spread to Africa and Europe possibly by migrating wild birds. The virus has become entrenched in Africa and Asia. As of January 20, 2011, 518 laboratory-confirmed human cases of H5N1 avian influenza with 301 deaths have been reported to the WHO. Egypt and Indonesia have reported the majority of human cases, with additional cases reported in China, Cambodia, and Vietnam in 2010. In the vast majority of cases, there is a history of direct contact with sick or dead poultry. Transmission to humans probably takes place via the respiratory route but infection via the gastrointestinal tract is possible and has been demonstrated in zoo animals that were fed infected poultry and in human infections presenting with diarrhea after consuming raw duck blood. The incubation period appears to be slightly longer than that seen with seasonal influenza virus, about 2–4 days after contact with infected poultry. H5N1 influenza has a propensity to infect young individuals, with a median age of 20 years. H5N1 influenza preferentially infects the lower respiratory tract and most patients die from primary viral pneumonia.[3]

Along with the usual symptoms of cough, fever, and malaise, gastrointestinal symptoms are often prominent with nausea and vomiting. Encephalopathy can be seen. Multisystem organ failure and acute respiratory distress syndrome can develop and are ominous signs. Laboratory abnormalities such as leukopenia and thrombocytopenia and elevated transaminases are common. Although bacterial superinfection can occur, primary viral pneumonia is more common after infection with H5N1 influenza virus.

Most patients will present with bilateral infiltrates on chest x-ray. Respiratory failure may develop, requiring ventilatory support. Renal failure and multisystem organ failure can ensue. Unlike seasonal influenza, evidence suggests that H5N1 influenza virus can replicate in tissues outside of the respiratory tract and replicating virus has been isolated from peripheral blood in infected persons. Human infection with H5N1 influenza virus has a high mortality rate; approximately 58% of infected persons will succumb.

LABORATORY DIAGNOSIS OF INFLUENZA

Influenza virus can be readily isolated or detected from a variety of respiratory specimens. Nasopharyngeal swabs are the most reliable specimen source for most assays. Influenza can be diagnosed by rapid diagnostic methods including immunoassays, by polymerase chain reaction (PCR) or by more traditional and time-consuming methods such as cell culture.[22] Results are most likely to be positive in children, who shed higher titers of virus, and in any patient during the first 48–72 h of clinical illness when viral shedding is the greatest. Immunoassays detect viral NP from the influenza virus in patient secretions and results are reported as positive or negative. Some rapid tests can also differentiate between influenza A and influenza B. Results are available quickly, often in 15 min or less. Some of these assays are eligible for a Clinical Laboratory Improvement Amendment (CLIA) waiver and can be performed in a clinician's office. This can be useful for clinical decisions regarding provision of antiviral therapy. Limitations for rapid influenza immunoassays exist however, primarily due to false negative results. The sensitivity of the test is in the range of 40%–70%, with a specificity of 90%–95%. During the 2009 pandemic rapid influenza, assays were falsely negative up to 88% of the time.[23] A negative rapid influenza test should not be used to withhold antiviral therapy in a patient with a clinical syndrome consistent with influenza virus infection when therapy would otherwise be indicated. Reverse transcriptase polymerase chain reaction assays (RT-PCR) are now commercially available and are the best method for a quick diagnosis (within hours) of influenza virus infection. Available multiplex assays can detect not only influenza but a variety of respiratory viruses.[23] These assays are comparable with real-time PCR and are more sensitive than viral culture. In patients with lower respiratory tract illness, endotracheal or bronchoscopic aspirates have higher yields than nasopharyngeal samples; however, negative lower respiratory tract samples have been noted in 10% or more of patients with severe 2009 H1N1 virus infection. Specimens for viral culture or for RT-PCR should be collected, and then placed in containers of viral transport medium and brought promptly to the laboratory. Influenza virus replicates in a variety of cell types, kidney cell cultures are most commonly employed although embryonated eggs can also be used for viral culture. More than 90% of influenza viral cultures are positive within 3 days, and the remainder of positive cultures will be positive by 7 days after inoculation. Serologic testing can be used to retrospectively diagnose influenza virus infection. As most people have been infected with influenza virus in the past, diagnosis of a recent acute infection requires paired acute and convalescent serum specimens (the latter should be obtained 10–20 days after acute illness) run simultaneously to assess for an increase in antibody titer.

Decisions regarding treatment of influenza should not be exclusively based on the results of tests for the presence of influenza virus, especially when the virus is known to be circulating in the community and a patient presents with signs and symptoms consistent with influenza. Several studies have demonstrated that the clinical diagnosis of influenza can be made with 77%–90% accuracy when influenza is present in the community and patients present with typical symptoms.[24] It is reasonable to test only in those circumstances where the results will impact clinical decision making.

PREVENTION

Vaccination is the best way to prevent influenza virus infection. Some studies suggest that vaccinating children against influenza may be more effective in preventing the flu in the elderly than vaccinating older adults themselves, as children are very effective at spreading influenza, and older adults

may have a suboptimal response to vaccination.[25] As influenza virus is spread primarily by inhalation of small droplet particles, maintaining a distance of 6 ft from persons coughing or sneezing is prudent. Although environmental contamination is a relatively unimportant mechanism for the spread of influenza, cleaning hands after contact with common high-touch public areas, such as doorknobs, makes sense especially during flu season. This is particularly important before making hand contact with one's face or eyes. Persons ill with the flu or other respiratory viruses should make an effort to "cover their cough" with a tissue, or cough into their elbow or shoulder to avoid exhaling viral particles into the air and infecting others. After coughing into a tissue, it should be discarded in the trash and hands should be cleaned.

Vaccination

Immunity to influenza virus is mediated by secretory IgA and serum IgG antibodies specific for the viral surface proteins HA and NA. Infection results in resistance to reinfection with the same viral strain and possibly some degree of protection within a subtype. Due to ongoing antigenic changes of influenza virus that lead to escape from immunologic control, routine vaccination is the best strategy for control of influenza epidemics. The Advisory Committee on Immunization Practices (ACIP) issues yearly updated recommendations for influenza vaccination through the CDC.[26] In response to antigenic variation of influenza viruses, the content of influenza vaccine may change on an annual basis. Seasonal influenza vaccines are formulated as trivalent preparations, with two influenza A components and one influenza B component. The components of the seasonal vaccine may vary year to year and are chosen based on the viruses that are circulating at the end of the previous influenza season. Influenza vaccines are available as either live attenuated intranasal vaccine (LAIV) or intramuscular inactivated vaccine (TIV). Inactivated influenza virus vaccines were first licensed in the United States in 1943. Live attenuated influenza virus vaccines are licensed for persons aged 2–49 years and should not be given to persons who are immunocompromised or at high risk for complications of influenza, or children aged 2–4 with asthma. Antibody titers after live attenuated influenza virus vaccine are higher in children, and lowest in older adults. Whether this lower antibody titer would correspond to less protection after vaccination with LAIV is not clear. It is possible that the main mechanism of protection of LAIV is via mucosal antibodies. A new trivalent intramuscular vaccine containing a higher dose of antigen has recently been approved for adults aged 65 years or greater. Immunity develops about 2 weeks after vaccination but can take longer in children. Increases in HAI antibody are seen in about 90% of healthy adults after vaccination with inactivated influenza virus vaccine. Peak antibody titers occur about 2–4 months after vaccination and return to baseline prior to the next influenza season. A recent review of influenza vaccination studies, conducted in healthy adults, estimated that when high levels of influenza virus circulate, and there is a good match between vaccine strain and circulating virus, about 4% of unvaccinated adults will develop influenza symptoms versus 1% of vaccinated people, giving a protection rate in the 70% range.[27].

Currently, influenza vaccine is recommended yearly for all persons over 6 months of age. This recommendation is an expansion of previous target groups and was prompted in part by the fact that many persons who developed complications after infection with novel 2009 H1N1 were members of groups not previously recognized as at risk for severe disease. Children aged 6 months to 8 years of age who have not had a previous influenza vaccination are recommended to receive two doses of vaccine. Side effects of vaccination are generally mild. Local soreness at the site of injection is common after inactivated influenza virus vaccine. Low-grade temperature elevations can be seen after vaccine administration but these are only slightly more common than after placebo. Side effects of live attenuated intranasal influenza vaccine are nasal congestion and sore throat, which occur at a slightly higher rate than that seen with placebo. Live attenuated vaccine viruses can be transmitted to close contacts, although this does not seem to occur frequently. Hypersensitivity to hen eggs is a contraindication to administration of inactivated influenza vaccine; the vaccine is generally safe in people who can eat eggs or products containing eggs. In 1976, an elevated rate of Guillain–Barre syndrome (GBS) was observed in person who received the swine flu vaccine. The estimated risk was one in 100,000 vaccinees. Very slight increases in the risk of GBS have been seen after administration of other influenza vaccines, an excess of one case per one million persons vaccinated.

Chemoprophylaxis

Antiviral medicines taken daily during a period of exposure are 79%–90% effective at preventing influenza. Chemoprophylaxis should be started within 48 h of exposure to be effective. Indiscriminate use of prophylaxis is not recommended as it can promote antiviral resistance. The recommended dose of amantadine or rimantadine in adults for the prophylaxis of influenza A virus in adult patients under the age of 65 years is 100 mg orally twice daily. The recommended dose of oseltamivir for chemoprophylaxis against influenza in adults is 75 mg orally once a day. The recommended dose of zanamivir for prophylaxis of influenza (types A and B) in adults in a household setting is two inhalations (5 mg per inhalation) orally once daily. The recommended duration of postexposure prophylaxis is 10 days after a household exposure or 7 days following exposure in other situations. The dose should be given at approximately the same time each day.[28]

Self-Care for Persons with Influenza

Most persons with influenza virus infection do not need antiviral drugs or require attention from a medical professional. Persons more likely to develop complications, such as the elderly, young children, pregnant women, immunosuppressed patients, and those with asthma, should consult their

health care provider about whether they need to be examined, as should any person who is concerned about severe symptoms. The CDC recommends that persons remain at home and avoid public places as much as possible until at least 24 h after fevers abate (without antipyretic use). Antipyretics can reduce fever and aid in comfort, but aspirin should not be used by children or teenagers who have influenza. Persons with fever should consume adequate fluids to compensate for increased fluid losses associated with sweating and increased respiration. Usual activities including exercise can be resumed when recovery is adequate and the person who had influenza feels ready to take part in those activities. Whether hand washing prevents influenza transmission is unclear, as the virus is not known to survive for a long period of time on surfaces and transmission through the air via respiratory droplets is felt to be the most important means of transmission. However, hand washing has been shown to be of benefit for preventing transmission of other respiratory viruses and gastrointestinal illnesses and is prudent to practice. Covering the mouth when coughing should be practiced routinely no matter what the reason for the cough, using a tissue that is then discarded in a waste receptacle or by coughing into one's shoulder if a tissue is not available.

ANTIVIRAL THERAPY

Antiviral medicines active against influenza virus include the NA inhibitors oseltamivir and zanamivir, and the M2 inhibitors amantadine and rimantadine. The M2 inhibitors, classified as adamantanes, are only active against influenza A, which can limit their clinical usefulness unless a patient is known or highly suspected to be infected with a type A virus. The NA inhibitors are active versus both A and B viruses. The antiviral activity of amantadine and rimantadine is due to inhibition of the M2 ion channel in susceptible influenza A viruses. Disruption of the ion channel interferes with viral uncoating and thus viral replication. Amantadine is administered at a dose of 100 mg twice a day for 5 days in adults less than 65 years of age with normal renal function. Common side effects include dizziness, insomnia, and difficulty in concentrating. In the elderly, confusion can occur as a side effect of the drug. Seizures have been reported in those with an underlying seizure disorder. Amantadine is not metabolized by the body and has a half-life of 12–18 h. Dose adjustment is necessary in renal insufficiency and the elderly. Rimantadine is extensively metabolized and does not need dose adjustment unless the creatinine clearance is less than 10 mL/min. The usual recommended dose of rimantadine for the treatment of influenza A virus in adults is 100 mg orally twice daily. The dose of both drugs needs adjustment in the elderly. Efficacy of amantadine and rimantadine are essentially equivalent when compared in a randomized trial. They are associated with a decrease in duration of fever by approximately 24 h, more rapid cessation of cough as well as sore throat and less nasal discharge. In recent years, much of the circulating influenza virus has been resistant to adamantanes on the basis of single point mutations in the genes coding for the membrane spanning portion of the M2 viral protein. Resistant virus can be transmitted and cause disease in susceptible hosts. As an example, the 2009 H1N1 virus and most H3N2 viruses currently in circulation are resistant to the adamantanes.

The NA inhibitors oseltamivir and zanamivir inhibit the function of the NA protein of influenza viruses. This protein cleaves sialic acid residues and is necessary for budding of virus from infected cells. Although influenza A viruses are more sensitive to the NA inhibitors than influenza B viruses, influenza B viruses are inhibited well within achievable drug concentrations in humans. All avian influenza strains including H5N1 are sensitive to NA inhibitors. Oseltamivir is rapidly absorbed from the gut and is converted in the liver to the active metabolite. The metabolite is eliminated unchanged in the urine. Dose reduction is recommended for persons with creatinine clearance of less than 30 mL/min. There are no formal recommendations for dosing in renal failure. The most common side effect of oseltamivir is nausea and vomiting, which can be reduced if the drug is taken with food. Oseltamivir is not licensed for children under the age of 1 but was used for younger children during the H1N1 pandemic under an Emergency Use Authorization from the Food and Drug Administration that has since expired. Zanamivir is not orally bioavailable and is supplied as a dry powder for oral inhalation, given as a dose of two inhalations twice a day. It can precipitate bronchospasm if given to patients with underlying pulmonary disease. Zanamivir is not recommended for persons with underlying lung disease, that is, asthma or chronic obstructive pulmonary disease, or for children under the age of 7. The tolerability and efficacy of inhaled zanamivir has not been studied in persons with severe influenza but in some instances seriously ill persons given inhaled zanamivir have had respiratory distress. Intravenous zanamivir may be available for compassionate use and is currently in phase 3 clinical trials. Another intravenous NA inhibitor, peramivir, is also in clinical trials and may be available on a compassionate use basis for treating seriously ill adults.

Oseltamivir and zanamivir have similar efficacy in clinical trials of person infected with influenza A and influenza B. In healthy adults, early treatment (within first 36 h of illness) results in a 30%–40% shorter duration of symptoms and an earlier return to work. Antiviral medication can reduce the duration of illness when started within 2 days of onset of clinical illness. In a study among healthy volunteers, NA inhibitors reduced the duration of illness by 1–2 days. The standard dose of oseltamivir for treatment of mild-moderate illness with susceptible influenza virus is 75 mg orally twice a day in adults with normal renal function. Higher doses of oseltamivir (150 mg twice a day) and an increased duration of therapy have been used in severely ill patients.[29,30]

Antiviral therapy is indicated as early as possible for persons hospitalized with influenza, those with severe progressive illness and those at higher risk of severe illness.[28,30] Early therapy with oseltamivir in patients with 2009 H1N1 virus infection may have reduced the incidence of hospitalization and the risk of progression to severe disease. Initiating

therapy after 48 h should be considered for persons at high risk for complications of influenza as well as for hospitalized patients with severe illness. Persons at higher risk of severe illness recommended for antiviral therapy include children less than 2 years of age, adults aged ≥65 years old, women who are pregnant or less than 2 weeks postpartum, persons with chronic cardiac disease (except hypertension alone), chronic pulmonary disease, renal disease, hepatic disease, hematologic disease (including sickle cell), metabolic disorders including diabetes mellitus, neurologic or neurodevelopmental conditions, immunocompromised states including HIV, persons aged <19 on long-term aspirin therapy (due to the risk of Reye's syndrome), persons who are morbidly obese, and residents of long-term care facilities. Selection of antiviral therapy should take into consideration the susceptibility pattern of circulating influenza virus in the community. Oseltamivir is recommended for treatment of H5N1 influenza virus infection as isolates have been resistant to the adamantanes. It is unclear at this time what the therapeutic efficacy is of antiviral therapy for H5N1 virus infection. Drug resistant viruses have been detected including in persons who had no history of treatment with NA inhibitors. Many oseltamivir-resistant influenza viruses remain sensitive to zanamivir.

SUMMARY

Influenza is a common upper respiratory infection caused by a virus of the *Orthomyxoviridae* family. There are three viral subtypes although most illness is caused by influenza A or B. Genetic variation allows the influenza virus to escape host defenses and infect an individual multiple times during a lifetime. Clinical illness from influenza virus ranges from a mild upper respiratory illness to a fatal viral pneumonia depending on the virulence characteristics of the virus and the immune system and physical characteristics of the individual host. Complications of influenza virus infection can occur directly from viral infection and due to bacterial superinfection of the respiratory tree. Efforts to prevent or minimize the impact of seasonal influenza center on the use of vaccines. Antiviral medications are available and ameliorate disease in healthy adults and may also have an effect in seriously ill patients.

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57 Indoor Air Quality

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CONTENTS

Introduction 709
Secondhand Smoke 709
Carcinogens and Suspected Carcinogens Found in Secondhand Tobacco Smoke 710
Risks of Exposure to Secondhand Smoke 710
Reducing the Risk 711
Radon 711
Prevalence and Health Impact 711
Detection and Mitigation 711
Carbon Monoxide 712
Nitrogen Dioxide 712
Formaldehyde 713
Household Cleaning and Cooking 713
Home Heating and Ventilation and Air Cleaning Devices 714
Indoor Mold, Pet, Dust Mite, and Cockroach Exposure 715
Fungi 715
Animal Dander 715
Dust Mites 715
Cockroaches 716
Home Hobbies and Gardening 716
Summary 716
References 716

INTRODUCTION

Clean environmental air is a basic right for all humans. The relationship between health and air quality has been recognized as far back as Hippocrates. Indoor air quality is particularly important to humans since we spend up to 90% of time indoors.[1] Outdoor and indoor air quality in the United States of America is regulated by the U.S. federal government through the Environmental Protection Agency (EPA). Although indoor air quality is important in the workplace, this chapter concentrates on home indoor air quality and highlights the sources of potential morbidity of indoor air quality as it pertains to lung health.

One of the most important tasks of the health care worker meeting a patient for the first time is to take a comprehensive history of environmental exposures both at work and in the home. A comprehensive assessment of the respiratory history has been recently published.[2] The health care worker taking a complete exposure history will ask the patient about contemporary exposures and also about exposures "in the home in which you grew up."[2] Household factors which may affect respiratory health include home water damage, heating and ventilation, renovation work, cleaning product accidents, the presence of a pool or hot tub, and hobbies including arts and crafts and model building. Also discussed are activities such as do-it-yourself repair work, gardening, pet exposure, wood and, coal fume exposure, and dirty work clothes exposure. This chapter discusses also some of the latest findings on home exposure of secondhand smoke, which is now recognized as an important risk factor for respiratory disease.

SECONDHAND SMOKE

Today, the awareness of smoking and its adverse effects is at the peak at any point of time in history. Yet, smoking is still a highly prevalent lifestyle. Secondhand smoke exposure comes in a close second as a leading public health problem. Over the recent few years, there has been a concerted effort from various national and international organizations to increase the awareness of problems associated with secondhand smoke exposure.[3–6] There have also been multiple public health initiatives undertaken to minimize the levels of secondhand smoke exposure. In this section we attempt to summarize and outline the scope, effects, and dangers of secondhand smoke. We also summarize measures to reduce and combat secondhand smoke exposure.

Secondhand smoke is composed of side stream smoke (the smoke released from the burning end of a cigarette) and exhaled mainstream smoke (the smoke exhaled by

the smoker).[6] While secondhand smoke has been referred to as environmental tobacco smoke (ETS) in the past, the term "secondhand" smoke better captures the involuntary nature of the exposure. The 2006 Surgeon General's report uses the term "involuntary" in the title because most nonsmokers do not want to breathe tobacco smoke.[4] Individuals can be exposed to secondhand smoke in homes, cars, the workplace, and public places, such as bars, restaurants, and recreational settings. In the United States, the source of most secondhand smoke is from cigarettes, followed by pipes, cigars, and other tobacco products. The term "thirdhand smoke" has been referred to as cigarette byproducts that cling to smokers' hair and clothing as well as to household fabrics, carpets, and surfaces—even after secondhand smoke has cleared.[7] These invisible tobacco toxins pose danger to small children, who are especially susceptible when they come in contact with contaminated surfaces.[8]

Secondhand smoke exposure can be measured by testing indoor air for nicotine or other chemicals in tobacco smoke. Secondhand smoke exposure can also be tested by measuring the level of cotinine (a by-product of the breakdown of nicotine) in a nonsmoker's blood, saliva, or urine.[9] Nicotine, cotinine, carbon monoxide, and other smoke-related chemicals have been found in the body fluids of nonsmokers exposed to secondhand smoke.

More than 4000 chemicals that have been identified in secondhand tobacco smoke and more than 50 of the toxic chemicals in secondhand tobacco smoke are carcinogenic.[10] Table 57.1 contains a list of some of these compounds.

TABLE 57.1
Carcinogens and Suspected Carcinogens in Secondhand Cigarette Smoke

Carcinogens	Suspected Carcinogens
Arsenic	Acetaldehyde
Benzene	Acetone
Beryllium	Acrolein
1,3–Butadiene	Acrylonitrile
Cadmium	2-aminonaphthalene
Chromium	Ammonia
Ethylene oxide	Benzo[a]pyrene
Nickel	Butyraldehyde
Polonium-210	Carbon monoxide
Vinyl chloride	Catechol
	Cresol
	Crotonaldehyde
	Formaldehyde
	Hydrogen cyanide
	Hydroquinone
	Isoprene
	Lead
	Methyl ethyl ketone (MEK)
	Nicotine
	Nitric oxide
	NNN, NNK, and NAT
	Phenol
	Propionaldehyde
	Pyridine
	Quinoline
	Resorcinol
	Styrene
	Toluene

Carcinogens and Suspected Carcinogens Found in Secondhand Tobacco Smoke

Risks of Exposure to Secondhand Smoke

In June 2002, the International Agency for Research on Cancer (IARC) concluded that "involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) is carcinogenic to humans." Further, the IARC concluded that there is a "statistically significant and consistent association between lung cancer risk in spouses of smokers and exposure to secondhand tobacco smoke from their spouse who smokes. The excess risk is on the order of 20% for women and 30% for men."

In January 2005, the U.S. Public Health Service's National Toxicology Program issued its 11th report on Carcinogens. This report unambiguously states that "environmental tobacco smoke is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans that indicate a causal relationship between passive exposure to tobacco smoke and human lung cancer. Some studies also support an association of environmental tobacco smoke with cancers of the nasal sinus."[11] Evidence for an increased cancer risk from environmental tobacco smoke stems from studies examining nonsmoking spouses living with individuals who smoke cigarettes,[16] exposures of nonsmokers to environmental tobacco smoke in occupational settings, and exposure to parents' smoking during childhood.[6,7] Many epidemiological studies, including large population-based case-control studies, demonstrate an increased risk of developing lung cancer following prolonged exposure to environmental tobacco smoke. A meta-analysis found an overall increase in risk of 20% for exposure to environmental tobacco smoke from a spouse who smokes. Exposure to environmental tobacco smoke from spousal smoking or exposure in an occupational setting appears most strongly related to increased risk. Lifelong nonsmokers living with smokers had, on average, a 24% higher chance of contracting lung cancer than those living with nonsmokers, and that those exposed to the heaviest smokers for the longest time had the highest risks.[13]

There is some evidence to suggest that secondhand smoke may have a causative role in other cancers such as breast cancer, nasal sinus cavity cancer, and naso-pharyngeal cancer in adults and increases the risk of leukemia, lymphoma, and brain tumors in children.[12] However, the proof is not conclusive as in the case of lung cancer, and more research is being done to answer these questions.

Secondhand smoke exposure may have other consequences. Individuals exposed to low-dose tobacco smoke

from the environment or occasional smoking are also at risk for developing respiratory symptoms. When small airway epithelial cells of individuals exposed to low-dose tobacco smoke was compared to those of nonexposed, biologic changes that are likely the earliest biologic abnormalities in the lung in response to smoke exposure were noted, and there were a significant number of genes up- and down-regulated in the low-level smoke-exposed individuals compared with the nonsmoker.[14]

Secondhand smoke also has significant effects on the cardiovascular system. Higher concentrations of serum cotinine among nonsmokers was shown to be associated with an excess risk of coronary heart disease of about 50%–60%.[15] In its 2009 report, the Institute of Medicine concluded that current data consistently demonstrates that secondhand-smoke exposure increases the risk of coronary heart disease and heart attacks and that smoking bans reduce this risk.

Children are particularly vulnerable to the effects of secondhand smoke. Children exposed to high doses of secondhand smoke are at a higher relative risk of asthma even in children who have not previously exhibited symptoms; sudden infant death syndrome and lower respiratory tract infections such as pneumonia and bronchitis are also increased. Children who regularly breathe secondhand smoke are also at increased risk for middle ear infections and may exhibit a small but significant reduction in lung function.[16–18]

Reducing the Risk

There is no safe level of exposure to secondhand smoke. Even low levels of secondhand smoke can be harmful. The only way to fully protect nonsmokers from secondhand smoke is to completely eliminate smoking in indoor spaces. Separating smokers from nonsmokers, cleaning the air, and ventilating buildings cannot completely eliminate exposure to secondhand smoke.

On the national level, several laws restricting smoking in public places have been passed. Federal law bans smoking on domestic airline flights, nearly all flights between the United States and foreign destinations, interstate buses, and most trains. Smoking is also banned in most federally owned buildings. The Pro-Children Act of 1994 prohibits smoking in facilities that routinely provide federally funded services to children. Many state and local governments have passed laws prohibiting smoking in public facilities, such as schools, hospitals, airports, bus terminals, parks, and beaches, as well as private workplaces, including restaurants and bars. Some states have passed laws regulating smoking in cars and multiunit housing to reduce the incidence of thirdhand smoke exposure which can also affect respiratory function. More than half of the states in the United States have enacted statewide bans on workplace smoking. Despite scientific evidence of its respiratory and cardiovascular consequences to innocent bystanders, the elimination of secondhand smoke in indoor air remains a challenge to individuals and public health officials nationwide.

RADON

Prevalence and Health Impact

Radon (Rn-222) is a radioactive colorless, odorless gas and is a breakdown product of radium (Ra) which is a breakdown product of uranium (U). Radon-222 has a half-life of 3.8 days and is found in the earth's rock and soil. Radon-222 itself does not pose a great biologic threat. However, radon breaks down via alpha decay into unstable polonium-218. Polonium-218 breaks down via alpha decay into lead-214, bismuth-214, and polonium-214, which are "short-lived" radioactive by-products referred to as "radon progeny." These "short-lived" progeny are hazardous to uranium workers and can decay via alpha radiation into the "long-lived" radon progeny of lead-210, bismuth-210, and polonium-210. These "long-lived" progeny are principally responsible for the radon found in homes.

Radon can easily dissolve into and evaporate out of water. Radon can seep through porous soil under buildings, through cracks or gaps in building foundations, floors, walls, and along with gaps around pipes, pumps, and drains.[19] In contrast to community water supplies, it is much more common for deep private well water to be infiltrated with radon if this water is in contact with rocks and soil containing uranium. This water in turn can enter the home through any home water supply such as showers, faucets, washing machines and dishwashers. Inhaled radon poses a much higher risk of lung cancer than radon which is ingested.[20,21] If radon is detected in home drinking water, it may be treated with "point-of-entry treatment," which can remove radon from the water before it enters the home, or "point-of-use" treatment devices. "Point-of-use" treatment devices only remove a small portion of the radon from water at the taps in the home leaving radon progeny which can be inhaled.

Inhaled radon progeny are the number one cause of lung cancer in never smokers and the second leading cause of lung cancer overall. The EPA estimates that radon exposure may account for over 20,000 lung cancer deaths each year including approximately 2,900 never-smokers and the remaining deaths in smokers with lifetime radon exposure of as low as 2 picocuries per liter of air (pCi/L). Simple home testing and correction of home radon levels above the EPA recommended action guideline level of 4 pCi/L per yearly average would reduce these deaths significantly. There is no safe level of radon exposure. According to the EPA, 1 out of 15 homes in United States has levels at or above the EPA action guideline level.[22] The chances of getting lung cancer from radon exposure is a function of the levels of radon in the home, the amount of time spent in the home, and whether or not one is a former or current smoker.[22]

Detection and Mitigation

Home short-term testing and long-term testing for radon are available. The EPA recommends testing for radon levels in schools and in all homes below the third floor as toxic levels are rarely seen in higher levels of high rise dwellings.

"Do-it-yourself" testing kits must have an accuracy of ±25% or ±1 pCi/L in order to meet the EPA approval. "Short-term" testing kits may be in your home for 2 or 3 days or for up to 90 days depending on the testing device. Several "passive" testing devices are available and include the activated charcoal canister, the alpha track device and the electret ion chamber which is used only by professional radon inspectors. These devices remain in the basement or first floor of the home while all windows and doors are kept closed, and fans bringing in outside air are shut off. Once testing is completed, the device is sent to a lab for analysis of radon levels via either gamma ray counting or liquid scintillation detectors. Because of their low cost and ease of use, the activated charcoal canister radon test kit accounts for approximately 95% of all radon testing, or approximately 250,000 test kits annually, in the workplace or in the home in the Unites States. An example of a short-term "active" device is the continuous radon monitor used for 48 h by professional radon inspectors with specialized training. This testing is usually reserved for real estate transactions.

"Long-term" radon testing devices are left in the home for more than 90 days and are usually performed with an alpha track device or an electret ion chamber. Long-term testing gives a better estimate of a home's year-round average radon level when compared to short-term testing. Long-term testing may be performed when a short-term testing radon level returns as 4 pCi/L or higher. The U.S. Congress has legislated that indoor radon levels be no more than 0.4 pCi/L of radon. This is the level usually detected in outdoor air and a level which is very difficult to achieve indoors. A more achievable indoor radon level is 2 pCi/L or below.

If high levels of radon are detected within a home, a radon contractor should be hired to evaluate the problem and decide which method would be best to treat that particular problem. Sealing cracks and gaps in the home foundation can help reduce radon levels. Another method to reduce radon is a vent pipe system and a fan known as a soil suction radon reduction system which removes radon from below the surface of the house via pipes and a sump suction pump. This system removes radon from the home through pipes vented to outside of the home. Even after installing a removal system, retesting for elevated radon levels should be conducted biannually. Recommendations from the EPA for building a radon-resistant new home may be located on the EPA website at: http://www.epa.gov/radon/rrnc/index.html

Perhaps the most significant event in radon risk reduction was the The Federal Radon Summit held on November 30, 2010. Convened by the EPA, representatives from the Department of Housing and Urban Development, Department of Defense, the Veterans Administration, the Department of Energy, the General Services Administration, the Department of Health and Human Services, the Department of Agriculture, and the Department of the Interior were also all in attendance. Leaders from these organizations discussed strategies available to the U.S. Government to reduce the risk of morbidity caused by radon in federally owned homes and buildings. Future follow-up meetings to discuss residential home radon reduction are planned.

CARBON MONOXIDE

Carbon monoxide (CO) is a colorless and odorless gas. It results from incomplete oxidation of carbon in the combustion processes. CO has a high affinity for hemoglobin forming carboxy-hemoglobin (COHb) and disrupts oxygen transport. Tissues with highest oxygen needs such as myocardium, brain, and exercising muscle are the first effected. The initial symptoms of low to moderate CO poisoning may mimic influenza and include headache, fatigue, shortness of breath, nausea, dizziness, and tachycardia. At higher concentrations, CO poisoning results in progressively more severe symptoms which include cognitive impairment, loss of muscle coordination, coma, and death. Symptom severity is related to both the CO level and the duration of exposure.[23–25]

Common sources of CO are unvented kerosene and gas space heaters, leaking chimneys and furnaces, back drafting from furnaces, gas water heaters, wood stoves, fireplaces, gas stoves, generators and other gasoline powered equipment, automobile exhaust from attached garages, and tobacco smoke. When power outages occur during emergencies (hurricanes or winter storms), using alternative sources of power can cause carbon monoxide (CO) to build up in a home and poison the people and animals inside. On average, about 170 people in the United States die every year from CO produced by nonautomotive consumer products.[24]

The Centers for Disease Control and Prevention estimates that several thousand people go to hospital emergency rooms every year to be treated for CO poisoning. Average levels in homes without gas stoves vary from 0.5 to 5 parts per million (ppm). Levels near properly adjusted gas stoves are often 5–15 ppm and those near poorly adjusted stoves may be 30 ppm or higher. Most people will not experience any symptoms from prolonged exposure to CO levels of approximately 1–70 ppm. As CO levels increase and remain above 70 ppm, symptoms become more noticeable. At sustained CO concentrations above 150–200 ppm, disorientation, unconsciousness, and death are possible.[25]

CO levels can be monitored at home with a commercially available detector. The Consumer Product Safety Commission (CPSC) recommends that a detector be located near the sleeping area, where it can wake you if you are asleep. They should not be directly above or beside fuel-burning appliances, as appliances may emit a small amount of carbon monoxide upon start-up. A detector should not be placed within 15 ft of heating or cooking appliances or in or near very humid areas such as bathrooms.[26]

NITROGEN DIOXIDE

Nitrogen dioxide (NO_2) is one of the nitrogen oxides, a group of air pollutants produced from combustion processes. In urban outdoor air, the presence of NO_2 is mainly due to traffic. Nitric oxide (NO), which is emitted by motor vehicles

or other combustion processes, combines with oxygen in the atmosphere, producing NO_2. Indoor NO_2 is produced mainly by unvented heaters and gas stoves. NO_2 and other nitrogen oxides are also precursors for a number of harmful secondary air pollutants such as ozone and particulate matter, and play a role in the formation of acid rain.

NO_2 is a major problem in individuals with respiratory illnesses such as asthma and chronic obstructive pulmonary disease (COPD). Exposure can irritate the lungs and increase the incidence of respiratory infections such as influenza. Major lung function effects shown in humans are reduction in forced expiratory volume in one second (FEV1), increased specific airway resistance (SRaw), and increased responsiveness in bronchial provocation tests. However, these effects are noted only in asthmatic subjects at levels relevant to exposures found in indoor and outdoor environments.[27] In people with mild asthma, NO_2 is capable of the inducing activation of prostanoids, leukotrienes, and histamine which may enhance airway inflammation.[28] The effects of short-term exposure are still unclear, but continued or frequent exposure to concentrations that are typically much higher than those normally found in the ambient air may cause an increased incidence of acute respiratory illness in children.[29]

The ratings for acceptable limits of NO_2 vary considerably among the various government and private organizations concerned with indoor air quality. The allowable limit according to Association of Heating, Refrigeration and Air conditioning is 0.3 ppm. To reduce exposure and minimize the effects of NO_2, all gas appliances are required to be properly fueled, adjusted, vented, and maintained. Wood stove doors should fit tightly and homes should be checked by an heating, vaccum, air conditioning (HVAC) or indoor air quality (IAQ) specialist for proper ventilation.[30]

FORMALDEHYDE

Formaldehyde is a common indoor air pollutant. It is used as a disinfectant and preservative and commonly found in wood building material, plastics, textiles, carpet, furniture, pesticides, paint glue, and cleaning products. It is one of the volatile organic compounds emitted from various building products like paint, adhesives, insulation, cabinets, false ceilings, etc. Formaldehyde levels are higher in residential homes because of relatively large ratio of pressed wood products to air volume in homes.[31] The main effect of this compound on the respiratory system is irritation of mucous membranes in the airways. Formaldehyde also interferes with airway epithelium integrity and function, and may modulate the onset and the severity of asthma.[32]

The conditions, concentration, and duration of formaldehyde exposure determine any potential effect it may have on the human respiratory system. The recommended maximum level of continual indoor exposure per the American Society of Heating, Refrigeration and Air Conditioning Engineers is 0.1 ppm. Levels greater than 0.5 ppm can cause burning of the eyes and irritation of the upper airways.[30] The recommended measures to reduce exposure are to use exterior grade pressed wood products and to use air conditioning and dehumidifiers to maintain moderate temperature and reduce humidity.[33]

HOUSEHOLD CLEANING AND COOKING

Household cleaning products when used properly and in small amounts are usually safe and do not effect indoor air quality adversely. However, it is well documented in the medical literature that accidents at home may entail the inhalation of toxic fumes and result in significant respiratory morbidity sometimes requiring emergency medical attention.[34] Although societal changes over the past several decades have seen more women in the workplace, women are still more at risk than men to experience a home chemical accident and inhalational injury which may affect their respiratory health.[35]

Household bleach consists of a 5.25% sodium hypochlorite solution (NaOCl). If bleach is mixed with an acid such as either 4% phosphoric acid (a rust, mineral deposit, water stain remover), household ammonia (NH_3) or hydrochloric acid (HCl), chlorine gas, and water are released. Chlorine gas and hydrochloric acid can cause both upper respiratory tract injury such as mucous membrane irritation and lower respiratory tract damage manifest as chest pain, shortness of breath, cough, pneumomediastinum, bronchospasm, pulmonary edema, and reactive airways dysfunction syndrome.[36,37] Chlorine released from aerosolized swimming pool tablets has also been reported to cause partially reversible asthma-like symptoms.[38]

Oven cleaners contain sodium hydroxide, monoethanolamine (MEA), diethylene glycol monobutyl ether, and butane or isobutene and may cause inhalation injuries especially if sprayed into a hot oven. Inhalation of these compounds has been reported to cause chemical pneumonitis, asthma-like symptoms, and bronchiolitis obliterans organizing pneumonia (BOOP).[39] It is known that janitors, maids, and other professional cleaners who use certain cleaning products may be at higher risk for asthma. However, it has been shown that frequent use of household cleaning sprays in the home in subjects 20–44 years old may also be an important risk factor for asthma. In subjects without a previous history of asthma, there was an association of asthma symptoms, the use of asthma medications and wheezing in 42% of those who used cleaning sprays at least once weekly. The diagnosis of asthma was higher in those who used sprays at least 4 days weekly. This association was linked to the most commonly used glass cleaner, air-freshener, and furniture cleaning sprays and was not related to atopy. The same association was not seen with liquid home cleaners presumably because aerosolized spray cleaners are more likely to be inhaled.[40]

Laundry detergents contain sodium phosphates, sodium carbonate, and sodium aluminosilicates and are alkaline with a pH of 10–12. Inhalation of granulated detergent with respiratory injuries usually occurs in young children, but may occur in adults and may be the cause of respiratory distress.[41]

Cooking accidents with overheated oil fumes have been reported to cause significant airflow obstruction.[42] However, cooking with vegetable oil, which is biologically inert, does not have significant adverse effect on the lungs when exposure levels

are kept within the limits recommended by the Occupational Safety and Health Administration and the National Institute for Occupational Safety (NIOSH).[43] Unlike vegetable oil, cooking with certain plant oils such as castor bean, sesame, acacia, and cashew nut have been reported to cause asthma and respiratory irritation such as rhinitis, cough, watery eyes, and wheezing.[43] It is known that frying on a gas or electric stoves may result in the release of polycyclic aromatic hydrocarbons (PAHs), nitrogen dioxide, and particulate matter that may have mutagenic activity and may be a risk factor in lung cancer. A Norwegian study showed that frying on a gas stove, versus frying on an electric stove, resulted in the release of higher concentrations of mutagenic aldehydes and naphthalene. However, the detectable levels of these compounds were below the Norwegian occupational exposure limits for PAHs.[44] In adults with asthma, one study was unable to show an association between gas stove use and FEV1, FEF25-75, cough, wheeze, sputum production, or dyspnea.[45] Despite these negative studies, it is recommended that exposure to cooking fumes be avoided "as much as possible."[45]

HOME HEATING AND VENTILATION AND AIR CLEANING DEVICES

Good ventilation in the home is essential to good respiratory health and dilutes and removes stale air and excessive moisture from the home environment. There are two approaches to ventilating a home: spot ventilation and general ventilation. "Spot ventilation" employs exhaust fans that intermittently remove pollutants in kitchens, laundry rooms, bathrooms, workshops, or home offices. "General ventilation" utilizes fans which run continuously to remove pollutants that are constantly being released into the environment, and not amenable to spot ventilation removal, such as bacteria and viruses, body odors, and moisture. Current recommendations suggest 8–10 air exchanges per hour when utilizing general ventilation.[46]

Because of the air-tight construction methods used in modern homes built within the past 15 years, these dwellings are considered "tight homes." These tight homes are a result of more energy efficient building methods which utilize better windows, high efficiency air conditioners and furnaces, weather stripping on door frames, and more insulation such as cellulose and spray foam.

General ventilation mixes outdoor air with indoor air by two methods: "exhaust-only ventilation" and "supply-and-exhaust ventilation." Exhaust-only home ventilation pulls stale air out of a house through exhaust-only fans such as bathroom or kitchen fans which may run intermittently or continuously at a low speed. This type of one way ventilation results in the need for fresh air, or "make up air" having to enter the house by chance through any available opening such as cracks around an outdoor bulkhead, unused exhaust fans in the house with ducts exiting to the outdoors, opened windows or doors, spaces under indoor doors, a fireplace, or a fresh air intake vent. Although exhaust-only ventilation may reduce odor in a kitchen or moisture in a bathroom, it does not improve the indoor air quality of a new tight house and may actually increase indoor radon levels and levels of stale indoor air.

A second method of home ventilation is "supply-and-exhaust ventilation" which employs continuous exhaust fans to pull stale, humid, or polluted air from inside the house to the outside, in addition to intake fans which draw fresh outside air into the home through existing cooling and heating ducts. Commercially available home "heat recovery ventilation (HRV)," is a type of supply-and-exhaust ventilation which can filter pollen, reduce indoor carbon dioxide levels, and warm or cool incoming fresh outside air before it distributes that fresh air throughout the house. It is generally accepted that supply-and-exhaust ventilation is the preferred method of home ventilation for a tight home or an older home which has undergone an improved energy efficiency upgrade.[46]

In a study of Inuit children in Canada, a comparison was made between households with active HRV or placebo HRV. There was a significant reduction in the odds ratio for wheezing (12.3%) in addition to a decrease in the rate of rhinitis (OR 0.20 at 1 month). Although there was no reduction in the number of health center encounters for the children in the study, the use of HRV was associated with air quality improvement and a reduction in respiratory symptoms.[47]

Even high quality home construction can have unintended consequences. "Back drafting" may occur in tight houses when home appliances such as a central vacuum cleaner system, a clothes dryer, a fireplace, kitchen or bathroom exhaust fans, a gas hot water heater, or a gas furnace suck air from the inside of a tight house to the outside thereby creating negative pressure within the house. If enough negative pressure is created within the house, this process can result in carbon monoxide being pulled back into the home through a fireplace and its chimney. This potential health hazard may be remedied by having a "fresh air intake vent" installed, which can supply "make up air" needed for fuel burning equipment within the home. These vents consist of an intake valve on the outside of the home and two pipes on the inside of the home. One of the inside pipes supplies air to the cold air return of the home's furnace, and the second pipe supplies combustion air for fuel burning appliances within the home.[48] In addition to good ventilation, air purification within the home may improve indoor air quality. Many air purification systems are commercially available and include ozone generators, electrostatic precipitators, ionizers, HEPA filters, and charcoal and zeolite filters.

The allotrope of oxygen (O_2), ozone (O_3), is formed when ultraviolet radiation from the sun splits oxygen atoms forming O_3. Stratospheric ozone is located 6–30 miles above the Earth's surface, and this "ozone layer" protects humans from potentially damaging ultraviolet light from the sun. Ozone closer to the Earth's surface can induce airway inflammation, cough, chest pain, throat irritation, reduce exercise capacity and pulmonary function testing results, and exacerbate asthma and COPD.[49] The EPA lists primary standard levels of indoor ozone as 0.08 ppm averaged over 1 year.[50]

Some indoor home air purifiers, "electrostatic precipitators" or "ionizers," produce ozone not intentionally but as a by-product of their function. These air cleaners electrically charge particles in the air, remove them, and produce low levels of ozone in the process. Some commercially available home air purifiers intentionally utilize ozone to reduce home odors and mold concentrations. These air purifiers are called "ozone generators" and may release potentially toxic levels of ozone. In 2007, after two Consumer Report articles and a class-action lawsuit, one national brand ozone generator home air purifier was taken off of the market for emitting toxic levels of ozone.[51,52] Alternatives to ozone producing air purifiers are HEPA (high efficiency particulate air) filter air purifiers and HEPA vacuum cleaners that utilize a fiber mat made of fiberglass fibers to trap airborne particles such as cooking fumes, spores and pollen, dust and dust mites, and tobacco smoke. A recent study suggested that HEPA air purification may reduce cardiovascular morbidity by reducing short-term particulate matter exposure to subjects.[53] Other portable filtration units utilize zeolite and charcoal filters.

INDOOR MOLD, PET, DUST MITE, AND COCKROACH EXPOSURE

Fungi

Fungi are eukaryotic, parasitic organisms with rigid cell walls which contain chitin. Unlike plants, fungi must absorb all of their nutrients from their environment. By producing a variety of enzymes, fungi may digest and utilize as nutrient materials in the home environment deemed unusable by other organisms. These materials include keratin, cellulose, chitin, and lignin allowing fungi to grow on home materials such as carpeting, drywall and ceiling tiles, and building materials made from organic matter. Although fungi are ubiquitous in air, water, and soil, damp and warm conditions can promote exponential fungal spore germination and growth as reported by many investigators in the aftermath of hurricanes Katrina and Rita in the U.S. Gulf Coast region in 2005.[54]

In general, fungi may be separated into (1) yeast which are unicellular, (2) molds which are multicellular, and (3) mushrooms. Some dimorphic fungi can exist as molds in the environment and yeast in the human body. Most studies that evaluate environmental mold are referring to mold with visible growth and not specific fungal species. Fungal illnesses may be divided into infectious and noninfectious. Although invasive fungal infections are rare in immunocompetent individuals, *Aspergillus* exposure may cause serious pulmonary infections such as pulmonary aspergillosis and aspergillomas in immunocompromised patients.[54]

Symptoms of excess indoor mold exposure include headache, sore throat, non-asthmatic cough, sneezing, and wheezing or cough due to asthma. Energy efficient tight homes may have high indoor temperatures and high humidity promoting dust mite and mold growth.[55] Asthma due to damp conditions and mold exposure may account for up to 21% (confidence interval 12%–29%) of current asthma in the United States.[56] Damp indoor environments and mold exposure have been shown to cause exacerbations of asthma in "sensitized" asthmatics, those who have developed IgE antibodies to allergens, but not in individuals without a previous diagnosis of asthma.[57] Independent of asthma, damp and moldy indoor conditions can also cause cough, wheezing, and upper respiratory symptoms. Other noninfectious respiratory effects known to be caused by mold exposure include hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis (ABPA), and allergic fungal sinusitis due mainly to dematiaceous fungi, such as those from the genera *Fusarium*, *Helminthosporium*, *Cladosporium herbarum*, *Alternaria alternata*, *Bipolaris*, *Curvularia*, *Exserohilum*, *Drechslera,* and less so *Aspergillus fumigatus*.[57]

Animal Dander

In addition to damp and mold exposure, other household allergens that worsen air quality and asthma symptoms are animal dander, saliva and urine, house dust mites, and cockroaches. Animal allergies usually develop from furred pets such as cats, dogs, rabbits, and guinea pigs, and the allergens are derived mainly from sebaceous gland secretions from the animal's dead skin (animal dander). Animal urine may also contain allergens. Approximately 10% of Americans have some allergy to cats. The most common allergen associated with cat allergies is the Fel d1 protein found in cat saliva and salivary glands. These cat allergens are approximately 2.5 μm in diameter, are suspended in the air, and can penetrate deep into the lung because of their small size. It is important to convey to patients that nonallergenic cats and dogs do not exist. Some cats and dogs are less allergenic than others however.[58] Simple measures such as not having furred pets, restricting furred pets from bedrooms, regular washing of cats and dogs, and HEPA air filtering devices may reduce the allergenic burden of indoor cats and dogs.[58]

Dust Mites

Dust mites, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, are members of the *Acarid* family and represent the most prevalent allergen worldwide. Dust mites most frequently inhabit homes in humid and temperate climates, but are not usually a significant problem at high altitudes. As with mold, tight home construction may lead to higher indoor temperatures and humidity and increase a home's house dust mite burden. Although dust mites can be found in bedroom carpeting and upholstered furniture, bed mattresses are the most common source of dust mites where as many as 100,000–10 million mites might live and feed on dead human skin (dander). It is not the dust mite itself, but rather the fecal particles, that are the most allergenic. It is estimated that approximately 26% of Americans have dust mite allergies.[59] Environmental controls to reduce the home dust mite allergy burden are listed in Table 57.2.[60]

TABLE 57.2
Environmental Dust Mite Control Measures for the Home

Use of hypo-allergenic, non-feather pillows
Use of impermeable pillow and mattress covers
Removal of rugs from rooms
Frequent vacuuming
Laundering bedding in hot water
Remove clutter and stuffed animals from bedrooms
Eliminate cloth upholstered furniture

Cockroaches

Cockroaches have been on earth for more than 300 million years and can be found worldwide with approximately 3500 species. In the United States there are some 55 species. Cockroach infestation is a major inner city problem for many reasons, and high levels of cockroach antigens (Bla g 1 and Bla g 2) have been found in urban schools, daycare centers, and substandard housing. Much like dust mites, the fecal particles of the cockroach are the source of the allergen. Uncovered food, damp, warm conditions, poor sanitation, and crowding all promote cockroach infestation.[61] Children who experience cockroach antigen exposure can get sensitized and exhibit positive skin test responses to cockroach allergen. Rosenstreich showed that children who were exposed and sensitized to cockroach antigen in high levels (>8 U/g) could develop wheezing and asthma and have a higher asthma morbidity, more medical visits, and more hospitalizations due to asthma.[62] Several techniques have been recommended to reduce cockroach allergen exposure and include environmental controls of humidity, ventilation and temperature, improved indoor sanitation, chemical and nonchemical extermination, and enforcement of public housing codes.[61]

HOME HOBBIES AND GARDENING

Home hobbies and gardening are often overlooked, as a potential cause for respiratory illnesses, even by experienced clinicians. This is mainly because of the rarity of such occurrences. Nevertheless, identifying and eliminating such exposure is critical when evaluating such illnesses. It is a common misconception that men are more likely to suffer from such exposure, but research suggests that the role of household exposure as a risk factor for adverse respiratory effects is as important in women.[63] Not infrequently, multiple family members in the same household could be exposed to a similar toxin leading to lung injury. An exhaustive list of such activities and the offending agents is not practical. However, in terms of respiratory disease, avocations of relevance include painting, metal works including metal refining, wood working, use of synthetic polymers and adhesives, auto-repair chemicals textile work to name a few. For example, severe lung injury has been reported from home gold refining work with mercury amalgams.[64] Home plumbing repair has been reported to cause exposure to hydrogen sulfide, which is a mucous membrane and respiratory tract irritant; pulmonary edema, which may be immediate or delayed, can occur after exposure to high concentrations. Agricultural products for gardening, including herbicides and plant allergens, are another source for respiratory ailments. For example, the herbicide paraquat is selectively toxic to the lungs and has been shown in many studies on agricultural workers across the world.[65]

SUMMARY

Excellent indoor air quality is vital to excellent health. This chapter has briefly outlined some areas to address in the home to improve indoor air quality. Keeping pollution out of your home by checking radon levels, not allowing smoking indoors, reducing conditions which promote mold growth, dust mites and animal dander, monitoring carbon monoxide levels, providing adequate ventilation, and using chemical products with care are just a few examples that can improve the indoor air you breathe. Since we spend most of our lifetime indoors, continued lifelong awareness and elimination of potential indoor environmental hazards is essential for our long-term respiratory well-being.

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Part XII

Sports Medicine and Orthopedics

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58 Sports Supplements

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CONTENTS

Introduction 721
Anabolic Androgenic Steroids 721
Dehydroepiandrosterone 722
Human Growth Hormone 723
Creatine 723
Beta-Hydroxy Beta-Methylbutyrate 724
Amphetamine 724
Methylphenidate 724
Ephedrine/Pseudoephedrine 725
Blood Doping 725
Caffeine 725
Energy Drinks 726
Carbohydrate-Electrolyte Beverages 726
Sodium Bicarbonate 726
Chromium 727
References 727

INTRODUCTION

Nutritional and performance-enhancing supplement use is growing in popularity among athletes and nonathletes of all ages [1–6]. Although the exact prevalence of their use is unknown, limited studies show that the number seems to be significant [1–9]. The Food and Drug Administration (FDA) regulates nutritional supplements under the Dietary Supplement Health and Education Act of 1994 (DSHEA), instead of as "conventional" foods and drug products (prescription and over-the-counter) [10]. As a result of the DSHEA, manufacturing and use of these supplements have increased dramatically in the United States, with estimated annual sales of $20 billion [2,4,5]. Under the DSHEA, the manufacturer is responsible for safety and accuracy of the label information of a dietary supplement before it is marketed [10]. In reality, the content of a supplement is not always consistent with the claimed label. The FDA monitors the post-marketing safety of the supplements. Due to the lack of scientific evidence, the effectiveness of most supplements is unknown [1–8]. Marketing strategy for the efficacy of a supplement is usually based on individual testimony, especially from famous people and athletes. Most medical and sports organizations are against using drugs to enhance human athletic performance [1,11]. Table 58.1 summarizes the effectiveness, adverse effects, and legal aspects of common sports supplements.

ANABOLIC ANDROGENIC STEROIDS

Anabolic androgenic steroids (AAS) are used to increase strength and lean muscle mass [2,3,6–8]. This may enhance performance or aid in recovery after exercise [12–20]. Steroid supplements are synthetic derivatives that mimic the effects of the male sex hormones testosterone and dihydrotestosterone. These hormones exert their effects on many different body tissues including muscle, bone, kidneys, liver, hematologic system, hair, immune system, and central nervous system. This is thought to be done by several different mechanisms including modulating androgen receptor expression by intracellular metabolism and physical alteration of the androgen receptor, as well as anti-catabolic activity via inhibition of glucocorticoid (stress hormone) receptor expression [13,20]. In the muscle tissue, this results in increased muscle mass by increasing muscle protein synthesis (promotes anabolism) and may also reduce recovery time by blocking the effects of stress hormones on muscle tissue (inhibits catabolism).

There is a paucity of controlled studies on the effects of AAS. This is likely due to a combination of their use being banned in almost all athletic realms, the fact that many athletes who supplement with steroids are also concurrently using other substances, and the severe side effects that anabolic steroids produce. The available literature demonstrates that short-term use of anabolic steroids by athletes can increase both strength and bodyweight [4,19]. Strength gains of about 5%–20% and 2–5 kg of increased bodyweight have

TABLE 58.1
Effectiveness, Adverse Effects, and Regulation of Common Sports Supplements

Supplement	Claimed Effect	Evidence for Efficacy	Side Effects[a]	Regulations
Anabolic androgenic steroids	↑muscle mass, ↑lean body mass, ↑strength	Effective	Significant on multiple organs	Prohibited by IOC and NCAA
Dehydroepiandrosterone	↑muscle mass, ↑lean body mass, ↑strength	No evidence	Significant	Prohibited by IOC and NCAA
Human growth hormone	↑muscle protein synthesis, ↑lean body mass, ↑strength	Very limited	Significant on multiple organs	Prohibited by IOC and NCAA
Creatine	↑muscle mass, ↑strength, ↑power	Limited (↑anaerobic exercise capacity)	Minimal	None
Beta-hydroxy beta-methylbutyrate	↑muscle mass, ↑strength	No evidence	Minimal (lack of reports)	None
Amphetamine	↑focus, ↑alertness, ↑energy, ↓fatigue	Limited, studies mainly in sleep-deprived individuals	Significant	Prohibited by IOC and NCAA[b]
Methylphenidate	↑focus, ↑alertness, ↑energy, ↓fatigue	Very limited	Significant	Prohibited by IOC and NCAA[b]
Ephedrine/pseudoephedrine	↑energy, ↓fatigue	No evidence	Significant	Prohibited by IOC and NCAA
Blood doping	↑endurance, ↑O_2 delivery	Effective	Significant	Prohibited by IOC and NCAA
Caffeine	↑energy, ↑strength, ↓fatigue	Most likely effective	Minimal	Prohibited by IOC and NCAA (urinary level > 12 mcg/mL and 15 mcg/mL, respectively)
Energy drinks	↑energy, ↓fatigue	No evidence	Minimal (lack of reports)	Depends on ingredients
Carbohydrate-electrolyte beverages	Improve performance, ↑endurance	No evidence	Minimal (lack of reports)	None
Sodium bicarbonate	↑endurance, ↓fatigue	No evidence	Minimal (lack of reports)	None
Chromium	↓body fat, ↑muscle mass, improve performance	No evidence	Minimal (lack of reports)	None

[a] For more information refer to the text; [b] except when medically necessary.

been observed. This may be attributed to an increase in lean body mass. Currently, there is limited evidence to support that anabolic steroids aid in muscle recovery. There is no evidence to support reduction in overall fat mass or an increase in endurance performance from anabolic steroids.

Some acute adverse effects of anabolic steroids include fluid retention, headaches, gastrointestinal (GI) upset, jaundice, dysmenorrhea, and hypertension [2,3,6,21]. Long-term use has been linked to premature mortality (especially from cardiovascular death and suicide), cardiovascular disease (hypertension, myocardial infarction, stroke), decreased HDL levels, aggressive behavior ("roid rage"), suppressed spermatogenesis and testicular atrophy, liver damage, predisposition to tendon injury/rupture, acne, irreversible gynecomastia in males, and virilization in women.

Anabolic steroids are illegal at all times (in and out of competition) according to athletic regulatory agencies such as the World Anti-Doping Agency (WADA), International Olympic Committee (IOC), and National Collegiate Athletic Association (NCAA) due to their strength enhancement and numerous dangerous side effects [22,23]. Several new anabolic substances have being created that may evade current techniques of detection. Therefore, enhanced methods of detection are being explored, such as gas or liquid chromatography attached to a variety of mass spectroscopy instruments.

DEHYDROEPIANDROSTERONE

Dehydroepiandrosterone (DHEA) is believed to enhance performance by increasing muscle mass, strength, and power while decreasing fat mass [8,24–26]. It is one of the most abundant steroids in the human body. The majority is synthesized in the zona reticularis of the adrenal cortex, with the remaining 5% produced via the gonads. Peak DHEA levels in the body are present during early adulthood and then slowly decline throughout the remainder of life. DHEA has androgenic effects mediated by its conversion to testosterone and dihydrotestosterone. Administration of exogenous DHEA in humans produces significant increases in the circulating levels of these sex steroids, which have anabolic effects in the body (see "Anabolic Androgenic Steroids").

Studies of DHEA have not demonstrated any significant effects on performance enhancement in athletics [8]. This is

likely because even though endogenous DHEA is a precursor of testosterone and dihydrotestosterone, DHEA supplementation does not result in a significant elevation in testosterone in the body. Consequently, there is no change in regards to muscle mass, body fat composition, power, or strength. At higher doses of daily DHEA supplementation, there are some transient elevations in serum testosterone levels; however, these levels return to baseline by 12 weeks. The higher DHEA dosing also does not correspond with increased lean muscle mass or strength. On the other hand, DHEA supplementation does appear to elevate circulating levels of estrogens, primarily via peripheral aromatization. This has shown no effect on athletic performance. Interestingly though, almost all of these studies regarding estrogens have primarily focused male subjects. Therefore, this effect of DHEA supplementation causing elevated estrogens in female athletes has yet to be adequately evaluated.

Adverse effects of DHEA supplementation are not well described as few long-term studies have been done [6,8]. The most common reported side effects have been gynecomastia in males and virilization in females. In both sexes, there is evidence of decreased HDL levels and increased risk of coronary artery disease. Some theoretical but currently unsubstantiated adverse effects caused by elevated hormone levels may include increased risk of hormone-related cancers (i.e., breast and prostate), liver damage, diabetes, and aggressive behavior.

Even though there are no proven ergogenic benefits of DHEA supplementation, there is concern that DHEA is too similar to anabolic androgenic supplements as it is a precursor to dihydrotestosterone and testosterone. As a result, DHEA is classified in a similar manner as anabolic androgenic steroids and is deemed illegal at all times (in and out of competition) according to athletic regulatory agencies such as the WADA and NCAA [22,23]. Current testing for DHEA is not adequate and revisions need to be made in order to properly detect this substance.

HUMAN GROWTH HORMONE

Human growth hormone (HGH) is used to enhance athletic performance mainly by increasing muscle mass while decreasing fat mass [2,3,8,27–30]. It may also be used to decrease recovery time. HGH is a protein-based peptide hormone that has many anabolic effects throughout the body. Normal functions of HGH include increased height during childhood, increased bone mineralization, increased protein synthesis, increased lipolysis, growth of internal organs, promotion of liver gluconeogenesis, and stimulation of the immune system.

The effect of growth hormone on physical performance in healthy adults has not been extensively studied [27–30]. Current limited evidence shows that growth hormone does not significantly improve muscle strength and power, does not increase aerobic exercise capacity, but may improve anaerobic exercise capacity. There is some anecdotal evidence that HGH excess may increase tolerance for hard training, shorten recovery time after exercise, and accelerate recovery after soft-tissue injury.

Acute side effects from HGH may include edema, "pins and needles" sensation, carpal tunnel syndrome, arthralgias, sweating, fatigue, and dizziness. More significant side effects may arise with chronic levels of excess growth hormone, as demonstrated by patients who develop acromegaly. They often present with complications such as diabetes, left ventricular hypertrophy, and hypertension and have an increased risk of malignant neoplasms. In those with acromegaly, there is a twofold increase in mortality rate and a life expectancy decrease of 10 years compared to the general population. These effects may also be increased with simultaneous use of anabolic steroid supplements.

HGH use is prohibited by the WADA and NCAA in and out of competition [22,23]. In the United States, HGH is available only by prescription and its licit uses are narrowly defined including growth hormone deficiencies, childhood metabolic disorders, and wasting syndromes (such as in HIV/AIDS). Any off-label use, such as for athletics, is deemed illicit.

CREATINE

Creatine is claimed to enhance performance by providing increased power during anaerobic, short-duration, high-intensity activity, and enhancing muscle mass [1,31–36].

Creatine is an amine that is synthesized normally in the human body in the liver, pancreas, and kidney. It supplies energy to all cells, but primarily skeletal muscle, by increasing the formation of ATP via regeneration from ADP and transferring ATP to utilization sites. Creatine supplementation aims at saturating these bodily stores to maximize its function [2,3,5,8]. Exogenous creatine is not degraded during digestion and approximately 99% is either taken up by muscle or excreted in the urine. Studies consistently indicate that creatine supplementation increases muscle creatine and phosphocreatine concentrations from 15% to 40%. It has also been shown to enhance anaerobic exercise capacity, thereby allowing for improvements in muscle mass, strength, and power. There may be some variation in responsiveness to creatine among athletes, however, as up to 25% of athletes may already have saturated creatine stores. Therefore, the demonstrated performance-enhancing effects may be more prominent in certain individuals with lower baseline stores.

The only clinically significant side effect that has been demonstrated in the literature is weight gain (which may often be a desired effect in athletes). There have been some case reports of side effects that have not been validated in large-scale studies. These include GI distress, muscle cramping, dizziness, propensity for muscle injury (i.e., tears), renal injury, and inhibited insulin production.

Creatine is allowed by the WADA, NCAA, and most professional sports [22,23]. Even so, the NCAA does not allow colleges and universities to supply creatine to their students with school funds. Students are permitted to buy creatine on their own and the NCAA has no plans to ban creatine unless

medical evidence indicates that it is harmful [23]. Also with current testing methods, detection of supplemental creatine is not possible as it is normally synthesized in the body and any excess is excreted in the urine.

BETA-HYDROXY BETA-METHYLBUTYRATE

Beta-hydroxy beta-methylbutyrate (HMB) is claimed to improve performance by increasing lean body mass and strength as well as promoting recovery in trained athletes [1,2,5]. HMB is a by-product of leucine (amino acid) metabolism and is a cholesterol precursor [37,38]. It is believed that it produces its effects on athletic performance by decreasing the catabolism of muscle protein and promoting muscle mass increase via its role as a precursor of muscle cell cholesterol, thereby providing substrate for muscle cell membrane formation. HMB is produced in small amounts endogenously and dietary sources include catfish and citrus fruits.

Research on HMB has shown some benefit in studies done on various small populations. In 2009, a meta-analysis of nine different studies was done which showed that the average strength increase and fat mass decrease with HMB supplementation was trivial [38]. When broken down into "untrained" and "trained" groups, there was a small increase in strength in the untrained group while there was no significant increase in the trained group. There is need for further large-scale and longer-term studies in order to investigate the true effectiveness of HMB and explore why the biggest increase in strength was present in untrained athletes.

Research on adverse effects of HMB is also limited in quantity and study length, but no specific problems have been proven to this point [2,5,37,38]. One 6-week study showed no adverse effects of HMB on complete blood count, lipid panel, testosterone, cortisol, electrolytes, urea, glucose, sperm count/motility, or psychologic state. Due to the lack of long-term studies, adverse effects of continued HMB supplementation are unknown. As there have been no definitive ergogenic effects of HMB and no reported side effects, it is currently allowed for use by the WADA, NCAA, and other organizations both in and out of competition. There needs to be more research into both efficacy and adverse effects to determine if HMB should be allowed as a sports supplement.

AMPHETAMINE

Amphetamine is believed to enhance performance through a strong stimulant effect which increases focus, alertness, and energy as well as decreases fatigue [39,40]. Amphetamine was originally introduced as a synthetic analogue of ephedrine for treatment of asthmatic and allergic reactions. It is structurally similar to norepinephrine and stimulates further norepinephrine release in the body, therefore having a stimulant effect on the sympathetic nervous system. In addition, amphetamine acts to increase levels of dopamine and serotonin neurotransmitters in the central nervous system, having a significant effect on the brain's reward pathways. Amphetamine may also be a major or minor metabolite of many other stimulants. Amphetamine's effect on well-rested subjects is unclear as it has mostly been tested in sleep-deprived individuals [40,41]. It may possibly allow more rapid learning of new tasks and provide increased physical energy, confidence, and well-being. In addition, amphetamine may improve short-term power performance, possibly through tolerance of longer periods of anaerobic metabolism; however, controlled data are again minimal.

Short-term effects of amphetamine may consist of tachycardia, flushing, hyperactivity, anorexia, headache, dizziness, insomnia, palpitations, tremors, euphoria, aggression, and hypo- or hypertension. Chronic adverse effects can include acne, psychosis, dependence, violent behavior, anxiety, and brain damage. All amphetamines are banned by the WADA and NCAA during competition, except when deemed medically necessary. The WADA may grant athletes a Therapeutic Use Exemption (TUE) [41–44]. The athlete must submit paperwork and then this is evaluated by a group of independent physicians, specializing in the area of concern for that patient, called a Therapeutic Use Exemption Committee (TUEC). The TUEC will determine whether or not the medication is necessary and if it would provide an unfair advantage over fellow competitors. The NCAA permits amphetamines during competition only with substantial and current documentation of the medical indication for their use. It is only legal if this documentation is provided before an athlete has a positive test. Professional sports also allow exemptions for use of stimulants with physician documentation for their medical necessity. This appears to be a less rigorous process in professional sports compared to the WADA and NCAA. Allowance of exemptions for this medication (and other stimulants) may lead to over-prescription in athletes. For instance, in U.S. professional baseball, the number of therapeutic exemptions for the use of stimulants to treat ADHD increased almost fourfold in 2007 after stimulants were "banned" in 2006 [39]. Consequently, the rate of ADHD diagnosis in professional baseball players is about five to eight times higher than in the general U.S. adult population [39].

METHYLPHENIDATE

Methylphenidate is thought to enhance performance by providing stimulant effect and therefore increasing focus, energy, and cognition [44]. Methylphenidate stimulates dopamine and norepinephrine release and also acts as a reuptake inhibitor. It therefore exerts its effects as a central nervous system and sympathetic stimulant [44]. Due to its dopaminergic action, methylphenidate also has an impact on feelings of pleasure and reward. These increases on norepinephrine and dopamine levels appear to be less significant than those with amphetamine. The efficacy of methylphenidate has not been extensively studied in relation to athletics, but does have proven benefits in relation to focus and concentration [39]. For instance, methylphenidate has been shown to reduce driving errors in adults with ADHD. Therefore, it is possible that similar improvement in concentration and

reduction of errors may be present on the playing field in athletes who take methylphenidate; however, further investigation is warranted. The short-term side effects of methylphenidate include nervousness, abdominal pain, insomnia, tachycardia, irritability, diaphoresis, headaches, dizziness, and palpitations [43–45]. Long-term effects are not as well described and frequently debated, but may include psychosis, medication dependence, and depression. Regulation of methylphenidate is similar to that of amphetamines [22,23,45,46].

EPHEDRINE/PSEUDOEPHEDRINE

Ephedrine and pseudoephedrine are claimed to enhance performance through stimulant effect, thereby improving energy levels, concentration, and alertness and decreasing fatigue [39,47–49]. Ephedrine and pseudoephedrine act as sympathomimetic amines. The principal mechanism of action is stimulation of endogenous norepinephrine from storage vesicles in presynaptic neurons. This results in a stimulant effect of the sympathetic nervous system [2,3,6,8]. The majority of literature shows no effect of ephedrine or pseudoephedrine on athletic performance, including strength, oxygen uptake, or time to exhaustion [2,3,6,8]. Two studies do show minimal effect on performance [48]. The first shows increased knee extension strength when using three times the normal dose of pseudoephedrine and the second shows improved muscle endurance in the first of three repetitions when using compounds containing both caffeine and ephedrine. Thus, there are no good large-scale data to conclude that ephedrine or pseudoephedrine have significant ergogenic effects.

Acute adverse effects of ephedrine and pseudoephedrine may include tachycardia, anorexia, nausea, irritability, flushing, diaphoresis, insomnia, mild euphoria, headache, and dizziness [2,3,6,8]. Effects associated with longer-term use can be acne, psychosis, cardiac arrhythmias, heat stroke, and aggressive/violent behavior. Ephedrine and methylephedrine are prohibited in competition by the WADA when concentration in the urine is greater than 10 μg/mL [22]. Pseudoephedrine is prohibited when its concentration is greater than 150 μg/mL. The NCAA has banned use of ephedrine completely, but does allow use of pseudoephedrine in competition [23]. There are no regulations on urine concentration of pseudoephedrine in NCAA competition.

BLOOD DOPING

Blood doping enhances athletic performance by increasing oxygen transport, thereby improving endurance capacity [50–52]. The term blood doping refers to any method that aims to increase red cell mass and enhance oxygen transport capacity [2,8]. Previously, this was mainly done via blood transfusions but current doping strategies usually involve erythropoiesis-stimulating agents (i.e., erythropoietin), so this will mainly be described here. Erythropoietin (EPO) increases the arterial oxygen content by increasing red blood cell mass and decreasing plasma volume. This results in an increased capacity for the body to tolerate endurance activities (via increased VO_2 max). EPO also decreases plasma renin and aldosterone levels as well as the proximal renal tubular reabsorption rate. This triggers a feedback mechanism that causes a fall in glomerular filtration rate and diminishes intrarenal oxygen consumption, resulting in suppression of endogenous erythropoietin. There are also some other possible non-erythropoietic ergogenic effects of EPO that have been postulated, but not confirmed, including angiogenesis, shift in muscle fiber type/composition, cognitive enhancement, and anti-apoptotic effects that may be linked to antioxidant activity. The scientific literature clearly demonstrates that exogenous EPO administration causes a significant increase in submaximal performance with prolongation of time to exhaustion during exercise [2,8,50–52]. A study by Thomsen et al. in 2007 found that after 4–11 weeks of treatment with recombinant human erythropoietin (rHuEPO), subjects increased submaximal exercise performance (at 80% of VO_2 max) by 54%. As described earlier, this is mostly due to increase in VO_2 max; however, it appears that this highly significant exercise improvement cannot be explained by the VO_2 max alone. Therefore, other non-erythropoietic effects of exogenous EPO should be explored. Adverse effects of exogenous erythropoietin may include elevated arterial blood pressure, increased cardiac stress, deep vein thrombosis, pulmonary embolism, and stroke [2,5,8]. Long-term EPO administration may also lead to autoimmune disease. If blood transfusions are used for doping, there is also a risk of infection (i.e., HIV, hepatitis) or transfusion reaction.

Blood doping, including both transfusions and erythropoiesis-stimulating agents, is prohibited at all times by the WADA and NCAA [22,23]. Urine testing for exogenous EPO has been present for several years. This issue has been most prominent over recent years in international cycling events, resulting in numerous disqualifications for positive tests and significant media attention. Continued strong enforcement of these rules and regulations is necessary as the ergogenic effects of blood doping appear to be quite substantial.

CAFFEINE

Caffeine is used to increase endurance and to enhance performance. Caffeine is classified as a stimulant; it can both increase alertness and delay fatigue [1,2,8,33,53,54]. There are claims that caffeine can increase the utilization of fat (adipose tissue) as an exercise fuel and spare muscle glycogen stores. Caffeine is a substance that occurs naturally in the leaves, nuts, and seeds of a number of plants. It has various effects depending on the particular body tissue acting as the substrate, as well as interindividual variability due to a combination of genetic and environmental factors. The average time to peak serum concentration is approximately 1 h, and half-life is about 3–7 h, although there are variations between individuals. Caffeine is a central nervous system stimulant, therefore altering perceptions of effort and fatigue. There are many different cellular actions that likely contribute to the observed effects of caffeine. These include potentiation of muscle contractility by causing sarcoplasmic

reticulum calcium release, inhibition of phosphodiesterase isoenzymes and concomitant cyclic monophosphate accumulation, inhibition of glycogen phosphorylase enzymes in liver and muscle, nonselective adenosine receptor antagonism, and stimulation of the cellular membrane sodium/potassium pump [53,54]. The most physiologically significant mechanism likely relates to adenosine receptor antagonism, although the precise mechanism supporting its ergogenic properties is unclear. Major dietary sources of caffeine typically provide 30–100 mg per serving. Some non-prescription medications contain 100–200 mcg of caffeine per tablet. Research has shown that caffeine enhances endurance and provides a small but notable enhancement of performance over a range of exercise protocols. Benefits have been seen with small to moderate levels of caffeine (1–3 mg/kg) taken before, throughout, and near the end of an exercise program. There have not been additional performance benefits shown with increases in the caffeine dose above 3 mg/kg. In trials, increased performance was noted at urinary caffeine concentrations less than the limit of 12 mcg/mL allowed by the IOC. Anxiety, irritability, tremulousness, muscle twitching, insomnia, and headaches. Dependence and withdrawal occur due to central nervous system effects [2,8]. Caffeine was removed from the IOC list of banned substances in 2004 and is now a "controlled or restricted substance." At this time, the upper limit for urinary excretion allowed by the IOC is 12 mcg/mL [22]. The NCAA allows up to 15 mcg/mL [23].

ENERGY DRINKS

Energy drinks have a variety of ingredients; therefore, claims of benefits differ according to the particular product and its corresponding marketing [1,55–58]. Energy drinks are often found displayed next to sports electrolyte drinks, which often misleads the purchaser into believing the products have similar actions. Athletes perceive energy drinks as a quick way to consume extra energy to fight fatigue and increase endurance. Certain energy drinks also contain vitamins, minerals, herbs, and other nutrients. They are used by some athletes in an attempt to burn fat and increase lean muscle mass. The primary ingredient in most "energy blends" is caffeine (reviewed separately). The most common other ingredients include taurine, guarana, L-carnitine, glucuronolactone, and B vitamins. Energy drinks typically provide a large carbohydrate (usually more than 25 g/oz) load beyond the amount generally recommended for physically active individuals. This amount of carbohydrate can decrease the rate of fluid absorption into the bloodstream secondary to osmotic effects, impeding rehydration during exercise. Some energy drinks have been found to have thermogenic effects as well. With regard to some of the specific ingredients of energy drinks, taurine is known to modulate skeletal muscle contractile function, and may modify exercise-induced DNA damage. L-carnitine has been shown to play a decisive role in preventing cellular damage. There is little research that has been done regarding the interactions of the various ingredients of energy drinks in the human body; therefore, the effects of these are poorly understood at this time. The effectiveness of energy drinks as performance enhancers remains unproven [1,58]. Most of the ingredients are categorized as "dietary supplements," and fall under the DSHEA. Therefore, they are not subject to the strict requirements for safety and efficacy data prior to human use. There are some studies showing limited evidence of benefits of both taurine and L-carnitine supplementation in improving exercise capacity and performance. However, the amounts of these substances found in popular energy drinks are often below the amounts expected to deliver therapeutic benefits. There are limited data on the outcomes of combining the additives in a single beverage. In studies, energy drinks have been associated with increased blood pressure and tachycardia. There are also risks of palpitations, restlessness, irritability, and dehydration. The large carbohydrate load found in energy drinks can cause GI distress.

CARBOHYDRATE-ELECTROLYTE BEVERAGES

Carbohydrate-electrolyte beverages aid in the replacement of fluid lost during exercise. Specifically, studies have shown benefits in high-intensity exercise and endurance events [58–60]. Evidence also indicates that use of carbohydrate-electrolyte beverages can improve athletic performance. Beverages contain electrolytes including sodium (10–25 mmol/L) and potassium (3–5 mmol/L) in a carbohydrate rich fluid (5%–7% carbohydrate). Compared to water alone, with carbohydrate-electrolyte beverages there is an increased uptake of water from the intestine into the blood. This effect occurs at a total carbohydrate concentration of approximately 5%–7%. Lower concentrations provide less performance benefit, and higher concentrations can actually interfere with rehydration. This aids in the replacement of ongoing fluid losses during sports. The sodium in the beverages also acts to stimulate thirst as well as to increase water absorption by the kidneys. Many beverages also contain calcium, magnesium, and other electrolytes, which play a relatively smaller role in terms of rehydration. Studies have shown that when carbohydrate-electrolyte beverages are consumed during activity, there is an improvement in times for a 20-m sprint as well as a delay in fatigue. Other studies conducted in soccer players have shown an increase in overall running distance and improved performance during the second half of games in distance run at speed. To obtain the maximum benefit, athletes should periodically consume carbohydrate-electrolyte beverages to replace fluid lost during activity [58–60]. There have been no reported side effects when properly formulated carbohydrate-electrolyte beverages are consumed.

SODIUM BICARBONATE

Sodium bicarbonate is claimed to improve endurance running, cycling, and swimming athletic performances [1,61,62]. It is said to decrease race times in 400–1500 m sprints, and delay exhaustion, demonstrated by improved performance during the second halves of prolonged intermittent cycling

events. The effect of sodium bicarbonate is to buffer the blood from the buildup of lactic acid that occurs with exercise due to release from muscle cells during anaerobic glycolysis [2,61,62]. Lactic acidosis contributes to fatigue via inhibition of enzymes used for the production of energy and reduction of muscle fiber contractility. Sodium bicarbonate reduces the level of blood and muscle acidity, therefore decreasing these effects of lactic acid. There is conflicting evidence regarding the efficacy across studies [1,2,61,62]. There is some evidence to show that bicarbonate supplementation may have benefits for high-intensity events of up to an hour in length as well as intermittent high-intensity team sports. Few adverse effects have been reported; GI distress (diarrhea, bloating, belching) is the most common. Supplementation is not currently prohibited by WADA or NCAA [22,23].

CHROMIUM

Chromium (as chromium picolonate) is used for weight loss and has been used by athletes to assist with fat loss, increase muscle mass, and enhance performance [2,5,35]. There is also suggestion that chromium decreases insulin resistance, particularly in diabetics. Chromium is thought to play a role in normal carbohydrate metabolism by potentiating the action of insulin. Chromium may increase insulin binding to cells and insulin receptor number, as well as activate insulin receptor kinase, leading to increased insulin sensitivity. Research has not supported claims of performance or endurance enhancement with chromium supplementation [2,5]. In a small study, there was no increase in muscle strength noted over a 6-week period of supplementation. Similarly, there has not been any evidence that chromium effects weight loss or body composition. At this time, reviews of meta-analyses have not shown a significant association between chromium and insulin resistance. There has been concern over potential serious side effects associated with chromium use. Previous studies indicated a potential for genotoxicity; however, this claim has not been well supported. Other possible side effects include liver and renal dysfunction, rhabdomyolysis, and gastrointestinal complaints. Chromium interferes with the metabolism of iron as well as zinc absorption. Chromium supplements are not currently regulated. Older commercial formulas containing chromium with ephedrine were banned with the regulation of ephedrine [22,23].

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59 Prevention of Injury

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CONTENTS

Introduction 729
Pediatric 730
- Warm-Up 730
- Stretching 730
- Anterior Cruciate Ligament 730
- Epiphyseal and Apophyseal Injuries 731
- Concussion 731
- Exercise-Induced Asthma 732
- Sudden Cardiac Death 732

Young Adult/Middle Age 733
- Heat-Related Illness 733
- Medical: Hypertension and Diabetes 733
- Muscle and Tendon Injury 734
- Joint Health: Arthritis and Cartilage 734

Older Adults 735
- Wellness 735
- Medical: Cardiovascular and Cerebral Vascular Disease 735
- Congestive Heart Failure 735
- Bone Health 736
- Fall Prevention 736

Conclusion 736
References 737

INTRODUCTION

Physical activity is paramount in society. Children participate in recreational activities and organized sports to stay active and engage in social activities. Adults exercise to improve health, lose weight, and stave off illness. The geriatric population may use activity to maintain their independence and to help manage chronic medical conditions. Physical activity has become a vehicle to improve the quality of life. Unfortunately, the risk of injury and illness associated with exercise and sports increases as people become more physically active.

Injury prevention has become a focus in the medical literature in recent years. Besides diagnosing and treating injuries, health care professionals can and should promote injury prevention. Dedicated research and initiatives have been undertaken to promote prevention. Over the past decade, several conferences, including three international meetings (the World Congress on Sport Injury Prevention), have been held to discuss current strategies for keeping athletes on the field and for keeping people active and healthy. A number of peer-reviewed articles, along with a specific journal, *Injury Prevention*, have been published to provide current updates on injury prevention. Additionally, several organizations have been created to help train active people on how to properly condition and participate in various sports. The shift toward prevention may help save expense and time loss associated with injuries.

Before identifying which injury prevention strategies may be effective, risk factors and injury-promoting behaviors need to be examined. These factors can be divided into extrinsic and intrinsic categories [28,38]. Examples of extrinsic risk factors are training, environment, and equipment [24,25]. Training "errors" may involve inadequate conditioning, improper neuromuscular balance, or overtraining. Environmental conditions and playing surfaces are factors that can place a person at risk for injury. Consideration for equipment such as braces and footwear needs to be given when evaluating for injuries. Intrinsic risk factors include age, gender, current health status, and comorbid medical conditions, and they can be primary or secondary causes of injury.

Injury prevention also includes motor vehicle safety, smoking cessation, home safety, fire precautions, and firearm safety. Although these are important factors and critical to injury prevention, they are beyond the scope of this chapter (see Chapters 121 through 128). This chapter discusses injury

prevention and important medical and musculoskeletal conditions by age group, specifically in the pediatric, adult, and geriatric populations.

PEDIATRIC

Warm-Up

A common approach is to begin exercise with a proper warm-up. This is a set period of time in which a person prepares for exercise in an attempt to enhance the upcoming event. A proper warm-up is traditionally composed of three phases. Initially, a period of aerobic exercise is performed to increase body temperature and shunt blood to the muscles, followed by nonspecific stretching, and ending with a set of functional activities that mimic sport-specific movements [10]. Although stretching is mentioned as part of the warm-up, this component is addressed individually in the following section.

The current medical evidence is controversial in regard to the relationship between a thorough "warm-up" prior to exercise and injury prevention. A number of studies point in favor of using a warm-up as a way to decrease risk of acute injury, including strains and sprains. However, even though a proper warm-up may prevent acute traumatic injuries, some studies demonstrate that a formal warm-up may not have a definitive effect on reducing overall injury risk [10,27]. There is evidence that performing an abbreviated warm-up after a rest period, such as halftime, has been found to reduce the number of acute strains and sprains that occur in the second half of a competition. Two additional benefits from a warm-up, however, can include a decrease in muscle soreness along with improvement in exercise performance [37].

Effective time for warm-up ranges from 3 to 4 min, with the amount of time tailored to time spent in actual physical exercise [10]. Additionally, the intensity of the warm-up needs to be set on an individual level to allow for maximum benefit without risking fatigue and a detrimental effect on performance.

Stretching

A universal component of exercise is stretching. Stretching has been a facet of physical education class, organized sports, and individual exercise regimens for decades. Stretching may have two benefits—reducing injury and improving performance—however, this is still debated in the medical literature.

Before discussing how muscle stretching plays a role in injury prevention, an important distinction should be clarified. Stretching and flexibility are two different entities that coexist, as stretching affects flexibility [27,35,37]. Stretching is an extrinsic factor performed to lengthen muscle tissue, while flexibility is an intrinsic factor affecting joint mobility [27,37]. Stretching decreases passive resistance, thereby increasing muscle compliance and decreasing muscle stiffness [27,35]. The increased muscle compliance allows a muscle to work more efficiently and decreases the susceptibility to muscle strain. The decrease in muscle stiffness is the goal of preperformance stretching.

Flexibility affects the functional range motion of a joint. Various forms of stretching, including active, passive, static, ballistic, and dynamic have been employed to improve flexibility. Most people use static stretching as the method of choice. Stretching does provide short-term improvement in flexibility [37]; however, several control studies have documented that stretching has no effect in preventing injuries other than muscle strains [28,35,37]. One reason that stretching is not effective is because most injuries occur within the normal range of motion [35]. Additionally, stretching has not been found to decrease postexercise soreness [37].

A concern associated with passive stretching is that it may lead to an acute loss of strength to the lengthened muscle. In contrast, there is no strength loss with dynamic stretching. Not only does the loss of strength negatively affect injury prevention, it also hampers muscle performance. Additionally, stretching can lead to a hyperflexible state, which can also compromise muscle performance [27].

Even though stretching has not definitively demonstrated a protective effect or a reduction in exercise-related injuries [35,37], several recommendations can be made to ensure that proper stretching technique is observed. Stretch muscle groups that are at risk for the sport-specific activity. Although there is no specific time threshold for holding a stretch, the longer the duration a stretch is held (at least 60 s), the more prolonged the effect of the stretch [27]. Along with passive stretching, incorporate dynamic stretching and drills to help maintain strength that is lost with stretching.

Anterior Cruciate Ligament

Anterior cruciate ligament (ACL) injuries represent one of the more prevalent and devastating injuries young athletes experience in all athletics. Unfortunately, female athletes experience noncontact ACL injuries at a rate of four to six times more often than their male counterparts [20]. Current research is being focused on why this injury befalls women at such an epidemic rate and the reasons appear multifactorial. Intrinsic and extrinsic factors are being investigated; research has demonstrated three extrinsic variables as risk factors. These risk factors include (1) greater knee extension and valgus movement during the landing phase of jump stopping, (2) less knee flexion combined with more knee and hip internal rotation with single leg jumping, and (3) primary use of quadriceps, with less hamstring and gastrocnemius muscle activity when stabilizing the knee [20]. Intrinsic factors to female ACL injuries may include hormonal receptors on the ACL leading to increased laxity, a narrow femoral condylar notch, and other gender-specific biomechanical factors such as a relatively wider pelvis.

ACL injury prevention strategies have focused on the modifiable extrinsic risk factors. Traditional stretching of the quadriceps muscles along with hamstring and gastrocnemius strengthening is targeted to help relieve the anterior shearing

effect of the tibia on the femur. Once the anterior and posterior muscles are balanced, the focus should be on neuromuscular control of the core and lower leg [20]. This factor is trained with plyometrics and sport-specific agilities. Specific training with box jumps, single leg landing, and single leg bounding will help reinforce the athlete's core and limb control. Additionally, education and training on stopping with several small steps instead of one large step or rounding off curves instead of cutting sharply will help limit the amount of lower leg internal rotation.

Several formal programs have been implemented with success in female basketball and soccer programs. All successful ACL prevention programs contain aspects of the aforementioned tools. Considering that at least 6 weeks is needed to increase motor recruitment, the training programs should commence at least 6 weeks prior to intense contact activity [20]. Additionally, for the program to be effective there needs to be a high level of compliance and commitment on the part of the athlete and, if there is a team involved, the coaching staff.

Epiphyseal and Apophyseal Injuries

During childhood development, growth occurs at two different sites. Epiphyseal growth centers are sites of long bone growth and respond to pressure. These centers contribute to height and length. In contrast, apophyseal growth centers are secondary growth sites where tendons attach and are affected by traction. Because of rapid changes in bone and muscle tissues, a child's bone physiology is different than an adult and responds differently to applied forces. Increased levels of intensity and repetitive loading can have a negative effect on these growth centers. Injury to physeal sites can lead to pain, interrupted growth, or altered joint mechanics.

The two most common physeal sites of injury are located in the upper extremity, the elbow and the shoulder. Injury to proximal humeral head, "little league shoulder," results from repetitive traction and rotational forces across the growth center. The pediatric elbow is at risk for two injuries related to overuse—a traction injury, "little league elbow," and osteochondritis dessicans, a result of repetitive compression injury. Both affect the medial aspect of the elbow. Because of the large number of adolescents who participate in overhead throwing or racket sports and are affected by these conditions, injury prevention has become a primary focus when discussing these conditions.

Prevention of pediatric elbow and shoulder overuse issues also focuses on two aspects: intrinsic and extrinsic factors [34]. Intrinsic prevention strategies include balancing appropriate strength and flexibility to reduce imbalances at the scapula, hip, and trunk [6]. One key risk factor is glenohumeral internal rotation deficit (GIRD). Two stretches that are helpful in reducing GIRD are the "sleeper stretch" (external rotators of the shoulder) and the "open book stretch" (pectoralis minor) [34]. Strengthening exercises to target weak scapular stabilizer muscles, serratus anterior, rhomboid, trapezius, and posterior deltoid muscles, will help muscular imbalances. Additionally, focusing on hip and trunk muscles will help reduce muscle fatigue. Both improved joint range of motion and increased strength will aid in proper mechanics. Lastly, establishing conditioning programs that are sports specific will build muscle endurance while maintaining a high level of compliance.

Injury prevention is directed toward extrinsic risk factors including pitch count and pitch type. Guidelines for little league pitchers include throwing no more than 80 pitches per game or 800 pitches in a season [34]. Guidelines have been established for a set number of days off after throwing a set number of pitches. Examples of pitch selection recommendations include only throwing fastballs until age 8 and not throwing a curve ball until age 14 [34].

Concussion

Concussion is a pathophysiological process affecting the brain, introduced by traumatic biomechanical forces. In addition to the acute injury, the possibility of developing post-concussion syndrome is of significant concern. Due to the seriousness of the injury and the potential for tragic and long-lasting effects, health care professionals have made this a focus for the past several years in sports medicine. In recent years, many U.S. states have enacted laws about concussion recognition and education for high school athletes, and the NCAA and the four major professional leagues have created policies to protect their athletes from sustaining a concussion or the sequelae related to this condition.

Significant research effort and resources have been dedicated to concussion prevention, both primary and secondary. The prevention strategies have focused on two aspects: protective equipment and rules [26]. Protective equipment designed to prevent concussion includes helmets and mouth guards; thus far, newer models in helmets and mouth guards have not definitively demonstrated an increased effectiveness in concussion prevention [26]. Helmets have been found to reduce impact forces directed to the skull and face. This reduction in force translates to a reduced incidence in skull fractures and facial injuries. However, because of the movement of the neck and the movement of the brain inside the skull, countercoup injuries can still occur. Mouth guards help protect from dental and orofacial injuries, but no reduction in brain trauma has been demonstrated.

Rule changes and education has had a more profound effect on concussion prevention compared to other interventions. Starting with adolescent football, teaching athletes to tackle with their head up has helped reduce neck and head injuries [26]. Enforcing rules of making head-to-head contact illegal has reduced the incidence of head injuries [26].

To help protect athletes diagnosed with a concussion, several measures have been put in place to prevent second impact syndrome. Guidelines have been created to assist with management and return-to-play issues. Neuropsychological testing provides objective data to help evaluate cognitive function [26]. Comparing post-injury results to either baseline results or national standards combined with physical

assessment helps health professionals prevent athletes from returning to activity too soon and being at risk for second impact syndrome. Once a concussion has resolved, a specific return-to-play progression [26] has been established to gradually return an athlete to competition through a series of more demanding tasks. The step-by-step protocol allows an athlete to increase activity while being closely monitored. The controlled return helps prevent exposing an athlete to sustaining a second concussion before the resolution of the first concussion.

Exercise-Induced Asthma

Asthma can take on many forms and have many triggers. Exercise-induced asthma is the transient narrowing of the airways that occurs after vigorous exercise. It is not possible to prevent asthma; however, strategies can be employed to reduce the risk of asthma-related problems associated with exercise and allow for peak performance. Identifying asthma-related triggers and proper use of medication are two necessary preventions that aid in this cause.

As derived from the name, exercise is the prime trigger for exercise-induced asthma. However, environmental triggers can worsen an exacerbation. If present, seasonal allergies need to be identified and can be treated with medication or desensitization. Cold air and aerosolized chemical products, for example, chlorine, can exacerbate attacks in some asthmatics. Even though it can be difficult to control for these factors, taking steps to warm and humidify air or enable proper ventilation can aid with close monitoring.

Medication treatment is the gold standard in preventing exercise-induced asthma issues. The most widely used medication is inhaled short-acting β_2–agonists [7]. Considering that most attacks of exercise-induced asthma occur after exercising for 20–30 min, taking these medications 10–15 min prior to activity is very effective. The maximum effect of this drug occurs 20 min after inhalation and remains effective for roughly 4 h [7]. If a bout of exercise is longer than 4 h, this medication may need to be repeated. In contrast, long-acting β_2–agonists can be used, which will provide longer coverage; however, tolerance has been observed after repeated dosing, decreasing its protective effect. Additionally, there is recent concern that regular use of long-acting β_2–agonists can increase the risk of severe cardiovascular side effects [7].

Alternative medications are available for the prevention of exercise-induced asthma exacerbations. Ipratropium bromide is another inhaled medication that has protective benefit; however, this medication has been found to be more beneficial when combined with β_2–agonists [7]. Inhaled corticosteroids and leukotriene antagonists are both effective in managing exercise-induced asthma [1] and may even help increase the protective effect of β_2–agonists. These medications are typically used in asthmatics that need additional help in controlling their symptoms. However, considering the systemic effects, the risk versus reward profile needs to be weighed.

Because some asthma medications can affect performance, the goal is to prevent asthma exacerbations and to reduce the impact of exercise-induced asthma on athletics, not to gain an advantage in performance. Prior to starting a medication, appropriate testing should be performed to determine if a medication is needed. Once the need is established, the athlete and health care professional need to ensure that all the rules are followed for the sport's governing body in the use of the desired medication.

Sudden Cardiac Death

Many people use exercise as a way to improve overall health and specifically cardiovascular condition. On the opposite end of the spectrum is sudden cardiac death related to exercise. Due to the all-encompassing nature of sudden cardiac death and its widespread effect on all involved parties, prevention has become paramount. There are various causes of sudden cardiac death, with certain conditions demonstrating prevalence at various stages of life. Adolescents are at increased risk of commotio cordis, young adults have a higher incidence of hypertrophic cardiomyopathy, while older adults are more prone to coronary artery disease. Whatever the etiology, the goal is to identify people at risk and prevent occurrence.

A major tool for prevention of sudden cardiac death is the preparticipation evaluation. The evaluation includes standardized questions and examination techniques to target patients who are at risk. Because of the difficulty in identifying abnormalities, often the history is more important than the exam. Specifically, all participants need to be questioned about a history of cardiac abnormalities or a family history of cardiac problems [8,12]. Further clarification of family history including sudden death, cardiac abnormalities, or myocardial infarction in family members younger than age 50 needs to be detailed [8,12]. A personal history of chest pain or shortness of breath that occurs during exercise along with syncope (or near syncope) during exercise needs to be questioned [8,12]. Any report of previous cardiac testing should be explained. The cardiovascular physical exam includes blood pressure measurement, auscultation of the heart, palpation of the pulses, and examination for clinical features of Marfan Syndrome. When performing cardiac auscultation, the heart should be evaluated in two positions while using maneuvers (inhalation, valsalva, and squatting); these maneuvers will aid in the detection of murmurs and will help distinguish between benign and pathologic murmurs. Any abnormal murmur warrants further evaluation.

A controversial and much debated topic is the use of screening electrocardiogram (ECG) and echocardiogram when performing the preparticipation evaluation in the asymptomatic adolescent athletes with no concerning family history of sudden cardiac death. The use of these tests is commonplace when an abnormality is identified during a preparticipation evaluation and a diagnostic evaluation is indicated, but not as a screening tool [3] for asymptomatic individuals. Some health care professionals believe that the preparticipation ECG would help identify underlying cardiac

disease; however, the concern for a high number of false-positives is among several reasons that the American College of Cardiology is not currently recommending use of screening ECGs in this population.

A rare cause of sudden cardiac death is commotio cordis. This condition results from a direct blow to the precordial chest area that results in a cardiac arrhythmia [4,22]. What makes this condition difficult to prevent is that it occurs in individuals with no history of cardiac dysfunction. Despite the difficulties in preventing this condition, investigation into two areas has produced mixed results. Because the condition revolves around direct trauma to the chest, both the chest protector and the projectile have been checked. Numerous research studies have failed to demonstrate the protective nature of chest protectors across multiple sports [4,9]. The failure of the chest protection results from either improper fitting or insufficient padding [4,9]. In contrast, the density of the projectile has provided a mechanism for prevention. Softer core balls or safety balls have been found to result in a lower risk of a commotio cordis event [4].

YOUNG ADULT/MIDDLE AGE

Heat-Related Illness

Summertime is a great time for participation in sports and exercise. Long days, bright sun, and warm temperatures create a perfect combination for people to go outside. However, prevention of heat illness and injury has to be a concern. Heat illness can present in various forms from heat edema and cramps to heat exhaustion and stroke. The symptoms can be mild to life threatening. Observing a few prevention strategies can reduce risk and allow for safe participation. In addition, heat-related illness is a condition relevant to all age groups and should be included in any discussion of preventable injuries in the pediatric and elderly populations.

Before heading outdoors, knowing the temperature and humidity can help determine if it is safe to exercise. Elevated temperature correlates with the amount of heat in the air, while humidity determines the amount of moisture. Together, temperature and humidity create the heat index. The air temperature will raise skin temperature and the body will attempt to cool through sweating. High humidity makes it difficult for the body to cool itself and more susceptible to heat illness. Since temperature alone cannot predict risk, wet and dry bulb thermometers and heat graphs have been used to determine safe zones for exercise. Using caution in temperatures above 85°F and 15% humidity is wise [18].

Continued exercise in anticipated warm temperatures makes acclimatization important to reduce risk and an important concept to discuss. Heat acclimatization involves the gradual increase of exposure to elevated temperatures with gradually increased workloads over days to allow the body to adapt to the environment. It takes 10–14 days to become fully acclimatized to a hot environment. Additionally, because of child's small mass, it may take even longer for a child to acclimatize [18]. Reducing workload to 50% on day 1 and gradually increasing over the next 2 weeks is critical. Safe acclimatization also involves gradually increasing exposure time; shorter training sessions and less protective equipment in the early stages of the progression. Finally, avoiding exposure in the hottest part of the day, from 11 am to 4 pm, may reduce risk and help prevent heat-related injury [18].

Two additional precautions include clothing and fluid hydration. Ideal clothing for exercising in a high heat index environment includes lightweight and light-colored clothing [18]. This allows for less heat absorption and improved body cooling. Fluid hydration is critical to preventing heat injury. Fluid intake prior to exercise at a minimum should be 500 mL [18]. Over the course of exercise 150–300 mL of fluid should be consumed frequently [18], approximately every 15 min during moderate to strenuous exercise. Finally, at the completion of exercise, drinking fluids is paramount over the next hour to replace what was lost. Ideal intake should consist of water and carbohydrate sport drinks, while carbonated beverages and alcohol should be avoided. Dehydration will have a negative effect on performance, and by the time thirst is perceived, the individual is already dehydrated.

Medical: Hypertension and Diabetes

Hypertension and diabetes are two of the most prevalent medical conditions affecting adults and geriatric patients. Either of these conditions can cause significant morbidity. Additionally, diabetes can potentiate the effects of hypertension because of the effect it has on blood vessels. To help limit the devastating effects of the aforementioned conditions and help prevent complications, regular exercise is strongly recommended.

Through various trials, regular exercise has been found to reduce both systolic and diastolic pressures in hypertensive patients both with and without diabetes. Exercise results in weight loss and redistribution of fat stores, leading to improved blood pressure control [5,36]. Two additional physiological responses to exercise include improved glucose tolerance and enhanced skeletal muscle insulin sensitivity [36].

Even with the effects of hypertension and diabetes, the level of exercises needed for an appreciable gain is attainable by most affected individuals. Aerobic activity can include walking, cycling, and swimming ideally maintained for 30–45 min [5,36]. Because of the negative effect that hypertension and diabetes have on the heart, heart rate is the primary guide for intensity. A target heart rate of 55%–80% of the maximum rate is the goal [36]. Resistance training should focus on the core muscle groups. Selecting 8–10 exercises and performing one set of 10 repetitions is sufficient. The American College of Sports Medicine recommends 150 min of moderately strenuous exercise per week (30 min five times a week) for all adults, as regular weight training resistance exercises. Moderately strenuous exercise can be any activity that continuously increases the heart rate and is at a level of effort that an individual could talk to a partner while exercising but would find it difficult to sing.

Exercise is an effective and critical part of the treatment of hypertension and diabetes. It may also play a role in the prevention of these conditions as well as the development of complications from these conditions (secondary prevention role). Hypertension and diabetes are two excellent examples of how exercise is really "medicine" to help individuals stay healthy and well. There are a number of other medical conditions that regular exercise also can play a key role in management including but not limited to heart disease, stroke, hyperlipidemia, depression, fibromyalgia, arthritis, and even some cancers.

Muscle and Tendon Injury

Muscle and tendon injuries represent some of the most common injuries experienced during physical activity. Both muscles and tendons are contracting tissues that respond to movement by stretching to lengthen and contracting to shorten. Injury occurs when force exceeds the elastic properties of the tissue. Acute muscle injuries are strains and one of the most commonly strained muscles is the hamstring. In comparison, tendons can be strained from one sentinel event or overused from repetitive trauma leading to tendinitis. Both of these injury types occur at the Achilles tendon and can be very debilitating. In contrast to acute injuries, chronic tendon injuries, tendinosis, occurs from overuse without proper healing, leading to disorganized and dysfunctional physiology. Because of the long-lasting effects and often difficulty in treatment, preventing muscle and tendon issues has become paramount for people engaging in physical activity.

Hamstring injuries are a good example of both the acute and chronic musculotendinous issues that can occur in this population. Hamstring injuries occur in many settings, but sports that have an emphasis on sprinting, including track, football, and rugby, place the athletes at the greatest risk. Additionally, dancers and water skiing participants are also vulnerable because of the extreme stretching that can occur. When a hamstring injury occurs, a tremendous amount of time can be lost; to combat this, prevention is important. Contrary to popular thought, stretching has not proven to be an effective strategy. However, increasing flexibility at the hip joint can be important to help balance forces of the opposing muscles, quadriceps and hip flexors [15,31]. Additionally, performing a warm-up prior to intense exercise allows the hamstring to lengthen and become conditioned. Greater force is needed to subject a preconditioned muscle to injury. A second preventive strategy is focusing on neuromuscular exercises involving the lumbopelvic region [15]. Examples of these exercises include high knee kicks, bounding, and single leg supports. These exercises improve lower extremity control and pelvic balance. An important intervention is the addition of routine eccentric hamstring exercises [15,31]. Performing eccentric exercises has multiple benefits: (1) muscle hypertrophy and greater surface area, (2) develop strength along the entire length of the muscle, (3) increase spring quality of the muscle, (4) overcome the strength deficit created by the stronger quadriceps muscle, and (5) mimic the force needed to overcome the explosive forces from activities that usually cause the injury [19].

If an athlete does sustain a hamstring injury, care needs to be taken to ensure that a reinjury is prevented. Once an athlete demonstrates full range of motion, full strength, and ability to perform all functional activities, a return to sport is usually granted. Similar to the aforementioned prevention interventions, balancing pelvic tilt created by the iliopsoas and quadriceps muscles is critical to reducing a pathological stretch at the hamstring muscles [15].

When treating tendon injuries, many of the same strategies can be employed, specifically, eccentric exercises that increase fibroblast activity and lead to tendon hypertrophy and increased tendon strength [19]. The increased size and strength allow tendons to become more compliant to stress and reduce individual fiber fatigue. Additional prevention tactics include delaying the use of nonsteroidal anti-inflammatory medications until day 3 of an acute injury [31]. This will prevent interfering with the body's natural healing process of repair and remolding for regenerating muscle tissue. Consider avoiding medications that may make tendons susceptible to injury, including fluoroquinolone antibiotics and corticosteroids [14]. One final preventative strategy directed toward Achilles tendinopathy is using orthotics to correct pathological foot malalignments, which contribute to injury [14].

The preceding section focused on two muscle–tendon units, but all the techniques translate to other muscles and tendons throughout the body including rotator cuff, medial and lateral epicondylitis, and patellar tendinopathy.

Joint Health: Arthritis and Cartilage

One of the most common and disabling musculoskeletal conditions faced by adults is arthritis. The Arthritis Foundation states that one in five adult Americans have some form of arthritis or an arthritis-related condition and that in the next 10 years, this figure will be one in four. Osteoarthritis is far and away the most common type of the over 100 subtypes of arthritis. Osteoarthritis has become easier to recognize, and over the years, health care professionals have refined the treatment of this condition. However, with the high prevalence of osteoarthritis, prevention has been difficult. Arthritis is typically a result of routine use and more often overuse. The overuse can be a result of work or exercise but unfortunately both lead to a common disabling result.

A common reason for early-onset osteoarthritis is injury [32]. This chapter has gone into great detail on how to prevent injury, but sometimes injuries are unavoidable. When dealing with an injury, prompt recognition and treatment will decrease the risk of later developing arthritis. Structured rehabilitation can help strengthen and correct muscle imbalances that become altered after an injury. There is a lot of research currently being devoted to developing ways to restore articular cartilage, damage to which is one of the end results of arthritis in the joint.

Technology and research has also played a role in helping to reduce injuries and subsequent development of osteoarthritis of the knee. The use of prophylactic bracing of the knee in football has seen reduction in ligament injuries of the knee [32]. Additionally, softer playing surfaces and surfaces that reduce shoe–surface friction have been found to decrease joint shearing forces [32]. These interventions help preserve the native biomechanical function and reduce excessive wear on the knee joint.

Exercise is the best way to maintain joint function and optimize joint function [30]. Both resistance training and cardiovascular training play a role in osteoarthritis prevention. Through exercise, bone mass and muscle strength are increased [32]. The increased mass leads to a large surface area and the increased muscle mass helps offload the bone and put more stress on the muscles. The abusive shearing forces are spread over a larger area and not focused on the venerable joint. Cardiovascular training helps control body weight, decreasing the total mass that is passed onto weight-bearing joints. Additionally, cardiovascular training also increases muscle endurance, which helps limit muscle fatigue. With less fatigue, the joint is protected during extended bouts of exercise. In many cases, osteoarthritis cannot be fully prevented, but if the deteriorating effects can be minimalized, pain can be reduced and function can be maintained. It is often said in sports medicine that movement (of the joint) is life; in fact, joint movement may help the joint secrete its own natural lubricant, thereby improving comfort and preserving function.

OLDER ADULTS

Wellness

As people age, the body changes and many older people experience increased body weight and slowed metabolism that lead to obesity. While gaining weight, there is often a loss of strength and endurance. The combination of obesity and decline in muscle performance often result in decreased mobility, loss of independence, and overall physical decline [40–42]. To help prevent this decline and maintain function, proper diet and exercise need to be a mainstay in the daily life of geriatric individuals.

Obesity is associated with a decrease in function as it becomes difficult to carry increased weight. The limited function and movement can reciprocally lead to a decrease in energy expenditure [42]. With a lower basal caloric need, intake needs to be adjusted accordingly. A balanced diet is recommended with less focus on fats and carbohydrates to prevent glycogen storage. Along with adequate calorie intake, proper hydration is also necessary.

Older people who engage in physical exercise enjoy multiple benefits. Along with helping to increase muscle strength and endurance, physical exercise helps maintain weight, improve balance, and increase gait velocity [40]. The benefits of exercise have an effect on medical conditions as it decreases joint stiffness and pain associated with osteoarthritis and prevents bone loss seen in osteoporosis [41]. To accomplish these goals, exercise should include a combination of both cardiovascular and resistance training. Moderate intensity cardiovascular exercise of at least 30 min five times a week is ideal for cardiovascular training [11,13,43]. If five times a week is not possible due to health or other circumstances, any amount of regular exercise is recommended. An ideal resistance training program will incorporate six to eight exercises covering all major muscle groups. To reduce redundancy, the exercises should be varied over the course of the week. To increase intensity of the resistance workout and limit risk, additional weight or a second set can be added, instead of increasing repetitions or decreasing rest time between exercises. It is recommended in this population that the individual consult their health care provider before starting a new exercise program; the health care provider may consider some evaluation to help ensure safe participation in sports and exercise.

To maximize health and wellness, the combination of physical exercise and diet control has been determined to be more effective than either alone [41]. Moderate intensity cardiovascular training with resistance training targeting major muscle groups on all days of the week is recommended and it has been determined that performing both in one session does not negatively impact the effects that would be observed by only performing one type of exercise on a given day.

Medical: Cardiovascular and Cerebral Vascular Disease

Many older Americans suffer from cardiovascular disease and cerebral vascular disease leading to premature death. Physical activity has been proven to reduce the risk of these conditions in multiple studies and has been found effective for both genders as well as various ethnicities [11,13]. The protective measures for cardiovascular and cerebral vascular events is a result of physical activity helping to control obesity, blood pressure, and increased blood sugar (diabetes).

At a minimum, the guidelines established by the Centers for Disease Control and Prevention recommend moderate exercise of at least 30 min on most days of the week [11,13]. Both aerobic exercise and strength training have proven benefit and should be considered in an exercise program. If a person is unable to perform moderate exercise, even light activities have proven benefit. However, more intense forms of exercise and longer duration have provided additional benefits.

Congestive Heart Failure

Congestive heart failure can also be affected by exercise. Moderate intensity aerobic and resistance training improved heart function by increasing early diastolic filling at rest and exercise. Additionally, exercise can increase left ventricular mass and increase oxygen uptake, thus preventing further deteriorating heart failure.

Bone Health

The most common bone disease diagnosis is osteoporosis. This condition affects both men and women and is viewed as an age-related condition. This condition results from low bone mass and leads to decreased bone strength and deterioration eventually resulting in bone fragility. The loss of bone mass is secondary bone reabsorption rates greater than bone replacement. Bone fragility can result in falls, fractures, and disability. Because of the significant consequences, prevention of osteoporosis is a necessity.

One key to prevention is screening. Guidelines have been established on when to screen people for the condition. Current recommendations include screening all women aged 65 years old or greater and younger women and men with risk factors [21,39]. However, prevention can begin long before screening occurs.

Early risk prevention for osteoporosis can begin at childhood and continue through adult years. Routine physical exercise, especially resistance training increases bone density and strength [17,19]. The strain on a bone from muscle pull during exercise forces the bone to adapt with equal force. Weight-bearing physical activity helps protect the spine and lower extremities, two areas that are susceptible to fracture from weakened bones. A second early intervention is dietary supplementation with calcium and vitamin D. Calcium is the building block of bone and vitamin D is needed for calcium to become active. In childhood, calcium stores can be increased with supplementation; however, calcium absorption decreases with advancing age. Once a person is over age 30, the supplemental calcium makes calcium more available for the body and less needs to be leached from bone for other vital functions. Current recommendation advises that supplemental calcium should be 500–1200 mg/day along with 800 IU/day of vitamin D [21,23].

Along with non-pharmacological interventions, prescription medications play a role in prevention. The most common prescribed agents are bisphosphonates. These medications work by inhibiting the action of osteoclasts, cells that break down bone tissue. Current recommendations include using these medications for only 5 years when low bone density is discovered [29]. Other agents that can be prescribed include raloxifene, nasal calcitonin, and teriparatide. Previously, hormone replacement therapy was used effectively. The effect of increasing estrogen provided a protective mechanism for bone health; however, because of cardiac and cancer concerns, the use of hormone therapy has fallen out of favor [23].

Fall Prevention

Closely related to bone health is fall prevention. Falls in the elderly are very common and represent the leading cause of accidental death. Besides death, falls place a person at risk for fracture, head injury, and prolonged disability. Due to the high risk of morbidity and mortality associated with falls and the subsequent high cost, fall prevention is crucial. Risk factors for falls can be divided into intrinsic and extrinsic causes. Thankfully, many of the fall risk factors have a preventable solution.

Intrinsic risk factors include gait and balance impairment, along with muscle weakness. Routine physical exercise can help prevent this deterioration [16,17]. Exercise helps strengthening muscles and bones. Additionally, exercise helps train proprioception [17]. Specifically, eccentric exercises help with restoring strength as a muscle lengthens [19]. This is critical for descending stairs—a common place where falls occur. A second major intrinsic risk factor is deteriorating medical health. Medical illness, impaired vision, medications, orthostasis, and dementia can all precipitate a fall. Routine follow-up with a physician for close monitoring and management is necessary. Finally, poor nutrition and vitamin deficiencies need to be considered and treated. A healthy diet provides not only needed calories for energy but also needed vitamins for overall well-being. One specific vitamin deficiency that can have deleterious effects and is implicated in falls is vitamin D deficiency. Appropriate vitamin D levels have been linked to bone, muscle, and nervous system health. Vitamin D supplementation is necessary to help strengthen bone, aid in muscle function, and provide postural balance and gait propulsion [2].

Extrinsic risk factors include environmental hazards and proper footwear. Performing a home inspection could identify misaligned floors, clutter, or inadequate lighting [33]. Injury prevention includes fixing cracked walkways and installing handrails [33]. Inside the home, picking up clutter, burying electrical cords, and securing rugs will help eliminate objects that can be tripped over. Additionally, using nonslip mats and installing hand grabs in a bathroom will limit accidental slips [33]. Proper shoes with good traction and an evenly worn sole will provide stability and balance [33]. Not all falls are preventable, but applying the aforementioned interventions can reduce the risk of an avoidable fall.

CONCLUSION

This chapter discussed injury prevention principles and strategies, and reviewed specific conditions and injuries by age groups. These issues ranged from the prevention of ACL injuries, sudden cardiac death, concussions, heat illness, tendinopathy, and arthritis. The role of exercise was also discussed. Exercise can and should be used to treat heart disease, diabetes, hypertension, depression, and cancer. It is worth repeating that the American College of Sports Medicine recommends moderately strenuous exercise 30 min a day 5 days a week for all adults, and there is a growing body of evidence to support this role of exercise in promoting and maintaining health and wellness.

Prevention of injury plays a significant role in sports medicine and exercise science. In the clinical setting, health care providers say that “prevention is the best medicine.” Prevention may be primary or secondary in nature. Primary prevention is preventing a condition from occurring, and secondary prevention is once a condition is established preventing further progression or complications. Injury prevention,

therefore, plays a critical role in health promotion. Injury prevention is ultimately about keeping individuals and communities active, preventing disease and its complications, and promoting health and wellness for everyone.

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60 Female Athlete Triad

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CONTENTS

Introduction 739
Definitions and Epidemiology 739
Pathophysiology 740
Screening and Diagnosis 741
History 741
Physical Exam 741
Laboratory Testing and Imaging 741
Prevention and Treatment 741
Prevention 741
Treatment 742
Conclusion 742
References 743

INTRODUCTION

Organized athletic participation in the United States has seen an 800% rise in the volume of female athletes at every level, since the passage of Title IX in 1972.[1] As a result, there has been increased understanding of the female athlete triad. The first published recognition of the effects exercise has on reproductive function took place in ballet dancers in 1980.[1] The relationship between disordered eating, amenorrhea, and osteoporosis was first formally defined as the female athlete triad in 1993.[2] In 2007, the American College of Sports Medicine (ACSM) updated a 1997 published position stand on the triad.[3] In this statement, an emphasis is placed on decreased energy availability, with or without a diagnosed eating disorder, as the initiating factor in athletes that can lead to abnormalities in menstruation, which in turn play a key role on bone health.

The ACSM stresses the importance in understanding each part of the triad as a spectrum from healthy to disease, with potential effects of even mild deviations.[4] This may be seen in athletes with mild disordered eating, a subclinical menstrual disorder, and have a slightly higher risk of stress fracture. At the other end of the spectrum would be athletes diagnosed with anorexia or bulimia, chronic amenorrhea, and osteoporosis.[5] Throughout the spectrum, athletes are putting themselves at risk and should be evaluated and treated accordingly.

DEFINITIONS AND EPIDEMIOLOGY

The prevalence of disordered eating is difficult to measure secondary to the wide variation in case definitions. Studies have shown prevalence to be anywhere from 0% to 50%.[6] However, two large studies using the *Diagnostic and Statistical Manual of Mental Disorders* as criteria estimated 25%–31% of elite athletes compared to 5%–9% of the general population to have criteria meeting a diagnosis of female athlete triad.[7,8] But, given the shift in defining female athlete triad as a decrease in energy availability as opposed to clinical disordered eating, comparing the prevalence of decreased energy availability in athletes and the general population would be a more accurate distinction. Some studies have defined decreased energy availability as less than 45 kcal/kg lean body mass/day, while others use less than 30 kcal/kg. A study looking at 80 varsity high school athletes and 80 sedentary control students found decreased energy availability, defined as less than 45 kcal/kg, in 36% of the athletes and 39% of the sedentary controls.[9] These findings suggest that low energy availability, and the complications of that deficit, may not be unique to athletes, but rather all adolescent females. Additional studies are needed to truly determine if a difference exists between athletes and controls, and the implications of these findings.

Menstrual function ranges from eumenorrhea to amenorrhea. Primary amenorrhea is defined as failure to menstruate by age 15, which has been lowered from age 16 due to a trend toward earlier age at menarche. Secondary amenorrhea is seen in women with previously normal menstrual cycles that later develop an absence lasting more than 3 months. Within that spectrum, oligomenorrhea involves less than 9 cycles/year.

In the general population, the prevalence of primary amenorrhea is less than 1%,[10] while the prevalence of secondary amenorrhea not due to pregnancy, lactation, or menopause is approximately 3%–4%.[11,12] In athletes, primary amenorrhea has been reported to be 22% in cheerleading, diving, and gymnastics. Reported prevalence of secondary amenorrhea in athletes is variable based on multiple factors

such as sport, level, and age. Studies have documented rates ranging from 26% among U.S. collegiate athletes from seven different sports,[13] to 65% in distance runners and 69% in dancers.[14,15] Perhaps even more important is the estimated menstrual abnormalities along the spectrum of departures from normal menstruation. One study noted among eumenorrheic recreational athletes, 78% were found to have luteal deficiency or anovulation during at least one out of three menstrual cycles.[16]

Similar to energy availability and menstrual dysfunction, bone strength also occurs along a spectrum. Osteoporosis, commonly seen in postmenopausal women, is the most severe form of low bone mineral density (BMD). The World Health Organization (WHO) Classification of Osteoporosis bases BMD on dual energy x-ray absorptiometry (DXA) measurements to a reference young adult population (T-score). In contrast, the Z-score is a comparison of the patient's bone mineral density to an age-matched population. Currently, there is no consensus on the terminology and cutoffs for classification among the International Olympic Committee (IOC), the International Society of Clinical Densitometry (ISCD), and the ACSM when classifying BMD in premenopausal women.[4,17,18]

Organization	Normal BMD	Osteopenia (Low BMD)	Osteoporosis
WHO[a]	T-score within 1 standard deviation (SD) or less of reference population	T-score 1–2.5 SDs below reference population	T-score more than 2.5 SDs below reference population[b]
ISCD	Z-score above −2.0[19]	Z-scores below −2.0	—
ACSM	—	Z-score −1.0 and −2.0[c]	Z-score ≤ −2.0

[a] Diagnosis in postmenopausal women.
[b] In the presence of one or more fragility fractures.
[c] Along with history of nutritional deficiencies, hypoestrogenism, stress fractures, or other secondary clinical risk for fracture (chronic malnutrition, eating disorders, hypogonadism, glucocorticoid exposure, and previous fracture).[3]

A complication to determining the prevalence of low BMD in athletes is that many healthy athletes in weight-bearing sports typically have a BMD 5%–30% higher than sedentary controls. This suggests any decrease in BMD on standard testing to actually be evidence of more advanced bone weakness in athletes versus nonathletes.[19–21] However, one systematic review using the WHO Classification for comparison of BMD, found that T-scores less than −2.5 were found in 0%–13% of female athletes compared to 2.3% in the normal population. But T-scores of −1.0 to −2.5 were found in 22%–50% of athletes compared to 12% in the normal population.[22]

Few studies estimate the prevalence of all three components of the female athlete triad, most have shown that while many athletes may experience one or two of the components of the triad, few will actually display all three. In one study that evaluated 112 U.S. college athletes, 10 athletes (8.9%) met criteria for a combination of two disorders, whereas only one athlete (0.9%) met criteria for all three disorders. It is important to note that in this study, within the testing for low BMD, if a Z-score cutoff of −1.0 was used for low BMD, then three athletes (2.7%) met criteria for all components of the triad.[13] Another study of 170 high school athletes found that 10 athletes (5.9%) met criteria for 2 components of the triad, whereas 2 (1.2%) met all 3 components.[23]

PATHOPHYSIOLOGY

Clinical eating disorders include anorexia nervosa, bulimia nervosa, and disordered eating not otherwise specified. Several predisposing factors for clinical eating disorders have been identified; dieting is the most common factor. Dieting at moderate or severe levels leads to 5 times and 18 times increased risk of a diagnosed clinical eating disorder 6 months later.[24] Other factors include low self-esteem and self-control. It is also important to recognize clinical eating disorders are often accompanied by comorbid psychological conditions, including depression, anxiety disorder, and obsessive-compulsive disorder.[25] And finally, there is also mounting evidence for a genetic component to eating disorders.[26,27]

The etiology of low energy availability in athletes is less clear. Athletes may attempt to lose weight or body fat for the benefit of their athletic performance. This may consist of knowingly restricting caloric intake or an unintentional lack of adjusting caloric intake to correspond with increased energy expenditure.[18] Nutritional guidance helps to show athletes how to eat accordingly to replace energy expenditure as opposed to in response to hunger, studies have shown that although decreased dietary intake does increase hunger, exercise that results in equal energy deficit does not increase hunger.[3,28]

When net energy availability is insufficient, the body's natural response to promote survival is to reduce the amount of energy used for growth and reproduction. In females with insufficient net energy, there is a disruption in the pulsatile secretion of gonadotropic-releasing hormone from the hypothalamus, thus causing a disruption in pulsatile secretion of luteinizing hormone (LH) from the pituitary. This results in a functional hypogonadotropic hypothalamic amenorrhea or dysmenorrhea in athletes, although the specific pathway of this disruption is yet to be identified.[3] This can occur even after just 5 days of low energy availability.[29] LH pulsatility is abruptly disrupted when energy availability drops below 30 kcal/kg lean body mass/day, as opposed to a linear relationship between LH pulsatility and energy availability.[30] Furthermore, neither low body weight nor the act of exercising itself can explain the disruption of LH pulsatility in athletes, suggesting that LH pulsatility depends more importantly on energy availability.[31]

Functional hypothalamic amenorrhea appears to also have a genetic component, and several genes may add to the

susceptibility of certain females to the functional changes in GnRH secretion.[32] There has also been some evidence that the hormone leptin may serve as a signal to the hypothalamus regarding energy availability, in one study treatment of amenorrheic athletes with recombinant human leptin restored menstrual cycles.[33] Several other hormones, including insulin, insulin-like growth factor-I, cortisol, and growth hormone are also being investigated regarding possible signaling roles, although their role is currently unclear.[34]

In postmenopausal women, the most important contributor to low bone mass and osteoporosis is estrogen deficiency, related to estrogen's suppression of osteoclast activity.[35] The relative estrogen deficiency in athletes with amenorrhea contributes to the increased osteoclast activity, although this is only partially responsible for low bone mass in amenorrheic athletes. This is demonstrated best by a lack of normalization of BMD even after years of estrogen replacement.[36,37] Undernutrition has also been shown to reduce the rate of bone formation.[38] One randomized trial placed women into either a dieting group or exercising group with the goal energy availability to be below 30 kcal/kg lean body mass/day. Within 5 days blood markers of bone formation were noted to be decreased, and bone resorption increased.[39] Other factors that affect bone acquisition include leptin, growth hormone, and insulin-like growth factor, and have been discussed in the literature as being affected by low energy availability, further explaining a mechanism by which low energy availability can translate into low bone mineral density.

The statement "Senile osteoporosis is a pediatric disease" alludes to the concept that failure to achieve peak bone mass during adolescence and young adulthood often leads to osteoporosis and increased fracture risk later in life.[40] Most women achieve peak bone mass during their 20s, and while the majority of variability in peak bone mass is determined by genetics, the remaining 30%–40% of variability can be attributed to environmental factors including diet and exercise.[41] This important understanding in the pathophysiology of osteoporosis in postmenopausal women again underscores the need to prevent or treat low energy availability, amenorrhea, and low bone density that can occur in young women.

SCREENING AND DIAGNOSIS

History

The opportunity to screen for the female athlete triad, or one of its components, occurs most frequently at pre-participation physical exams or annual health checkups. However, other visits that may prompt evaluation for the triad may include menstrual abnormalities, stress fractures, or recurrent injuries. Important information to ascertain includes dietary practices, changes in weight or weight fluctuations, exercise practices, feelings of being overweight or underweight, medication history, menstrual history, current menstrual status, and prior stress fractures. There are also screening questionnaires for disordered eating that clinicians may consider using with routine physical exams, including the Bright Futures guidelines and the SCOFF questionnaire (currently validated only in adults).[42,43]

Physical Exam

Exam findings to suggest components of the triad include bradycardia, orthostatic hypotension, cold hands and feet, hypothermia, hypercarotenemia, lanugo hair or thinning scalp hair, oral ulcerations, dental enamel erosions, and parotid gland enlargement. Pelvic exam may reveal atrophy related to hypoestrogenism. ECG, if obtained, may show prolonged QT interval if the patient has a clinical eating disorder. Often, the physical exam will be normal, which should not rule out the presence of any aspect of the triad.[44]

Laboratory Testing and Imaging

For athletes with disordered eating, lab testing should include complete blood count, serum electrolytes, calcium, magnesium, glucose, liver function tests, thyroid function tests, and urinalysis.

In patients with amenorrhea, additional studies should include urine pregnancy test, serum LH and FSH, LH/FSH ratio, and serum prolactin to rule out other causes of secondary amenorrhea, since functional hypothalamic amenorrhea is a diagnosis of exclusion.[42] If these are normal, serum estradiol or a progesterone challenge test can be performed to assess estrogen indirectly (administration of medroxyprogesterone acetate 10 mg once daily for 7–10 days). In functional hypothalamic amenorrhea, the patient would be expected to have a withdrawal bleed and low FSH and LH levels.[45]

Other studies to consider include screening for celiac disease, erythrocyte-sedimentation rate, MRI of the brain, and upper and lower gastrointestinal studies if there is uncertainty about the diagnosis.[42]

The International Society for Clinical Densitometry (ISCD) proposes that bone mineral density testing should be completed in premenopausal women who have a fragility fracture or a disease, condition, or medication associated with low bone mass or bone loss, or in any patient that pharmacologic therapy for the management of osteoporosis is being given or being considered. The current ACSM position stand recommends a bone mineral density assessment by DXA in any female with a history of hypoestrogenism, disordered eating or eating disorder for 6 months or more, and/or a history of stress fractures or fractures from minimal trauma. Additionally, re-evaluation is recommended after 12 months for any persistent female athlete triad disorder.[3]

PREVENTION AND TREATMENT

Prevention

Education is the key to prevention of the female athlete triad, with an emphasis on understanding energy availability, nutritional intake, and balancing intake with energy output.[3,39]

Adolescents, involved in athletics or not, are at risk for low energy availability, menstrual dysfunction, and low bone mineral density, suggesting that all adolescent females may benefit from education on these topics.[9] Specific teaching on daily caloric needs, caloric expenditure with activities, and intake of nutrients, especially calcium and vitamin D, is important. Those that have low energy availability because of a lack of awareness will benefit most from nutritional counseling. Furthermore, it should be stressed to athletes that amenorrhea is not a normal response to exercise and should be evaluated by a physician. The risks of impaired bone mineral density accrual, osteoporosis, and stress fractures should also be communicated to adolescent and young adult females.

For athletes, a multidisciplinary team approach to education is ideal, to include parents, physician, coach, registered dietician, athletic trainer, and mental health provider.[46] Societal and media-related pressures to be thin may play a role in disordered eating.[9] These pressures are compounded in specific sports where performance may be perceived to be enhanced by decreased body fat or weight. The decision to try to lose weight should not be based on a coach's recommendation, and the coach should not play a role in determining the athlete's ideal weight. Rather, any athlete that has concerns about her weight should be evaluated by a nutritionist, with an estimation of daily energy availability and intake of nutrients, followed by further testing as indicated and a discussion between the athlete and health care providers. If a decision is made that the athlete may safely make changes in diet and/or training to try to improve athletic performance, then the athlete should be followed up closely after the goal weight or body composition is reached.[18]

Treatment

The primary goal in therapy is to increase energy availability by modifying diet to at least 30 kcal/kg lean body mass/day and exercise behavior in order to have normal LH pulsatility and restore normal menstrual cycles.[30] With a reversal of amenorrhea, one study showed an 11% increase in bone mineral density, although not necessarily back to normal.[47] Another study in which participants underwent nutritional therapy with regain back to 90% of ideal body weight, increases in spine and hip BMD of 4.38% and 3.77%, were seen after 2.2 months.[48] In a study examining anorexia nervosa patients, those that improved weight and resumed menses showed a mean annual increase in bone mineral density of 3.1% at the posteroposterior spine and 1.8% at the hip.[49] From these studies, results show resumption of menses was most important for improved, spine BMD, whereas weight recovery was most important to the hip. Taken together the conclusion is "nutritional recovery, leading to recurrence of menses and reflected by an increased body mass index, is the best predictor of improved bone mineral density in these patients."[50]

Nutritional counseling is vital to restoring energy availability, including evaluation of the patient's current intake and daily output with training and the steps necessary to reach daily goals. Nutrition counseling should include recommendations on intake of calcium and vitamin D, which should be achieved by supplementation if not reached with dietary intake. For athletes that do not routinely meet these goals or are resistant to counseling or monitoring, restrictions on practice or competition may be necessary and enforced with a written contract.[3]

Treatment with hormone replacement therapy has provided mixed results. A systematic review found "fair" evidence of oral contraceptives showing a positive effect on bone mineral density in oligo/amenorrheic premenopausal women. Limited evidence of a positive effect is seen in anorexic premenopausal women with amenorrhea, with two studies showing a positive effect and five studies showing no effect.[51] Despite this trend toward improvement in bone mineral density, oral contraceptives are unlikely to fully reverse any deficiencies in bone mineral density in hypothalamic amenorrheic women, since "restoration of regular menstrual cycles with OCPs will not normalize the metabolic factors that impair bone formation, health, and performance."[3]

While there does not seem to be a negative effect of oral contraceptives on bone mineral density, it is important to note that hormone replacement therapy-induced menses may make it difficult for health care providers to determine the status of energy availability.[5] The decision to treat with oral contraceptives should be made on an individual basis, while keeping lifestyle and hormonal factors in mind. These factors may include desire for contraception or a failure to regain menses despite conservative measures.[51]

Bisphosphonates are approved only in the treatment of postmenopausal osteoporosis; they are not approved and should not be used in young women of reproductive age. There is a lack of safety data in this population. Furthermore, bisphosphonates are known to cross the placenta, and reside in a woman's bone for many years, potentially causing adverse effects on a fetus even several years after administration.[3,51] Bisphosphonates have been shown to be effective in patients with anorexia nervosa, increasing femoral neck and lumbar spine bone mineral density, but without long-term safety data they should not be used in young women.[52,53]

CONCLUSION

The female athlete triad, consisting of low energy availability with or without eating disorders, menstrual abnormalities, and decreased bone mineral density for age, has continued to evolve as the understanding of prevalence, pathophysiology, and treatment for these linked disorders has progressed. With an emphasis on the understanding of energy availability and its role within the framework of the female athlete triad, health care providers can help athletes to help prevent or minimize potentially significant health risks.

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61 The Role of Rehabilitation in Injury Management

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CONTENTS

Rehabilitation Considerations and Therapeutic Interventions 745
Rehabilitation Considerations 745
Pain and Edema 745
Joint Stability and Mobility 746
Neuromuscular Activation and Control 748
Determinants of Rehabilitation Progression 750
Phases of Tissue Healing and Rehabilitation 751
Destruction/Inflammatory Response Phase 751
Repair Phase 751
Remodeling Phase 751
Specific Rehabilitation Interventions for Chronic Injuries 751
Summary 753
References 753

The goal of this chapter is to present rehabilitation principles and common therapeutic interventions, and the role they play in the management of acute and chronic injuries. A common approach to injury management for many athletes is to rest from sport, take anti-inflammatories, and return to the pre-injury level of activity when pain decreases. This approach may be effective in cases where there is a mild well-defined injury, but risk factors that may have caused the original injury are rarely addressed. Reoccurrence is a common complication, and an acute injury often becomes chronic with the healing potential of the tissue compromised. Perhaps a more appropriate approach to injury management is to apply rehabilitation principles to improve tissue healing potential, reduce the risk factors associated with the injury, and provide training guidelines and assessment for the readiness to return to activity/sport. The goal of this approach is to return the athlete to pre-injury activity levels while minimizing the risk of re-injury.

REHABILITATION CONSIDERATIONS AND THERAPEUTIC INTERVENTIONS

The timeline for returning to sport is dependent on many factors including the extent of injury, healing properties of the respective tissue, and demands of the activity involved. There are many tools and techniques used to address the specific needs and goals of a rehabilitation program. When prescribing physical therapy, it is helpful to understand rehabilitation principles and the interventions appropriate for the given injury. The interventions chosen to address specific injuries are based on theoretical knowledge, evidence-based research, and the practical experience of the clinician. Common interventions by category are presented in Table 61.1.

REHABILITATION CONSIDERATIONS

Regardless of the injury, development of an effective rehabilitation program must include the assessment of the following elements: pain and edema, functional range of motion and strength, neuromuscular control, biomechanical efficiency, training habits, and sport-specific fitness levels [1].

Pain and Edema

Limiting effusion and edema is one of the primary goals in the acute phase of injury. Excessive or prolonged edema can cause secondary cell death creating a more extensive injury, increased tissue pressure, pain, and a reflex inhibition of the associated musculature [2]. Pain control is necessary to enable normal neuromotor recruitment, prevent reflexive muscle spasm, and advance through all phases of rehabilitation.

Therapy interventions used to assist venous and lymphatic function to reduce swelling and pain include modalities (Table 61.2), therapeutic exercise, and manual therapy techniques. Although modalities are commonly used in the management of acute and chronic injury, conflicting evidence

TABLE 61.1
Common Rehabilitation Interventions

Modalities	Ultrasound, phonophoresis, iontophoresis, electrical stimulation, cold, and heat therapy
Therapeutic exercise	Specific exercise interventions to restore bilateral symmetry and function include: ROM, flexibility, neuromotor re-education, strength training, plyometric training, endurance training
Manual therapy	Hands-on techniques to restore mobility of the joint and soft tissues, and modulate neural input include joint mobilization, soft tissue mobilization, myofascial release, trigger point therapy techniques, neural mobilization
Biomechanical analysis	Analysis of motion to identify pathomechanics and optimize mechanics of specific movements including gait training, running, throwing, and jumping
Program planning	Development of a home exercise program (HEP) and structured training program to define a logical progression of training and recovery in order to reduce the risk of re-injury upon return to sport

TABLE 61.2
Therapeutic Modalities

Modality	Therapeutic Effect
Cold	Decrease pain, inflammation, edema Ice massage: 5–7 min; ice pack: 15–20 min *Acute* every hour or multiple times/day; *Post rehab*: 15–20 min
Heat	Increase blood flow; tissue extensibility, and muscle relaxation; decrease pain; 15–20 min, after first 48 h
Heat/cold contrast	Increase blood flow; mobilize chronic edema Hot:cold ratio = 3:1
Ultrasound	Deep tissue heating; decrease pain; decrease inflammation; decrease chronic edema
Phonophoresis (ultrasound used to drive medication into tissue)	Hydrocortisone cream commonly used Decrease inflammation, swelling, and pain
Iontophoresis (delivery of medication via electrical current)	Corticosteroids commonly used Decrease inflammation, swelling, and pain
Electrical stimulation	Decrease pain; muscle contraction and re-education, decrease swelling

exists regarding their efficacy in the role of recovery [3–5]. Appropriate therapeutic exercises include passive and active ROM activities, such as sub-maximal muscle contractions, and light resistance cycling. Manual therapy techniques include gentle soft tissue and joint mobilization.

JOINT STABILITY AND MOBILITY

Joint mobility can be defined as the range a joint can move through before being restricted by the surrounding ligaments, joint capsule, musculature, and bony anatomy. Assessment of mobility is measured in degrees of range of motion (ROM). *Active ROM* (*AROM*) is the active movement of a joint by the muscles controlling the joint. *Passive ROM* (*PROM*) is the passive movement of a joint by an external source or gravity, and without muscular contraction. Both may be limited following injury secondary to pain, joint or muscle tightness, and muscle spasm. Therapeutic interventions including active and passive stretching exercises, joint and soft tissue mobilization techniques, and modalities to enhance tissue flexibility are employed to restore functional mobility.

Joint stability is the ability to maintain necessary joint congruency and alignment to reduce friction and wear of the joint, and control active movement of the joint. *Static stability* depends on passive restrictions to movement and includes the bony anatomy, ligaments, joint capsule, and cartilaginous structures. *Dynamic stability* depends on the strength, endurance, and neuromuscular recruitment of the joint and core stabilizing musculature to stabilize the joint with active movement and increased joint loads.

CLINICAL EXAMPLE: THE IMPORTANCE OF MOBILITY AND STABILITY IN SHOULDER FUNCTION

The shoulder joint has a large capacity for motion secondary to its anatomical configuration, but stability of the joint is dependent on the static and dynamic stabilizers. The glenoid labrum, glenohumeral ligaments, and joint capsule provide passive joint stability, while the rotator cuff and scapular stabilizers provide dynamic stability and control [6,7].

In dislocation or subluxation injuries, the ligaments and capsule of the joint are overstretched with a resulting loss of static joint congruency, and an increasing reliance on the dynamic stabilizers. Dynamic stability and function of the shoulder depends significantly on the strength, endurance, and coordination of the surrounding musculature. The *scapular stabilizers* link the scapula directly to the trunk of the body and include the rhomboids, upper, middle, and lower trapezius, and the serratus anterior. Their role is to provide the humerus with a stable platform from which it can efficiently operate. When the arm is elevated above 90°, the scapula has to upwardly rotate to prevent impingement of the humerus against the acromion. This requires a coordinated force couple of the upper trap, lower trap, and serratus anterior(Figure 61.1). *Scapular dyskinesia* is an alteration in the normal position or motion of the scapula during coupled scapulo-humeral movements and is a result of weakness or fatigue.

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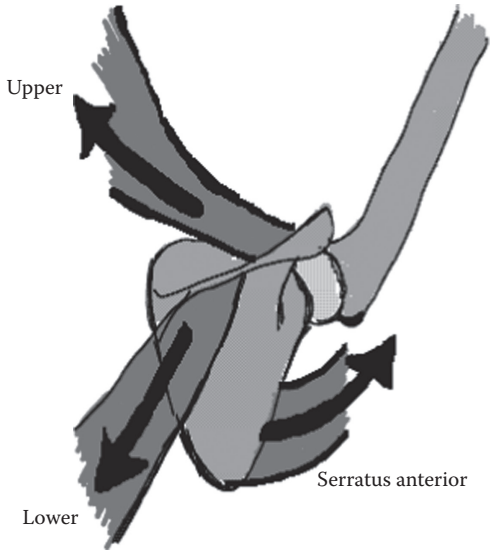


FIGURE 61.1 Muscular force couple for upward rotation of the scapula.

The *glenohumeral stabilizers* consist of the rotator cuff musculature (infraspinatus, supraspinatus, teres minor, subscapularis). Because of their length, alignment, and proximity to the joint, these muscles have an excellent biomechanical advantage to provide compression and stability to the humeral head. This is necessary to keep the humeral head centered in the glenoid and prevent superior migration as the arm is taken into an elevated position (Figure 61.2).

The scapular stabilizers and rotator cuff must work in coordination for efficient shoulder function, and common rehabilitation exercises for both are presented in Figures 61.3 through 61.6 [8–10].

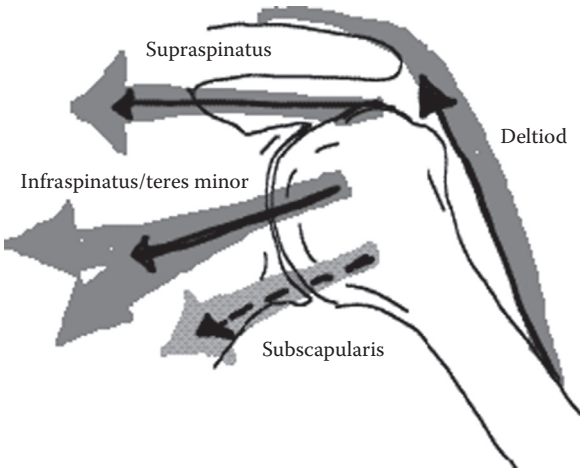


FIGURE 61.2 Compressive forces of rotator cuff with shoulder elevation.

(continued)



FIGURE 61.3 Full can: supraspinatus.



FIGURE 61.4 Sidelying rotation: infraspinatus.



FIGURE 61.5 "W" Squeeze: mid/low trapezius.

(*continued*)

(continued)



FIGURE 61.6 Push up plus: serratus anterior.

Neuromuscular Activation and Control

Neuromuscular inhibition is common in an acute injury secondary to pain or swelling. It is also present in injuries of a chronic nature secondary to pain, tightness, decreased proprioceptive feedback, or apprehension. Persistent muscle imbalances may result in altered motor control and mechanics, and increased risk for injury. Re-establishing efficient neuromuscular recruitment patterns is essential for restoring symmetrical balance, proprioception, and strength post injury [11].

Therapeutic exercise programs should incorporate closed chain exercises to stimulate articular receptors, and muscle co-contraction to enhance joint stability. *Balance, proprioception, and core stability* training is necessary to increase the ability to sense and control joint movement and position. It is also required to maintain balance and a stable base, despite forces generated from other body parts during athletic maneuvers [1,11–13]. Reactive neuromuscular training enhances reflexive stabilization. Strength and plyometric exercises have been shown to decrease the response time and develop reactive strategies to increased or unexpected joint

CLINICAL APPLICATION: NEUROMUSCULAR TRAINING TO REDUCE ACL INJURY

ACL injuries are very prominent in young athletes, especially females. The rate of injury is as common as 1/10 college athletes and 1/50 high school participants [11,13,14]. Common risk factors that may affect incidence of injury are landing in a valgus knee position, decreased trunk stability and awareness, poor knee flexion or straight-leg landing, quadriceps dominance, and imbalances between sides. Many programs have

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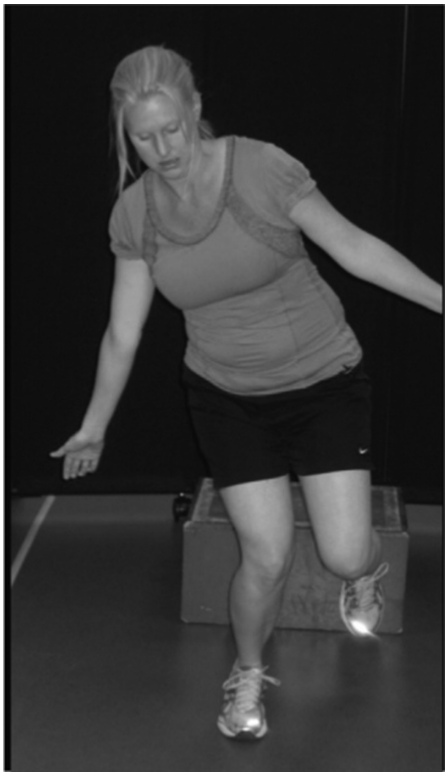


FIGURE 61.7 Valgus landing and center of mass outside base of support. Common presentation of poor body awareness and control, and inability to absorb and direct ground impact forces.



FIGURE 61.8 Good alignment with athletic stance landing position.

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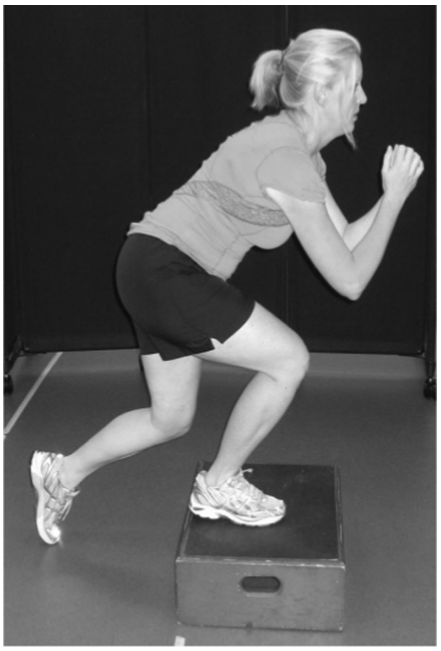


FIGURE 61.9 Step back exercise emphasizes strengthening in good lower extremity alignment with a bias of gluteal and hamstring recruitment.

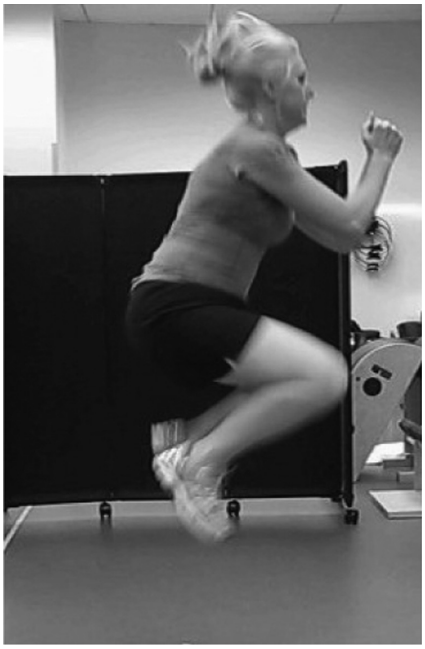


FIGURE 61.10 Tuck jump-plyometric rebound exercise to decrease ground response time and develop reactive strategies.

been developed which address the risk factors for ACL injury, and a common component of all programs is neuromuscular training. Programs to reduce injury focus on techniques that emphasize strong athletic positioning and body control, while eliminating excessive side to side motion. The programs are based on biofeedback and emphasize correct posture, body alignment,

(continued)

core stability, soft landings, and appropriate recoil in jumping. Proper neuromuscular training has been shown to reduce impact and decreases peak landing forces, thus lowering the injury risk in female athletes. The decrease may be due to increased dynamic stability of the knee through training (Figures 61.7 through 61.10) [14,15].

loads [11]. The goal of training is to progress from conscious to unconscious control of movement patterns and strategies.

Strength: is the ability to produce, resist, or control force, and is dependent on how well the nervous system recruits muscle fibers, as well as on the size and number of muscle fibers recruited. It is an important factor in injury prevention and return to play, and there is a critical level of strength needed to reduce the risk of injury or restore function which is determined by the demands of the sport. Strengthening major muscle groups throughout the ROM and demonstrating muscular power are components of *functional strength training*, and should focus on symmetry between limbs and between agonist/antagonist [10,13,16] (Table 61.3).

Biomechanics of activity: Subtle alteration in normal mechanics may have a profound effect, especially with repetitive movements over a period of time. It is important to evaluate and recognize pathological biomechanics that will lead to increased stress and subsequent tissue injury [17–20]. Evaluation of running form can identify loading patterns that have a high correlation to injury at the foot or ankle. Appraisal of landing mechanics can identify positions that correlate with increased risk of patella-femoral problems or ACL injury in the female population, and assessment of throwing mechanics can identify patterns that correlate with increased risk of injury to the shoulder or elbow.

Training modifications: Training modifications are necessary for most athletes returning to activity following injury. Structured programming should modify training by adjusting volume, load, and intensity to prevent interruption of the healing process. Integrating cross-training, multi-planar strengthening techniques, and activity diversification is an effective way to prevent tissue overload as programs addressing these factors have been shown to decrease rate of re-injury [21,22].

Return to sport: Return to sport is the final stage of rehabilitation for an athlete. Progressive increase of the load demands on the body while protecting it from injury is the main goal of return to sport programs. Training should gradually introduce more aggressive movements throughout unrestricted range of motion, and include the combination of balance, weights, plyometrics, agility, and sport-specific patterns or skills [23]. Sport-specific requirements of strength, endurance, speed, load, and flexibility determine readiness to play, and should meet predetermined criteria based on the imposed demands of the sporting activity [14,24–28].

TABLE 61.3
Training Definitions

Term	Definition	Clinical Example
Concentric	Contraction with muscle shortening	Ascent from a squatting position
Eccentric	Contraction with muscle lengthening "Negative or Braking" contraction	Decent into a squatting position
Open kinetic chain	Distal limb moves through space	Seated knee extension, bicep curl
Closed kinetic chain	Distal limb fixed	Squat, Step-up, push-up
Proprioception	Awareness of body position and movement	Wobble board, balance perturbations
Plyometrics	Exercise involving repeated rapid stretching and contracting of muscles to increase shock absorbing capabilities, neuromuscular coordination, and quickness	Rebound jumps, tuck jumps, overhead throws
Core stability	Muscles that contract to stabilize the spine, pelvis, and shoulder girdle and create a solid base of support for powerful movements of the extremities	Front bridges, side bridge, back bridge
Multi-planar	Are multi-joint, closed chain exercises in the sagittal, frontal, and transverse planes for the purpose to increase strength and stability in functional movement patterns and decreases repetitive stress in the primary plane of motion	Multi-planar matrix lunges, woodchops, dot drills

Functional fitness: Needs to be attained prior to unrestricted return to sport. Cardiovascular and muscular endurance detraining occurs at a more rapid rate than muscle atrophy, and athletes who do not maintain cardiovascular fitness are more likely to sustain another injury when returning to their sport [29]. The intensity of cardiovascular re-training should be sport specific, and the training load progressed to a level equal to or higher than the athlete's actual sport.

Determinants of Rehabilitation Progression

The initiation and progression of a rehabilitation program is primarily based on the healing properties of the involved tissues. Therapeutic interventions with specific criteria for progression are applied to optimize healing potential and minimize the risk of re-injury. The timeline for returning to sport is dependent on many factors including the extent of injury, healing properties of the respective tissue, and demands of the activity involved.

Tissue injury occurs by one of two mechanisms. *Macrotraumatic* injuries involve any single stress to the tissue beyond its tensile limit. These are typically acute injures with a specific history of insult. Examples of these types of injuries are fractures and acute musculoskeletal sprains or strains. *Microtraumatic* injuries occur in response to repeated stresses within the tensile limit of the tissue but with an insufficient recovery time between stress applications. These injuries tend to be more vague in exact onset and are usually described as a more chronic and persistent type of injury. Examples of these types of injuries include tendonitis, bursitis, and stress fractures [2].

Tissue vascularity is a critical component to healing. Avascular tissues have a longer healing time and often cannot

TABLE 61.4
Healing Characteristics of Specific Tissue

Tissue	Healing Considerations
Bone	Good vascularity. Overall healing potential is affected by age, severity, and site of the fracture. Healing usually requires immobilization for 4–8 weeks, with the gradual application of load following that to allow tissue adaptation to the stress applied
Tendon	Limited vascularity. The musculotendinous junction and bone/tendon interface vascularity is greater than that of the free tendon. 4–6 weeks of relative rest or immobilization is required for healing
Ligament	Limited vascularity. Frequently the structural strength of the scar produced is inadequate for strong approximation of the ruptured ligament. Immobilization for 6 weeks with many months of remodeling are necessary to restore full strength
Articular cartilage	Avascular. Limited capacity to heal
Menisci/fibrocartilage	Healing depends on pattern of blood supply. The periphery of the meniscus has adequate blood supply for healing and requires 4–6 weeks of restricted movement and weight bearing to heal. The inner portion of the meniscus is avascular and has poor healing potential
Nerves	Nerve cells can regenerate significantly if the injury does not affect the cell body. The closer the injury is to the cell body, the longer the healing time. The axon proximal to the cut begins regenerative process, and scar formation can obstruct regeneration. Healing occurs at a rate of 3–4 mm/day
Muscle	Vascular. Healing is affected by extent and location of injury. Re-injury is frequent due to altered neuromuscular input, and return to activity before tensile strength is regained. Healing occurs from 1 week to many months

produce a functional healing response or a strong scar. Other factors that may impede healing are excessive bleeding and edema, poor approximation of injured tissue, extensive tissue trauma, infection, advanced age, and an interruption of the inflammatory response [2]. (See Table 61.4 for healing consideration for specific tissues.)

Although different types of tissue have specific healing characteristics that determine rehab progression time frames, in general all go through three primary phases of a healing continuum with correlated stages of rehabilitation [30–39].

PHASES OF TISSUE HEALING AND REHABILITATION

Destruction/Inflammatory Response Phase

This is the acute response to injury and characterized by cell rupture and death. The initiation of an inflammatory response sets off a cascade of metabolic changes and formation of a hematoma resulting in a localization of the injured area. This phase is essential to an effective healing process and lasts approximately 2–5 days depending on the extent of the injury.

Phase 1 Rehabilitation: The goals of this stage are to do the following:

1. *Minimize pain, and limit edema*: Prevent neuromuscular inhibition and secondary cell death.
2. *Protect the scar formation*: Aggressive mobilization during this phase can result in rerupture of the healing tissues, and ultimately increased scarring.
3. *Minimize atrophy and maintain neuromuscular control*.
4. *Reduce associated muscle spasm*: Decrease pain and neuromuscular inhibition.

R.I.C.E

The first 24–48 h to prevent prolonged inflammation and excessive scarring [30,31,40].

Rest: Immobilization and non-weightbearing or non-loading of the injured extremity with use of crutches, braces, or splints

Ice: 15–20 min with cold pack several times a day to control swelling and pain

Compression: Wrap to decrease the pressure gradient between vessels and tissue, and assist lymphatic drainage

Elevation: Elevation of the injured body part above the level of the heart also promotes decreased blood flow and helps with absorption into the lymphatic system, reducing the amount of edema

Repair Phase

Important events of this phase are the phagocytosis of the necrotic tissue, tissue regeneration and revascularization, and production of a connective tissue scar. This process starts within a few hours of injury and can continue for 4–6 weeks again depending on the type of tissue injured and the extent of the injury.

Phase 2 Rehabilitation: The goals of this stage are to do the following:

1. *Stimulate the healing tissue*: To adapt and grow to the stress demands that will be placed on it. Gradual and specific application of stress will stimulate the tissue to increase structural strength, prevent inadequate scar formation, and reduce the likelihood of re-injury when functional load of sport is applied [30,31,40].
2. *Progress ROM and strength*: Based on patient tolerance and rate of improvement.
3. *Restore neuromuscular control*.
4. *Gradual re-introduction of functional*: Activity limited by pain.

Remodeling Phase

This phase consists of reorganization and remodeling of the scar tissue, and recovery of the functional capacity as the tensile strength of the scar increases. This process can take from a few weeks to months or years depending on the extent of the scar and the type of tissue involved.

Phase 3 Rehabilitation: The focus of this phase is to prepare the athlete for a safe return to sport:

1. Perform more aggressive movements through full unrestricted range of motion.
2. Restore functional and bilaterally symmetrical strength.
3. Sport-specific conditioning and training to prepare the athlete for return to sport.
4. Regain sport-specific skills.

SPECIFIC REHABILITATION INTERVENTIONS FOR CHRONIC INJURIES

What if the normal healing response is interrupted or dysfunctional? Many injuries of a chronic nature do not have a well-defined injury mechanism and do not follow the typical phases of healing. Although the exact mechanism of injury varies, repetitive stress, and overuse with lack of recovery time often play a key role in the development of these types of injuries [35–39,41–46]. With chronic inflammation there is a failure of the healing response, and poor tissue reorganization. The body is unable to keep up with

CLINICAL EXAMPLE: MANAGEMENT OF ACUTE ANKLE SPRAINS

Phase 1: Inflammatory, Acute Phase: The goal of this phase is to reduce pain and inflammation, and set up an optimal healing environment.

Relative rest	Remove the athlete from painful and irritating activities. Rest by non-weightbearing or unloading the effected ankle with crutch until the athlete can walk without a limp. A CAM walking boot is often used in this phase to immobilize the injured ankle. Continue modified conditioning program that does not involve the lower extremities
Decrease inflammation, swelling, and pain	R.I.C.E—Ice 20 min several times per day. Modalities such as electrical stimulation may be used to control pain and superficial swelling
Therapeutic exercise	Gentle ankle AROM within pain-free range. Toe gripping and spreading. General body maintenance exercises that do not stress the ankle
Manual therapy	Avoid aggressive soft tissue mobilization that may disrupt scar formation
Criteria for progression	Minimal pain at rest, ambulation without assistive device or limp

Phase 2: Restoration of Function: The goal of this phase is to restore normal biomechanics to the ankle joint, promote functional/dynamic mobility; Correct ROM limitations

Control pain and swelling	Compression, ice, and modalities to limit edema and pain. Sporting activity is limited as patient restores function to the joint
Therapeutic exercise	Restore full ROM through active and passive stretches Progressive strengthening of ankle musculature through pain-free ROM including calf raises, elastic band resisted exercises in eversion, inversion, plantarflexion, and dorsiflexion Balance and proprioception progressions: Single leg stance exercises starting on a stable surface with progression to unstable surfaces. Increase exercise challenge: eyes closed, barefoot, movement of opposite extremities, balance perturbations Maintain cardiovascular fitness with conditioning programs on bike, elliptical, and aqua-jogging as tolerated
Manual therapy	Gentle joint mobilization of foot and ankle to restore ROM Gentle soft tissue mobilization to decrease swelling
Criteria for progression	Full pain-free ROM, 5/5 pain-free manual muscle test of all ankle motions, pain-free initiation of sport-specific activities, minimal and controlled swelling following activity

Phase 3: Return to Sport: Goal is to return to full participation without reoccurrence of injury

Continued interventions	Bracing or taping for practice and sport to increase proprioception and stability Modalities as needed to control swelling and post workout discomfort
Training progressions	Progress training to include a more functional load, volume, and speed with parameters for advancement (return to running, jumping, kicking). Initially allow for long recovery, progressing to shorter recovery to advance to more sport-like scenario. Focus is given to equalizing ground reaction forces, improving confidence and stability with change in direction, and perfecting biomechanics. Activities incorporate cutting, agility drills, plyometrics, and power drills
Criteria for return to play	5/5 manual muscle test with repeated contraction, bilateral balance symmetry, sport-specific tasks (running, cutting, jumping) without pain or stiffness. Meet pre-injury or baseline fitness criteria

repair of the damage created from repetitive micro-trauma to tendons and muscles. Genetic predisposition, increased age, and tissue strength less than the task demands may also play a role in these types of injuries [35].

The rehabilitation goals for these types of injuries are to try to stimulate a healing response and limit repetitive stress to the injured tissue. Rehabilitation focuses on restoring functional mobility, strength, and stability, correcting faulty biomechanics associated with tissue overload, and creating a training plan to limit stress and increase recovery potential [47–50].

Components of a rehabilitation program to address chronic injuries include the following: (1) stimulation of a healing response; (2) correction of faulty biomechanics; (3) restoration of functional mobility, stability, and strength; and (4) modification of training programs to limit repetitive stress to the injured tissue.

CLINICAL EXAMPLE: ECCENTRIC TRAINING IN ACHILLES TENDINOPATHY

Achilles tendinopathy is a common overuse injury in athletes [51]. The term *tendinopathy* is used to describe a non-specific dysfunction of a tendon that occurs in response to an unaccustomed activity or stress. Further delineation of tendinopathies requires histological analysis of the involved tissue. *Tendonitis* is a dysfunction that involves an inflammatory process in the tendon or associated structures. *Tendinosis*, in contrast, is characterized by an absence of inflammatory cells, and a degradation of the tendon tissue with infiltration of abnormal nerve and vascular tissue [52–56].

While therapeutic interventions aimed at reducing inflammation may be helpful in reducing pain and inflammation in tissues surrounding the tendon, they are of limited benefit where there is a lack of inflammatory response in the tendon itself. The focus of rehabilitation in these cases is to stimulate a tendon-healing response. Mechano-transduction is the process of a cell converting mechanical stimuli into biochemical signals. Tendons adapt their metabolism and structural properties to meet mechanical forces applied. This is the reason *eccentric strengthening* programs are commonly used to elicit a remodeling response in tendinopathies [57–62].

There are many eccentric training programs presented in the literature [63–72] for the treatment of Achilles tendinopathies. The program presented next is illustrative of a common eccentric program:

ECCENTRIC TRAINING PROGRAM FOR ACHILLES TENDINOPATHY

Calf muscle soreness, and increased pain in the Achilles insertion, could appear during the first weeks of eccentric training

General instructions: Lift both heels off of the floor to a position of full plantarflexion. Transfer weight to injured leg and slowly lower heel down to the floor on a 3 count. (This can also be done with heels of the edge of a stair for more ROM.)

Program execution: 15 reps:2×/day, progressing to 2–3 sets of 15 reps:2×/day
7 days/week, × 12 weeks

Program progression: Increase load by adding dumbbells or weight in a backpack when there is no increased pain immediately after exercise or the following morning.

SUMMARY

The ultimate goal of rehabilitation is to return the athlete to sport as quickly as possible without recurrence of injury. Understanding the phases of healing as well as the therapeutic interventions and principles can assist the practitioner in determining a logical progression through the rehabilitation program. Specific criteria for advancement are the best strategy to minimize risk, but it is important to clarify that release from a rehabilitation program and return to sport does not necessarily correspond with full healing of the injury, and precautions may exist for the athlete [22,24].

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62 Physiology of the Athlete
Bioenergetics, Performance, Physiological Testing, and Monitoring

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CONTENTS

Physiology of the Performance Athlete: Central Adaptations versus Local Adaptations 758
Maximal Oxygen Consumption 758
Local Adaptations Start in Skeletal Muscle: The Muscle Contraction 758
Muscle Fibers 759
Type I Muscle Fibers 759
Type IIa Muscle Fibers 759
Type IIb Muscle Fibers 759
Basic Exercise Bioenergetics 759
Anaerobic Metabolism during Exercise 760
Aerobic Metabolism during Exercise 760
Carbohydrate Metabolism during Exercise 760
Lipid Metabolism during Exercise 761
Protein Metabolism 762
Lactate Metabolism 763
Training Adaptations to Exercise 763
Central Adaptations to Exercise 763
Local Adaptations to Exercise 764
Skeletal Muscle Fiber Changes 764
Adaptations to Training at the Cellular Level and Substrate Utilization 764
Physiological Testing and Monitoring of the Athlete 764
The Scientific Approach 765
Physiological Testing: Coaching 101 765
Physiological Testing in Laboratory and Field Tests 765
Laboratory Tests 765
Field Tests 766
Monitoring of the Athlete 766
Physiological Testing for Monitoring Purposes 766
Monitoring for Overtraining 767
Causes of Overtraining 767
Excessive Training 767
Poor Recovery and Assimilation 767
Improper Nutrition 767
Psychological Stress 767
Monitoring Overtraining: The Answer Is in the Blood 768
Hemoglobin 768
Biomarkers for Muscle Damage 768
References 768

The field of exercise physiology is an important part of an integrative sports medicine.

More and more athletes are competitive worldwide, regardless of the level of competition, age, or gender. From professional to recreational athletes, competitions in many different sports worldwide keep breaking records of audience and participation every year. We live in a very competitive society where competition is always present. Exercise physiology is part of integrative sports medicine programs in many professional and elite sport teams worldwide where the improvement and optimization of performance is the ultimate goal of any athlete and team and as important as the recovery and return to play after injury.

For recreational athletes, improvement in performance is a major goal as well. Hundreds of thousands of recreational athletes worldwide have become competitive athletes of their own. They enter many competitions with the purpose of improving their personal record, beating the opposite team, or just beating the next-door neighbor. Although not yet very well established in the United States, for recreational athletes, the field of exercise physiology has a very large potential and application in order to help this population in achieving their goals and optimizing their time.

The goal of this chapter is to present the audience with different approaches in the field of exercise physiology that are being applied nowadays to both elite and recreational athletes through different methodologies like physiological testing, training monitoring, nutrition, and prevention and detection of overtraining where the scientific approach and rationale are essential for the application of these methodologies.

PHYSIOLOGY OF THE PERFORMANCE ATHLETE: CENTRAL ADAPTATIONS VERSUS LOCAL ADAPTATIONS

The human body is the most fascinating and complex machine that has ever been built. It is so complex to understand that after centuries of study we still don't fully understand many processes happening in the human body. During exercise many physiological and metabolic process occur simultaneously and the study of these physiological and metabolic processes has occupied a vast space in many scientific studies. The field of exercise physiology is an evolving field and many concepts and knowledge have evolved from the first scientific studies in exercise physiology back in the eighteenth century to the present time. Central adaptations to exercise based on the cardiovascular and respiratory system were the main physiological parameters measured and understood for many years. The scientific advances in technology, infrastructures, and knowledge of the last part of the twentieth century have allowed us to know much more about exercise bioenergetics as well as the physiological and metabolic adaptations to exercise at the cellular level such as the muscle and enzymatic responses and adaptation to exercise, muscle fiber recruitment patterns, the regulation and utilization of energy substrates, and in general, the muscle metabolic integration of the athlete. The capacity of an athlete to exercise depends on the ability to convert chemical energy into mechanical energy, so ultimately all the events happening at the cellular level are crucial for skeletal muscle during exercise. Modern exercise physiology has in a way become exercise biochemistry due to all the knowledge that we have nowadays of the events happening at the cellular level during exercise. For example, we know now that the central adaptations to exercise (cardiorespiratory) are very similar among athletes of similar levels of competition, but we know that the local adaptations at the cellular level are the ones that set athletes apart during the competition.

MAXIMAL OXYGEN CONSUMPTION

Maximal oxygen consumption (VO_{2max}) is the main parameter representing central adaptations to exercise. VO_{2max} is the maximum capacity that the body has to transport and use oxygen during exercise. It is the major cardiorespiratory parameter used to measure physical fitness and aerobic capacity. Oxygen consumption during exercise was first measured by French chemist Antoine Lavoisier in 1873 [1], and ever since the measurement of O_2 consumption during exercise has been of great interest in the field of exercise physiology. VO_{2max} has been used for many years as the best assessment of cardiorespiratory fitness. The relatively easy measurement of VO_{2max} through indirect calorimetry with commercially available "metabolic carts" since the 1970s has made the "VO_{2max} test" very popular worldwide as a way to assess the fitness level of an athlete and is even used to predict performance and prescribe training zones and programs for athletes. However, it is well known that VO_{2max} is a poor indicator of performance [2]. Many exercise physiology laboratories worldwide can observe how athletes improve their records and performances over the years in spite of not improving their VO_{2max}. However, in these athletes, it is easy to observe improvements in lactate metabolism or fat and carbohydrate (CHO) metabolism during exercise, which means that the physiological and metabolic parameters that elicit an improvement in performance in these athletes are local, at the cellular level. Therefore, in modern exercise physiology it should be important to study and identify the metabolic responses to exercise at the cellular level like lactate metabolism or fat and CHO metabolism during exercise.

Local Adaptations Start in Skeletal Muscle: The Muscle Contraction

Skeletal muscles are surrounded by a layer of connective tissue, called epimysium, which attaches to the bone through the tendon. Each muscle is composed of fascicles and each fascicle is made of a bunch of muscle cells, called muscle fibers. Each muscle fiber is long and has multiple nuclei and specialized organelles. Each muscle fiber contains multiple myofibrils where muscle contraction ultimately happens. Myofibrils contain contractile proteins organized in

thin filaments (actin) and thick filaments (myosin), which repeat many times along the length of a myofibril in sections called sarcomeres. Muscles contract by sliding the actin and myosin filaments along each other and sarcomeres shorten. Adenosine-5′-triphosphate (ATP) is the compound necessary for muscle contraction. The binding of ATP dissociates myosin from actin. ATP hydrolysis results in a change in configuration that displaces the myosin head group. This change in configuration is followed by the binding of the myosin head to a new position on the actin filament and then the release of adenosine diphosphate (ADP) and phosphate (P_i.). When the myosin head returns to its original conformation, the actin filament slides, and this causes muscle contraction. This process also requires calcium (Ca^{++}), which is released from the sarcoplasmic reticulum. There is a protein called tropomyosin that prevents myosin from binding actin when muscle contraction is not needed. Tropomyosin exists on top of actin filament and has a regulatory protein called Troponin C. When an action potential generated by a motor unit arrives at the muscle, calcium is released from the sarcoplasmic reticulum and binds to troponin C. This "unlocks" tropomyosin from actin, allowing the myosin head to bind actin for the initiation of muscle contraction.

MUSCLE FIBERS

Skeletal muscle has three kinds of muscle fibers: slow twitch/red/oxidative muscle fibers also called Type I and fast twitch/white/glycolytic muscle fibers divided in two subgroups called Type IIa and IIb. Muscle fiber contraction obeys a sequential recruitment pattern where Type I muscle fibers are the first ones to be recruited, followed by Type IIa and finally Type IIb [3–5]. Each muscle fiber has different biochemical properties and behavior during exercise. The knowledge of the histological properties of these muscle fibers has been crucial to understanding muscle physiology.

Type I Muscle Fibers

These muscle fibers are also called slow twitch, slow oxidative, and red fibers. They have a high mitochondrial density and oxidative enzymes. Of all the muscle fibers, Type I's have the highest capacity to oxidize free fatty acids (FFAs) from subcutaneous adipose tissue and intramuscular triglycerides (IMTGs). They have the slowest contraction time of all fibers as well as the lowest force production. However, they have the highest resistance to fatigue. These muscle fibers are suited to endurance events and endurance athletes have the highest proportion of these muscle fibers.

Type IIa Muscle Fibers

Also called fast oxidative glycolytic or fast red, Type IIa muscle fibers have a high glycolytic capacity and somehow a good or intermediate oxidative capacity, although the latter is not as much as in Type I muscle fibers. Mitochondrial density is also considerably less than Type I fibers. Fat oxidation is less than in Type I muscle fibers and glucose oxidation is higher. Contraction time is fast, force production is high, and resistance to fatigue is intermediate. Type IIa muscle fibers are crucial for most athletes and sports, including endurance sports, as although the endurance aspect is very important, almost all competitions are decided at high intensities and therefore in the glycolytic state where these muscle fibers are the major players.

Type IIb Muscle Fibers

Finally, these muscle fibers, also called fast glycolytic or fast white, have the fastest contraction time of all fibers as well as the highest contraction force. Mitochondrial density is quite poor in these muscle fibers; therefore, lypolysis and aerobic glycolysis will be very low. The anaerobic component through anaerobic glycolysis and stored phosphocreatine (PC) and ATP of these muscle fibers is the dominant metabolic pathway. Type IIb muscle fibers are very important in athletic events of very short duration and very high intensity such as sprinting or 400 m.

BASIC EXERCISE BIOENERGETICS

The capacity of an athlete to exercise ultimately depends on the ability to transform chemical energy into mechanical energy. For this, skeletal muscle needs to synthesize ATP for muscle contraction. ATP is a nucleotide responsible for the energy processes in human cells. It is often called the "molecular unit of currency" for the cells. ATP is indispensable for muscle contraction so ATP needs to be synthesized constantly during exercise. ATP generation is achieved by two mechanisms: anaerobic and aerobic metabolism and through fats and CHOs mainly, with some contribution from amino acids. Fats and CHO are stored in skeletal muscle and in the case of fat it is stored primarily in the adipose tissue but also in skeletal muscle and in the liver. Each energy system and substrate will be activated depending on the metabolic and physiological stress, contractile necessities for ATP generation of the muscle (exercise intensity), and the fiber recruitment pattern. The process of ATP generation and activation of different energy process for muscle contraction is a complex mechanism that needs the regulation and coordination of different systems including the cardiovascular, respiratory, nervous, and endocrine systems, which ultimately will elicit different actions on skeletal muscle and its muscle fibers where all the of different physiological systems come into action in the cytosol and mitochondria of these muscle fibers. A large majority and range of exercise intensities can generate ATP through aerobic metabolism also called oxidative phosphorylation. Fat and CHO generate ATP during aerobic exercise. Depending on the level of fitness of an individual, fat can sustain the biggest part of ATP generation aerobically up to 55%–75% of VO_{2max} intensity, although CHO is also used at small rates during low and moderate exercise intensities. Beyond this point, ATP generation needs to be faster in order

to keep up with a higher frequency and power in muscle contraction and CHO will become the major energy used by skeletal muscle up to 100% of VO_{2max}. When exercise intensities are very high and maximal or close to maximal and therefore above 100% of VO_{2max}, ATP cannot be generated by the aerobic mechanism so the ATP needs to be generated through the anaerobic mechanism also called substrate phosphorylation.

ANAEROBIC METABOLISM DURING EXERCISE

At exercise intensities of 100% of VO_{2max} and more, ATP cannot be synthesized through aerobic mechanisms so anaerobic metabolism is necessary for its regeneration. Anaerobic metabolism has a very high rate of ATP synthesis. In skeletal muscle there is always a small amount of stored ATP ready to provide energy to muscle fibers. ATP is hydrolyzed (broken down) to ADP to produce energy for muscle contraction by an enzyme called ATPase in the myosin head of myofibrils. The human body has a remarkable capacity to restore ATP storage and production under any circumstance. The main sources for anaerobic ATP synthesis are PC and the anaerobic glycolysis. These two sources together can generate ATP up to six times higher than aerobic metabolism.

CP is a high energy compound that is stored in muscles about five to six times more than ATP. When ATP is hydrolyzed, ADP is produced and then binds CP to regenerate ATP (Fig):

$$\text{Creatine phosphate} + \text{ADP} + \text{H}^+ \underset{\text{Creatine kinase}}{\rightleftharpoons} \text{ATP} + \text{creatine}$$

Thus, anaerobic metabolism has a very high and fast rate of ATP synthesis, but it can only be maintained for very short periods of time (seconds to 1–3 min) due to PC depletion and accumulation of by-products from anaerobic metabolism, which interfere with muscle contraction.

Anaerobic glycolysis is the third source for anaerobic ATP synthesis. The amount of ATP yield by anaerobic glycolysis is 3 mmol of ATP per each mmol of glucose derived from glycogen as opposed to 38–39 mmol of ATP from aerobic CHO metabolism. However, the rate of ATP synthesis through anaerobic metabolism is about two times faster than the aerobic metabolism. In skeletal muscle most of the anaerobic CHO comes from glycogen stored in the muscles. Glycogen cannot be used for energy purposes so it needs to be broken down to glucose. This process is called glycogenolysis and it is larger in Type II muscle fibers that have more glycogen content and glycolytic enzymes than Type I muscle fibers. The process of glucose oxidation to obtain ATP is called glycolysis. The end product of glycolysis is pyruvate, which enters the citric acid cycle to further produce aerobic ATP. As described earlier, the aerobic metabolism of CHO produces 38–39 ATPs when anaerobic glycolysis produces 2 ATP although faster than aerobic metabolism. For many years it has been thought that lactate was the end product of anaerobic glycolysis. In fact, the anaerobic versus aerobic glycolysis has been a source of great debate and, probably, misunderstanding for many years. Important scientists like Louis Pasteur and AV Hill described the terms of aerobic and anaerobic a long time ago. It was observed that when glycolysis happened in the presence of oxygen, there was no lactic acid formation so pyruvate would be finally oxidized in the mitochondria for ATP production. It was also observed that when glycolysis happened without oxygen, there was lactic acid formation which led to the conclusion that lactate production was anaerobic [6,7]. However, and thanks to most of the work that Dr. George Brooks has conducted during the last 30 years, we know that lactic acid formation can perfectly occur under plenty of aerobic conditions and that lactic acid formation is more a result of excessive glycolytic flux in the cytosol. In fact, glycolysis per se (before pyruvate oxidation) is a process occurring in the cytosol, so no O_2 is required. The term anaerobic is probably an archaic term. When exercise is very intense, Type II muscle fibers are fully recruited as the contractile velocity and power requires it. Type II muscle fibers are highly glycolytic, which alone with a high adrenergic activation will elicit a high glycogenolitic response, resulting in a very high glycolytic flux in the cytosol and a large amount of pyruvate formation. In order to complete pyruvate oxidation in the mitochondria, it needs to be converted to acetyl-CoA (coenzyme A). This process is performed by an enzyme called pyruvate dehydrogenase (PDH), which saturates quickly when pyruvate formation is very elevated and cannot handle with all the pyruvate being formed when there is a very high rate of glycolysis like that observed in high exercise intensities. When this situation happens, pyruvate is reduced to lactate by an enzyme called lactate dehydrogenase (LDH). The provision of ATP by this process is faster but not necessarily anaerobic as this can perfectly happen under fully aerobic conditions. Thus, although the terms anaerobic and aerobic glycolysis are still widely used, it would probably be more appropriate to use the terms fast or slow glycolysis.

AEROBIC METABOLISM DURING EXERCISE

As described earlier, any provision of energy in the muscle at intensities below 100% of VO_{2max} is achieved through aerobic means (with oxygen), also called oxidative phosphorylation. CHO, fats, and protein are oxidized this way in order to generate ATP for muscle contraction.

CARBOHYDRATE METABOLISM DURING EXERCISE

CHO metabolism is of great importance during exercise, especially during high exercise intensity where it is the predominant energy substrate for skeletal muscle. Glycogen is the storage form of glucose and CHOs in animals and humans. CHOs are a very limited source of energy accounting for only about 1%–2% of total bodily energy stores [8]. Furthermore, about 80% of total CHO is stored in skeletal muscle; about 14% is stored in the liver and about 6% in blood in the form of glucose, so this would represent

about 300–400 g of glycogen stored in muscle and about 70–100 g stored in the liver [9,10]. Glycogen cannot be utilized for energy purposes by muscle, so it needs to be broken down to glucose 1-phosphate by the enzyme phosphorylase, which is the process called glycogenolysis. The process of glucose utilization is called glycolysis, which accounts for 15%–20% of peripheral glucose utilization in skeletal muscle at rest. At an exercise intensity of 55%–60% VO_{2max}, glucose utilization by skeletal muscle increases to about 80%–85% of whole-body disposal [11]. Thus, muscle glycogen is crucial for ATP synthesis during exercise. Proper glycogen storages are of great importance for athletic performance. Multiple studies show that fatigue and decrease in performance are often associated with glycogen depletion and that athletes who have low CHO diets or low glycogen storages will suffer a decrease in exercise capacity [12–18] as well as an increase in risk for overtraining [9,10,19]. McArdle's disease patients lack phosphorylase enzyme, impairing glycogen utilization and thus drastically decreasing athletic performance [20].

The rate of ATP synthesis is parallel to the exercise intensity. Glycolysis occurs mainly in the cytosol and this process can be aerobic through the complete oxidation of pyruvate (oxidative phosphorylation in the mitochondria) or anaerobic (substrate phosphorylation in the cytosol). Exercise intensity determines the substrate demands of skeletal muscle to generate ATP. During exercise, skeletal muscles use primarily fat and CHO for energy purposes, and at low exercise intensities, fat is the preferred substrate although there is always some glucose oxidation. At higher exercise intensities of about 50%–60% of VO_{2max}, ATP synthesis demand increases and fat cannot entirely meet the rate of ATP synthesis so glucose oxidation increases. Furthermore, at higher exercise intensities, fat cannot synthesize ATP fast enough for the contractile demands of skeletal muscle fibers. Although the oxidation of fat yields a much higher amount of ATP, glucose utilization is much faster, therefore necessary for ATP synthesis.

Exercise intensity is the main regulator for skeletal muscle CHO utilization and the mechanisms responsible for CHO utilization during exercise involve hormonal and local factors as well as glycogen availability. Epinephrine (adrenaline) is the main hormone involved in CHO metabolism during exercise. B-adrenergic activity increases with exercise intensity. Phosphorylase is the enzyme responsible for glycogen breakdown to glucose and it is regulated by epinephrine. The release of epinephrine from the adrenal medulla is directly proportional to exercise intensity. Epinephrine stimulates muscle glycogenolysis by increasing phosphorylase activity; thus, it is a major regulator of CHO metabolism during exercise. Availability of FFAs during exercise is also closely regulated by epinephrine. During high exercise intensities, epinephrine reduces the blood flow to adipose tissue, eliciting a constricting effect on adipose tissue, thereby reducing plasma FFA availability to the muscles during high intensity exercise [21,22]. Local factors regulating CHO utilization during exercise involve the activation of phosphorylase by an increase in cytosolic calcium during excitation–contraction coupling [23]. Muscle contraction also stimulates sarcolemmal translocation of glucose transporters, GLUT4 isoform, which makes glucose uptake by muscle non-insulin dependent during exercise. The muscle fiber composition and activation patterns play an important role as well. During high exercise intensities, contraction time is lower, shortening velocity is higher, and power production is higher as well, so Type II muscle fibers are recruited at these exercise intensities [5]. Since Type II muscle fibers have a higher glycogenolyic capacity and lower mitochondrial density, glucose utilization in these fibers will prevail over fat.

Exercise duration also plays an important role in CHO metabolism during exercise. Since glycogen storage capacity is about 500 g in muscle and liver, the length of the exercise activity will be very important for the regulation of CHO metabolism. Glucose uptake in skeletal muscle is dependent on glycogen content [24] and hypoglycemia during exercise can be prevented by the sufficient intake of CHO [25]. Exercise duration is intimately related to glycogen storages as low glycogen storages during endurance events are associated with hypoglycemia, fatigue, and decrease of performance [12–18].

LIPID METABOLISM DURING EXERCISE

Lipids are a very important energy source during endurance exercise. Although ATP generation for muscle contraction from lipids is slower than that from CHO sources, the amount of ATP produced by lipids is far higher than that from CHO, which makes lipids the fuel of choice by skeletal muscle during endurance exercise and will spare glycogen. The main source for lipid metabolism is subcutaneous tissue. Even the leanest athletes have more than 100,000 kcal of potential energy in their adipose tissue. Lipid metabolism during exercise is a highly coordinated and integrated process starting at the adipose tissue and ending at the mitochondria in skeletal muscle. This process involves mobilization or breakdown of adipose tissue, circulation from adipose tissue to skeletal muscle, uptake, and final mitochondrial oxidation in skeletal muscle. Lipolysis is the first step in lipid metabolism and it is the breakdown of adipose tissue as well as IMTG. Triglycerides in the adipose tissue and muscle are broken down into FFAs and glycerol by hormone-sensitive lipase (HSL). Hormonal control of lypolysis is tightly regulated by several hormones, especially catecholamines (epinephrine and norepinephrine), which are probably the major hormones regulating lipolysis. Catecholamines bind to both β-adrenergic and α_2-adrenergic receptors on the fat cell (adipocyte) membrane. This activates a cascade of cellular signals which starts by the activation of adenylate cyclase (AC) which increases cyclic adenosine monophosphate (cAMP) which activates cAMP-dependent protein kinase which ultimately phosphorylates HSL which finally elicits lipolysis. At rest, low level of plasma catecholamines bind to α_2 receptors, eliciting an inhibitory effect

on lypolysis, while during exercise, plasma catecholamines increase and stimulate β-adrenergic receptors, stimulating lypolysis [26]. However, during very high exercise intensities, catecholamines have an inhibitory effect on lypolysis probably by causing a constriction in capillarization and blood flow to adipose tissue [21,22] and eliciting potent glycogenolytic effects. Although there seem to be different catecholamine thresholds for both lipolysis and glycogenolysis [27], the exact mechanisms and catecholamine concentrations to elicit either lipolytic or glycogenolytic effects are not entirely understood.

Insulin also regulates lipolysis, although its effects during exercise are not as profound as when at rest or as powerful as catecholamines during exercise. At rest, insulin inhibits lipolysis [28–30], but during exercise insulin secretion decreases, allowing higher lipolytic activity [31].

Upon adipose tissue lipolysis, FFA must be transported to skeletal muscle. Adipose tissue blood flow (ATBF) is of great importance for FFA circulation as it delivers catecholamines to adipose tissue for lipolysis as well as albumin to transport FFA to skeletal muscle where the uptake of FFA is mediated by a sarcolemma, specific receptor, sarcolemmal fatty acid binding protein (S-FABP), which together with another FABP facilitates the transport of fatty acids throughout the cell for beta oxidation and generation of acetyl-CoA for TCA oxidation. Once in the cytosol, FFA needs to be activated to fatty acyl-CoA ester. FFA is attached to CoA, which forms fatty acyl-CoA, which then is transported across the outer mitochondrial membrane by carnitine-palmitoyl transferase I (CPT-I), and finally transported to the mitochondrial matrix by carnitine. Once inside the mitochondrial matrix, fatty acids undergo β-oxidation where fatty acyl-CoA is degraded to acetyl-CoA, which can then enter the citric acid cycle. During this process, NADH and $FADH_2$ are generated for ATP production through the electron transport chain.

Skeletal muscle also contains small lipid droplets called IMTGs, which are stored in the cytoplasm of skeletal muscle cells close to the mitochondria. Depending on different circumstances such as endurance exercise and low glycogen content, IMTG can play an important role in the contribution to lipid metabolism during exercise [32], which depending on the exercise duration and glycogen availability, can contribute to a great extent to lipid metabolism during exercise.

PROTEIN METABOLISM

Although not considered a major contributor to energy during exercise, the metabolism of proteins during exercise can be important, especially depending on the exercise intensity, type, duration, and nutritional status of the athlete. Proteins are made up of amino acids and there are over 20 amino acids divided in two groups: nonessential, which are those that can be synthesized in the body, and essential, those ones that need to be obtained from the diet. Amino acid metabolism is a sum of very complex and different mechanisms whose explanation goes beyond the nature of this chapter. Amino acids are basically characterized by having an amino group $(-NH_3^+)$ as part of their chemical structure. Before amino acids can be used in the body, the nitrogen group from the amino acid must be removed by two processes: oxidative deamination and transamination. Oxidative deamination is a reversible mitochondrial reaction triggered by glutamate dehydrogenase on the mitochondrial matrix and involves and generates intermediates for the TCA cycle as well as NADH for ATP production through the electron chain transport. The other process involved in amino acid metabolism is transamination, which transfers the amine group from an amino acid to a keto acid of the same amino acid. This reaction is achieved by a type of enzymes called transaminases. Glutamate-pyruvate transaminase (GPT/ALT), involved in alanine metabolism, and glutamate-oxaloacetate (GOT/AST), involved in aspartate metabolism, are two major transaminases in the body. Both of these reactions involve the production of α-ketoglutarate, an important intermediate for the TCA cycle. Carbon skeletons of amino acids are used to generate energy via different mechanisms, and depending on the final fate of these carbon skeletons, amino acids are grouped in glucogenic amino acids and ketogenic acids. Glucogenic amino acids degrade their carbon skeletons to pyruvate or TCA intermediates as a precursor for gluconeogenesis. Ketogenic amino acids cannot be converted to glucose but can be degraded to acetyl-CoA or acetoacetate and be used for energy production through the TCA cycle or converted to ketone bodies or fatty acids.

There are several amino acids that play an active role during exercise activity. Amino acids may provide between 3% and 10% of the total energy during exercise, depending on exercise intensity and duration [33–37]. These percentages may not be very high but may play a very important role in exercise performance. In exercises when glycogen levels are low the contributions to energy by amino acids will be greater [38]. Alanine is an important glucogenic amino acid, especially during endurance exercise and it is synthesized in the muscle and then exported to the liver to be converted to glucose through what is called the glucose-alamine cycle [33]. Branched-chain amino acids (BCAA) may also play an important part during exercise. Leucine, isoleucine, and valine make up the BCAA. Leucine is a ketogenic amino acid, isoleucine is both ketogenic and glucogenic, whereas valine is a glucogenic amino acid. BCAA seem to be the kind of amino acids most used by the muscle during exercise. Since these amino acids are building blocks of the muscle, an excessive utilization, as what happens during intense and long exercise, along with decreased glycogen content may lead to an excessive muscle breakdown and a catabolic situation for the muscles, which causes muscle damage and would be detrimental for performance. Therefore, a BCAA supplementation during endurance exercise may have some sparing effects on endogenous muscle BCAA utilization and, therefore, decrease the possibilities of muscle damage [39].

In general, amino acid metabolism, although accounting for a small percentage of total ATP synthesis during exercise, may play an important role in the intermediate metabolism and performance as well as recovery after training/competition.

LACTATE METABOLISM

Lactate is the by-product of the utilization of glucose (glycolysis). During glycolysis, lactic acid is formed, and under normal physiological pH, it rapidly dissociates to lactate and a hydrogen ion (H^+). It was for a long time believed to be just a waste product and the result of anaerobic glycolysis as a result of lack of O_2 [6,7,40]. However, the work done by some researchers at the end of the twentieth century, especially by Dr. George Brooks, showed that lactate production is not only the natural by-product of glycolysis but also a very important metabolite and regulator of the intermediate metabolism and even could be considered a "lactormone" due to its hormone-like properties [41–43]. During high intensity exercises (those typical of competition) ATP generation demands increase and glucose becomes the predominant muscle substrate for ATP generation. The higher the glucose flux into the cell, the higher the lactate production. As a matter of fact, lactate production is necessary for the continuation of glycolysis.

Lactate has two key functions in glycolysis. The first one is the equilibrium of the cytoplasmic redox status (NADH/NAD^+). During anaerobic glycolysis or excess glycolytic flux, pyruvate is reduced by LDH to lactate plus NAD^+ (nicotinamide adenine dinucleotide), which restores cytoplasmic NAD^+ for the continuation of the oxidation of glyceraldehyde 3-phosphate to 1,3-biphosphoglycerate, so during these circumstances, lactate is a key player for the continuation of glycolysis. The second important function of lactate is to release the saturation of the enzyme PDH. When the rate of pyruvate formation due to excessive glycolytic flux exceeds the rate of oxidation by the enzyme PDH lactate is then formed [44–46]. Pyruvate then will be reduced to lactate by LDH whose equilibrium constant (K_{eq}) favors lactate over pyruvate; therefore, small increases in pyruvate concentration will result in increases in lactate concentration during higher exercise intensities when glycolytic flux elicits a high production of pyruvate that exceeds the oxidative activity of PDH [46].

During intense exercise, lactate production is many times higher than that of resting levels and the equimolar release of H^+ can cause, in spite of a cellular important buffer capacity mediated by bicarbonate (HCO_3^-), an important reduction of muscle pH of 0.4–0.5 or 0.8–0.9 points as it has been observed [47–49]. This excessive accumulation of H^+, not only from lactate but also from ATP hydrolysis due to muscle contraction and calcium reuptake in the sarcoplasmic reticulum, may decrease muscle pH and can cause an important decrease in peak twitch force, a decrease in ATPase per active myosin head during contraction, and a decrease in maximum shortening velocity [50,51]. On the other hand, it is also possible that H^+ competes with Ca^{++} for troponin C binding site interfering with muscle contraction [48,51,52]. It is also possible that H^+ inhibits calcium release from sarcoplasmic reticulum [51,53] as well as may decrease the reuptake of Ca^{++} in the sarcoplasmic reticulum [51,52,54].

Recently, several authors have suggested that lactate is not involved in muscle acidosis associated with high intensity exercise and that, in fact, lactate delays and buffers acidosis, acting as a protective mechanism for muscle contraction [54]. According to this hypothesis, those athletes producing the most lactate would have an advantage during the competition. So the debate is open as to whether lactate is involved in muscle acidosis or assists in acidosis buffering. Whether one or the other is true would still need to be fully elucidated. The fact is that lactate is an excellent biomarker for muscle metabolic stress. What we also know today is that the better the competitive level of an endurance athlete and the better trained that athlete is, the less is the lactate accumulation that is observed [55–61], which is due to an enhanced lactate clearance capacity [43]. According to San Millán et al., world-class professional cyclists accumulate less blood lactate than the rest of their professional peers who at the same time accumulate less blood lactate than the amateur cyclists who accumulate less lactate than the juniors. These data clearly show that the better the performance level of a cyclist, the lower the blood lactate concentration at the same relative exercise intensity [62].

Lactate testing is probably the best method that we have to predict performance in endurance events [63,64], it is probably the parameter that discriminates the most between different levels of athletic performance [62] and it can also be a very good parameter to prescribe exercise training zones and training programs for athletes [64,65]. Lactate analysis can give us a lot of information on muscle metabolism during exercise where we can indirectly assess mitochondria density and oxidative enzyme function, substrate utilization or muscle fiber recruitment patterns. Lactate clearance capacity is of great importance for competitive athletes.

TRAINING ADAPTATIONS TO EXERCISE

The physiological adaptations to training are very important and can elicit profound improvements in athletic performance. The main goal of all these adaptations is to increase the body's efficiency during exercise. The body improves many physiological functions and metabolic pathways in order to become more efficient. The main adaptations to training result in the improved efficiency of both central (cardiorespiratory adaptations) and local responses (skeletal muscle structure and metabolism) to exercise.

Central Adaptations to Exercise

One of the main adaptations of training is an increased O_2 delivery to the muscles. This increased O_2 capacity is the result of a coordinated response and improvement of different cardiorespiratory functions (heart, lungs, and blood vessels). An increase in cardiac output (CO) is one of the principal cardiorespiratory respiratory adaptations and elicits an increased delivery of O_2 to the skeletal muscle. CO is the product of heart rate times the stroke volume, and an increase in stroke volume is the main contributor for an increase in CO, which will ultimately increase VO_{2max}. An increase in capillarization to the contracting muscles is another major

adaptation to training. Muscles increase the capillarization and therefore their blood supply during exercise. Other cardiorespiratory adaptations to exercise pertain to blood flow redistribution from tissues that don't need much blood during exercise so that contractile skeletal muscle can have an increased blood flow supply. Decreased blood flow to the kidneys and other viscera, spleen vasoconstriction, as well as increased blood flow to the coronary arteries and skeletal muscles are the main blood flow redistribution adaptations to exercise. An increase in blood flow to the skin is a very common adaptation as well in order to improve the capacity to dissipate heat.

Local Adaptations to Exercise

We know a lot more about cellular metabolism during exercise and the local adaptations are for the most part the most important adaptations as a result of training. These local adaptations to exercise training happen at the skeletal muscle level with structural changes and arrangements and elicit important changes in mitochondrial density and oxidative and glycolytic enzymes eliciting profound changes in substrate utilization during exercise.

Skeletal Muscle Fiber Changes

Muscle fibers can change the histological and biochemical characteristics toward more oxidative behavior due to training, which will increase fatty acid oxidation and increase lactate oxidation to pyruvate. Highly glycolytic muscle fibers acquire biochemical behaviors more typical of oxidative muscle fiber by increasing the content of oxidative enzymes and mitochondrial density as observed in different studies [4,66–70].

Type IIb muscle fibers can behave more like Type IIa's and the latter ones more like a Type I, improving their oxidative capacity.

Adaptations to Training at the Cellular Level and Substrate Utilization

There are important adaptations to training at the cellular level as well as in fat and CHO metabolism. After training, glycolytic flux is decreased at same relative intensities. There is a decrease in glycogenolysis and therefore a reduction of energy requirements derived from glucose. This observation was already discussed by Christensen and Hansen [71], and with the progress of science, it has been shown in numerous studies that glucose utilization, and thus the glycolytic flux, decreases with endurance training [12,57,72–77] and even can be higher in well-trained athletes at higher exercise intensities where blood lactate accumulation will still be lower due to a higher lactate oxidation [55,61]. An enhanced glycolytic capacity at high exercise intensities would ensure a higher level of performance of an athlete at those intensities.

Mitochondrial density and oxidative enzymes can largely increase with training, which will have an important impact on fat utilization. Endurance training can double the mitochondrial capacity to oxidize FFA and pyruvate [66,67,76,78,79]. Increases of up to 60% in mitochondrial content have been observed [66,80] as well as important increases in the activity of oxidative enzyme citrate synthase [81,82].

One of the most important adaptations observed in athletes is the decrease in blood lactate levels observed after training as well as lower glucose utilization and higher fat utilization, respectively. The increase in mitochondrial density increases the oxidation of cytosolic pyruvate via PDH and the intracellular lactate system through which will increase lactate clearance capacity through an increase in mitochondrial lactate dehydrogenase (mLDH) [45,83]. LDH is involved in the reversible reaction of oxidation of lactate to pyruvate and reduction of pyruvate to lactate. LDH-M isoform is more prone to a reduction of pyruvate to lactate where the LDH-H isoform is more prone to oxidation of lactate to pyruvate. Endurance training decreases LDH-M, so less lactate production will result [84,85], and increases LDH-H isoform.

Endurance training also has a great impact on specific lactate transporters called metacarboxylates (MCTs) that facilitate lactate transport in and out of the muscle cell. There are two major isoforms of MCTs in skeletal muscle. MCT1 are highly expressed in oxidative muscle fibers (Type 1) and involved in lactate transport inside the cell and into the mitochondria for later oxidation. Endurance training increases MCT 1 expression [85,86] which would result in a higher lactate clearance capacity. MCT 4 isoforms are expressed mainly in glycolytic fibers and are involved in lactate transport out of the cell from glycolytic fibers to more oxidative fibers and increases with endurance training [43,85–87], increasing lactate clearance capacity by facilitating lactate transport to oxidative cells.

PHYSIOLOGICAL TESTING AND MONITORING OF THE ATHLETE

All the knowledge described earlier is of little use if we don't correctly apply it to athletes. Unfortunately, many times the impressive work and knowledge of brilliant researches stay in a scientific journal as they are either not applied or incorrectly applied to the athletes who could really get an advantage to optimize their performance, whatever the level of performance is. When the scientific approach is not applied, "urban legends" grow where athletes train based on misleading information or many times just "by the feeling." In today's society, most fields are based on scientific research and evidence but, in general, many athletes lack that scientific approach to training and preparation despite using the most advanced equipment. The fastest bicycle, running shoes, or skies represent just a minimal ("marginal") gain when it comes to performance and in most situations not even that, as most athletes nowadays have the same access to the same fast, top equipment … so those marginal gains could represent zero or no gain. However, and despite spending thousands

of dollars in those "marginal gains" through using the best equipment, many athletes never find out how they can optimize their performance by training better and smarter or using their heart rate monitor more efficiently or eating properly. This kind of gains and improvements in performance regardless of the level of activity are far larger and more important than the "marginal gains," and the proper application of the scientific approach can result in dramatic improvements and optimization of performance.

THE SCIENTIFIC APPROACH

Science is derived from the Latin word "Scientia," which means knowledge, so the scientific approach should always be applied. There are many effectors of athletic performance (Fig-); a thorough evaluation of these effectors should be performed and for this, the knowledge of the physiological parameters of the athlete is essential in order to obtain maximum optimization of performance. An integrative approach in exercise physiology should be able to control different effectors of performance such as physiological parameters, training, monitoring, and nutrition.

PHYSIOLOGICAL TESTING: COACHING 101

The only way where athletes engaged in any sports and activity level can have a customized, individual training program is by knowing how their bodies respond to exercise. Therefore, performing a physiological test in order to know the many different parameters that can be improved and then design the right training and individual training program should be the first step before starting a training program or working with a coach. We live in the Internet era where many athletes hire coaching services from "cybercoaches" who most of the times just email "copy and paste" training programs without either knowing the athlete in person or knowing his or her physiological parameters in order to prescribe an individual training program. The "cyberspace-prescribed" coaching service could be quite detrimental for performance as for the most part it is just a "hit and miss" service missing the most basic information on an athlete's physiology or "engine" whatever the level of competition could be. Many times coaches tend to prescribe generalized training programs and routines using training zones, intensities, and durations based on generalized formulas and standard training programs. However, in order to optimize performance, it is necessary to individualize training programs as much as possible. In order to achieve this, it is essential to obtain the knowledge of the individual physiological and metabolic parameters of each athlete through physiological testing.

The best coaches in the world are characterized by their strict methodologies and scientific application when it comes to coaching as well as preparation and for this they know very well that knowing an athlete's physiological parameters and responses to exercise permits them to prescribe the most adequate, individual, and correct training program in order to maximize performance. So for the best coaches, physiological testing in the field and in exercise laboratories is a constant partner and ally when it comes to improving the performance of their athletes. In the United States, there are many exercise laboratories in universities and sports medicine clinics opening their doors not only to elite athletes but also to recreational ones. Unfortunately, many recreational athletes are not aware of this or may think that physiological testing only pertains to the elite/professional athlete. The fact is that whether an athlete wants to run a marathon for the first time, improve the PR in a triathlon competition, or win the Tour de France, the optimization of performance should start by performing physiological testing in order to have an adequate, individualized, and optimized training.

There are several important parameters that can be obtained through physiological testing:

- VO_{2max}
- Lactate metabolism
- Fat metabolism
- CHO metabolism
- Metabolic efficiency
- Power
- Speed
- Strength

The measurement of all these parameters puts into application all the knowledge, as described in the first part of this chapter, of the individual physiological and metabolic responses to exercise of an athlete. A professional exercise physiologist should be able to measure in the exercise physiology laboratory most or all of the parameters that have been presented in the first part of this chapter in order to provide the best information such as individual training zones in order to prescribe the most adequate training program for an athlete or working in conjunction with coaches to provide them with individual physiological information of their athletes so that they (coaches) can work better with their athletes and with more scientific information.

Physiological Testing in Laboratory and Field Tests

Physiological testing can be performed in the laboratory as well as in the field. The majority of universities and sports medicine clinics have nowadays very well-equipped laboratories run by professional exercise physiologists, opening the doors to the community and recreational athletes, so athletes of any level should not be shy to go to an exercise laboratory in order to get tested. There are two possibilities of physiological testing: laboratory tests and field tests. A physiological test in a laboratory is probably the best way to measure physiological parameters.

LABORATORY TESTS

As the name indicates, they are physiological tests performed in the laboratory. The great advantage of performing a test in the laboratory is that the environmental conditions are always controlled and always the same, so an athlete can repeat the

test later on in the year or the following year to measure the progress and improvement and maybe change or tweak the training zones prescribed and yet be sure that the environmental conditions are identical. Another important aspect is that exercise physiology laboratories use very delicate and many times big and heavy equipment to measure different metabolic and physiological parameters and the portability outside the lab can very difficult sometimes.

FIELD TESTS

Field tests have the advantage of being performed on the same ground where competition or physical activity happens. This way it is possible to reproduce very similar performing conditions for an athlete. The main disadvantage of field tests is that repeatability is not possible when tests are done outdoors as the environmental conditions cannot be replicated as in the laboratory and these environmental conditions (wind, rain, heat, cold, etc.) would affect the results of the tests. The other disadvantage of field tests is that heavy and delicate laboratory equipment cannot be used or transported outside the laboratory, so we can lose valuable physiological and valuable data. There is some portable equipment such as small handheld lactate analyzers but these may not be very accurate when compared to laboratory analyzers and, therefore, we may be losing precision and therefore accurate information, which can be crucial in order to establish training zones and individualized training programs. All in all, field testing is quite useful to complement and confirm, in real athletic event conditions, the data obtained in the laboratory.

In summary, physiological testing is of great importance for any athlete regardless of the sport and the level of competition in order to measure physiological and metabolic responses to exercise to assess performance potential but mostly important to prescribe an individualized training program to optimize performance.

MONITORING OF THE ATHLETE

Over the years, many books and articles have been written regarding different training methodologies. Although the many different training methodologies, theories, applications, and results are beyond the scope of this chapter, it seems that as per what we can read from the literature on training, most training methodologies seem to work. There is a general assumption among many athletes and coaches that training per se will always improve performance. In team sports, there is a general assumption that form improves during the season when the reality is that many times athletes and teams deteriorate during the season and they tend to "take a dive" toward the end of their competition year. The fact is that even at the highest level of competition, little is done, in general, to monitor athletes to make sure they are assimilating training and competition in order to avoid overtraining and fatigue. As an example, the majority of professional teams monitor every single ticket they sell, every single t-shirt they sell, and even every single soda or popcorn they sell. However, many teams of professional sports don't monitor the most important part of the entire show—the engine of their players. Strenuous competition throughout the season elicits important physiological and metabolic stress on players' bodies, and the evaluation of how well or how bad they are dealing with recovery from training and competition should be critical in order to improve or at least preserve performance throughout the season and avoid overtraining that could have catastrophic consequences for the performance of the team and therefore important negative economical consequences. From the individual standpoint, individual athletes also need to monitor how well they assimilate training and, if it applies, competition. Most recreational athletes have evolved to competitive athletes and they have real 40 h/week jobs, traveling, families, etc. and they are at a high risk of overtraining. Many of them are often tired and fatigued and most think that it is a normal state of being an athlete or they may think that they just need to toughen up and shake off that fatigue and tiredness when the fact is that they may be quite overtrained and they don't even know.

This part of the chapter will deal with the scientific approach to monitor the physiological status of an athlete in order to prevent or at least detect overtraining situations. Several methodologies are of great importance and value for many athletes, coaches, physiologists, and physicians.

Physiological Testing for Monitoring Purposes

Through physiological testing throughout the season, it is possible to identify and quantify the improvement in physiological parameters and therefore performance or athletic form. There are many training methodologies but none of them are an exact science so it is possible that the training methodology that works best for one athlete may be detrimental for another as it may cause too much training overload. The best way to quantify how much an athlete is improving or deteriorating throughout the season is to perform physiological testing on athletes throughout the season. Many times, if repeatability conditions permit, field tests at their training facilities may work so they can avoid several visits to the laboratory. Top coaches of both individual and team sports find this physiological testing very useful in order to identify the elements that are going wrong and interfering with performance and then have the possibility to correct them in order to restore performance. In team sports, many head coaches need to improve the vision of monitoring their athletes, as many don't know what it is. Ironically, in many cases, this turns against them when they are fired after the performance of the team has plummeted in the second half of the season as there is no monitoring of their athletes and nobody is able to identify that players are fatigued and overtrained. Therefore, blame will be put on the head coach for technical/tactical underperformance of the team when the reality could be that players are trying to execute the correct technical and tactical aspects directed by the head coach but they are just too fatigued and overtrained, and unfortunately this is completely undiagnosed in many situations. Individual or recreational athletes may be deteriorating and obtaining

very poor results. For example, it is not uncommon to see an athlete attempting his/her first marathon or triathlon quit the sport after a very hard time during the race or during training leading to the race. They may think that they are not good enough for the sport they like when the truth is that they were fatigued and overtrained and therefore could not perform at the desired level.

MONITORING FOR OVERTRAINING

Overtraining is a great unknown among athletes. Overtraining affects many athletes and many are not aware of the condition. There are a few definitions of overtraining, but we can define it as an accumulation of training and nontraining stress resulting in a decrement in performance capacity. Another term commonly used is overreaching, which is a form of short-term overtraining. Normally, overreaching or short-term overtraining is undetected by the athlete and becomes long-term or chronic overtraining, which interferes with performance.

CAUSES OF OVERTRAINING

There are different causes of overtraining, but the following is a list of the most common causes for overtraining.

Excessive Training

Many athletes train more than what they can assimilate. In many cases athletes, coaches, and trainers don't know how much training an athlete can assimilate. As explained earlier, physiological testing can identify and quantify the proper dose of training of an athlete, which can be very helpful to avoid overtraining due to excessive training.

Poor Recovery and Assimilation

There are two main principles of training: overload and supercompensation. The overload principle pertains to the training phase, which elicits a physiological stress on the body and many times a catabolic (destructive) effect. That overload on the body is followed by a supercompensation, which is the regeneration phase of the training where the body regenerates, supercompensates, and gets stronger so increases adaptation to training and results in an increase in form and performance. This is an anabolic (constructive) process that is achieved by proper recovery. Many times, the recovery component is absent or not enough to elicit a regeneration and supercompensation and eventually overtraining will strike. Professional and elite athletes are very prone to this misbalance between training and recovery. In many situations the physiological stress of training or competition is too much and recovery may not be that well adjusted so overtraining occurs. In recreational athletes, this is a very common way to get overtrained as many don't pay enough attention to recovery (or they can't). Many recreational athletes have full-time jobs with busy schedules, travel, stress, etc. and they may jump on the bike for 1:30 h at lunch time and right after that continue their workday, which may be too physical, intellectual, or both so recovery will be inadequate or sometimes absent, eventually resulting in an overtraining condition.

Improper Nutrition

Nutrition is a key part of the training regime of any athlete. Not ingesting enough amounts of calories (kcalories—kcal) can result in a lack of important macro- and micronutrients. This is especially true when it comes to CHOs. Modern societies tend to "demonize" CHO and there are multiple books and diets out there claiming that high protein and or high fat diets with important restriction of CHO are the appropriate way for an athlete to lose weight and have a healthy diet. However, most of these books and diets lack scientific evidence. This is especially true for athletes who restrict CHO as the massive amount of scientific evidence clearly shows that a good CHO diet is crucial to maintain performance. As previously discussed in this chapter, multiple studies show that fatigue and decrease in performance is associated with low CHO diets causing glycogen depletion [12–18] and how low glycogen levels may cause overtraining [9,10,19]. Since glycogen storage capacity is very limited, many high-performance athletes may find it difficult to even keep up with CHO intake and therefore have some patterns of glycogen depletion [88–90].

When glycogen levels are low or there is a glycogen depletion, the muscle increases the utilization of protein and amino acid utilization as a gluconeogenic precursor increases [37,38]. Since protein and amino acids are the building blocks of muscle, the latter one may enter a catabolic situation (muscle breakdown) as the muscle may "eat itself to feed itself" by increasing the amount of protein and amino acids used for energy purposes. This situation may lead to muscle damage and, furthermore, this may lead to chronic overtraining as it has been shown that muscle damage limits and interferes with glycogen storage and synthesis [91,92], so even with a high CHO diet, it would be difficult to maintain glycogen storages and therefore enter a vicious circle that may lead to overtraining and decrease in performance.

Psychological Stress

Athletes may experience two different kinds of psychological stress. Elite athletes typically develop a psychological stress derived from the high psychological and physiological demand of training and competition. Recreational athletes may develop a different kind of stress derived from their busy schedules from a full-time job and the difficulty to train around their schedules. Many may be the effects of stress on performance and although the physiological issues derived from psychological stress and how it affects performance are beyond the scope of this chapter, there are many studies linking different kinds of psychological stress with overtraining [93].

MONITORING OVERTRAINING: THE ANSWER IS IN THE BLOOD

There are many indirect parameters to assess overtraining [94–97], but they may not be very sensitive and are difficult to quantify and interpret. Examining direct biomarkers of overtraining from the blood is a very useful tool and weapon to prevent and detect overtraining. Overtraining can be also interpreted as a physiological aggression to the body and this "aggression" leaves traces in a similar way that several pathophysiological conditions do. Through blood analysis, monitoring of the athlete and the evaluation of several biomarkers make it possible to detect those traces and use them to detect and/or prevent overtraining. There are many different parameters in the blood indicators that can be used to monitor overtraining. Different hematological, biochemical, hormonal, and serological biomarkers can be found in the blood. To describe all these parameters we would need an entire chapter so this is a short review of the most common parameters and biomarkers used.

Hemoglobin

Hemoglobin (Hgb) is a protein existing inside red blood cells (erythrocytes) that carries oxygen (O_2). Each Hgb molecule is made up of four heme groups containing iron to which O_2 ultimately binds. In a way, red blood cells are the taxi for O_2, and Hgb is the seat where O_2 sits. Each gram (g) of Hgb transports 1.34 mL of O_2. So for a normal male with 15 g/dL of Hgb in the blood, he can transport 20.1 g/dL of O_2 in the blood. This is also called the oxygen-carrying capacity. Hgb is a sensitive parameter affected by overtraining and decreasing exercise performance [98–101]. Any decrease in Hgb in the blood would lead to a decrease in the O_2-carrying capacity. As an example, if a normal person with 15 g/dL of Hgb (20.1 g/dL of O_2 capacity) decreases the Hgb content to 14 g/dL, the O_2 capacity would theoretically decrease to 18.76 g/dL of O_2, which would represent close to a 7% decrease in the O_2-carrying capacity, which can have an important impact on athletic performance. It is also not very rare to see athletes decreasing their Hgb content, i.e., from 15 to 13 g/dL, which will represent a theoretical decrease in O_2 capacity of about 13%, which could have profound consequences for performance.

Biomarkers for Muscle Damage

Although Hgb content and O_2-carrying capacity may be appropriate in an athlete, there may be muscle damage associated to overtraining as discussed earlier, and by analyzing several biomarkers, it is possible to assess muscle damage. Excessive eccentric exercises, excessive intensity training and competition, or training and competing under low muscle glycogen content or even depletion state may lead to excessive muscle damage. When this happens, muscle fibers break down and their cellular content escapes to the blood where it can be analyzed for muscle damage assessment. This cellular content is mainly made up of enzymes and if muscle damage is more severe it can also involve some contractile proteins. There are different muscle enzymes that can be used for the assessment of muscle damage. Creatine kinase (CK) and LDH are the enzymes most used as biomarkers for muscle damage [2,99,102–107]. Other enzymes that can be altered are alanine aminotransferase (ALT/GPT) and aspartate aminotransferase (AST/GOT). A contractile protein, Troponin I is also used to evaluate muscle damage [108]. Several inflammation mediators like the cytokines [109] free radicals or more appropriate, reactive oxidative species (ROS) [110], and hormonal responses [111] are also used for muscle damage assessment.

In summary, blood analysis is a very helpful and scientific methodology to monitor overtraining and fatigue in athletes of all levels.

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63 Evaluation of Acute Sports Injuries in the Adult Athlete

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CONTENTS

Inspection, Palpation, ROM, Strength, and Special Tests 774
Acute Knee Injuries 774
- Meniscal Injuries 774
- Anterior Cruciate Ligament Tears 774
- Posterior Cruciate Ligament Tears 775
- Medial and Lateral Collateral Ligament Injuries 775
- Patellar Instability 776
- Quadriceps Tendon and Patellar Tendon Ruptures 777
- Acute Chondral Injuries 777

Acute Shoulder Injuries 778
- Acromioclavicular Joint Injury 778
- Anterior Shoulder Dislocation 778
- Posterior Instability 779
- Rotator Cuff Tear 779
- Clavicle Fractures 779
- Pectoralis Muscle Injuries 780

Acute Foot and Ankle Injuries 780
Common Injuries 780
- Ankle Sprains 780
  - High Ankle Sprain 781
  - Ankle Fractures 781
  - Peroneal Tendon Injuries 781
  - Osteochondral Lesions 782

Specific Injuries 782
- Achilles Tendon Rupture 782
- Calcaneus Fracture 782
- Jones Fractures 782
- LisFranc Injuries 782
- Turf Toe 783

Acute Hip Injuries 783
- Hamstring or Quadriceps Strains or Avulsions 783
- Hip Dislocation 783
- Proximal Femur Fracture 783

Acute Hand, Wrist, Elbow Injuries 784
Hands: Jersey, Mallet, Gamekeeper's Thumb 784
- Mallet Finger 784
- Jersey Finger 784
- Gamekeeper Thumb 784

Distal Radius Fractures 785
Elbow Dislocation 785
References 785

As health care providers we have the opportunity to observe acute athletic injuries in many contexts. On the field, management and evaluation can be critical in making the appropriate decisions for return to play. An athlete presenting a few days after an injury may have significant swelling or ecchymosis that obscures the diagnosis.

In this chapter, the goal is to outline some general principles in acute injury evaluation and identify, by body region, common differential diagnosis and pearls for assessment and management. This chapter has been divided into sections on knee, shoulder, foot/ankle, hip, and hand/elbow. It is important to start with comments on an overall approach and management to acute musculoskeletal injuries in the adult.

INSPECTION, PALPATION, ROM, STRENGTH, AND SPECIAL TESTS

A good initial evaluation begins with a systematic approach. The clinician should then progress in the order of inspection, palpation, range of motion, and then strength and special tests. The first emphasis is on inspection with direct visualization. This can be difficult in some environments and thus may necessitate moving the athlete to a different setting. For example, a skier with a shoulder injury may need to be moved indoors before disrobing and fully inspecting the injury.

Inspection is then followed by palpation. Specific attention is paid to crepitus and deformity, as these are keys in evaluating for fracture or perhaps tendon rupture. In the subacute setting, the amount of ecchymosis and the presence or absence of a defect is also helpful. The contralateral extremity is usually available for comparison and thus provides a good context to interpret the findings. This is then followed by an assessment of the neurovascular status of the extremity and then by functional testing. After functional tests are performed, including range of motion and strength, special tests or maneuvers may further delineate the injury based on the specific region. Some of these tests will be outlined further in the sections of this chapter.

ACUTE KNEE INJURIES

Meniscal Injuries

Anatomy/pathology/epidemiology: The medial and lateral menisci of the knee are C-shaped fibrocartilaginous disks between the femoral and tibial condyles. They provide shock absorption and contribute in part to joint stability. The vascular supply to meniscus cartilage is poor, particularly to the inner portion; thus, the healing ability of meniscal tears is very limited. Injury to a meniscus predisposes the knee to degenerative arthritis. Traumatic meniscal tears typically result from an injury involving the twisting of a slightly bent knee while the foot remains fixed in place. Medial meniscus injury is more common than lateral meniscus injury. The patient may develop gradual swelling over the days following injury, and complain of stiffness and pain located predominantly over the medial or lateral joint line.

History/exam: Symptoms may wax and wane to some extent but often recur with twisting or squatting motions such as getting out of a car. The patient may also describe the sensation of mechanical symptoms of a meniscal tear, such as catching, popping, or locking. Common physical exam findings can include joint effusion (often less dramatic than those associated with an acute ACL tear or patellar dislocation, given the relative avascularity of the inner portions of the menisci) and pain with maximal flexion. Tenderness along the medial or lateral joint line is one of the most sensitive findings in meniscal injuries.[1] Meniscal rotation tests, such as McMurray's and Apley Grind, attempt to reproduce pain and clicking of the injured meniscus, and are considered more specific signs of a meniscal tear.[1]

Imaging: Standard knee radiographs are important in the evaluation of suspected meniscal injury to rule out bony pathology that could explain joint line pain or mechanical symptoms. However, an isolated acute meniscal tear will not be visualized on x-ray. MRI is very useful in confirming the diagnosis and characterizing the type of meniscal injury, being both sensitive and specific for meniscal pathology.

Treatment: While some small peripheral meniscal tears may heal nonoperatively, typically, arthroscopic partial meniscectomy or repair is indicated in the young, active population, particularly those with mechanical symptoms. In contrast, degenerative meniscal tears, more common in the older population, are typically best managed conservatively (rest, ice, NSAIDs) rather than surgically.

Anterior Cruciate Ligament Tears

Anatomy/pathology/epidemiology: The anterior cruciate ligament (ACL) originates from the posteromedial aspect of the lateral femoral condyle in the intracondylar notch, and inserts onto the anterior tibia between the tibial condyles. This thick ligament, approximately 10 mm in width, is composed of two principal parts, the anteromedial and posterolateral bundles. The ACL is the primary stabilizer of the knee, and acts to resist anterior translation of the tibia. Contrary to popular belief, ACL injuries most frequently occur with a noncontact mechanism in more than 70% of cases,[2] though contact injuries certainly do occur as well. Common noncontact mechanisms of injury include a sudden deceleration prior to a change in direction, a pivot on a planted foot, or hyperextension of the knee during a landing motion, whereas contact-related injuries classically occur as a result of a forced valgus collapse of the knee. Approximately 70% of ACL injuries occur during sports participation,[3] particularly in activities such as football, basketball, soccer, and skiing.

History/exam: With traumatic ACL rupture, the patient often describes feeling or hearing a "pop" at the moment of injury. Rapid and dramatic swelling of the knee typically follows within the first few minutes to hours after injury. The patient is almost always unable to continue in the activity due to pain and a sensation of knee instability. On examination,

a significant effusion is typically present. The Lachman test, in which an anterior force applied to the tibia results in laxity evidenced by excess anterior translation and lack of a firm endpoint compared to the nonaffected knee, is one of the most reliable physical exam findings of an acutely ruptured ACL.[2] The positive pivot-shift test, in which an anterior subluxation/reduction of the tibia is felt as the knee is passively brought from extension into flexion while applying an internal rotation, gentle valgus force, and axial load to the tibia, is another highly sensitive and specific test for ACL injury.[2] Clinically, however, the pivot-shift test can be more challenging to reliably evaluate in a nonanesthetized patient, particularly one demonstrating protective guarding.

Imaging: Standard knee radiographs should be closely examined for associated injuries such as a tibial spine avulsion or tibial plateau fracture. Additional supporting evidence of an ACL tear may be seen on plain radiograph of the knee. For example, a Segond fracture is an uncommon lateral capsule avulsion fracture from the proximal tibia, which is highly specific for ACL tear. On lateral knee images, visualization of a lateral femoral notch, which is deeper than the normal <2 mm notch size, is associated with impaction injury at the time of the original pivot shift. MRI of the knee is useful in confirming the diagnosis of an ACL injury, as well as evaluating for associated injuries that may influence surgical planning, such as osteochondral damage or concomitant meniscal tears.

Treatment: The goal of treatment in ACL injury is to prevent any further pivot-shift events, as every episode of instability has the potential to result in further chondral damage and predispose to degenerative arthritis. Most young, active patients engaged in activities requiring lower extremity agility will require surgical reconstruction of the ACL with various options of allo- or autograft tendon tissues. ACL reconstruction is typically performed at least 3 weeks after injury, to allow decrease in swelling and increase in range of motion prior to surgery.

Return to play: Postoperative rehabilitation is extensive, and patients should understand that safe return to full activities is expected to take at least 6–12 months. However, a subset of patients, considered "copers," have been shown to have satisfactory outcomes with rehabilitation alone without ACL reconstruction surgery, despite the inability of the torn ACL to heal itself, through optimizing muscular stability.

Posterior Cruciate Ligament Tears

Anatomy/pathology/epidemiology: The posterior cruciate ligament (PCL) is broader than and almost twice as strong as the ACL, and is less commonly injured. The PCL originates from the anterolateral aspect of the medial femoral condyle, anterior to the ACL, and inserts over the back of the tibial plateau, approximately 1 cm distal to the joint line. Like the ACL, the PCL also consists of an anterolateral bundle and a posteromedial bundle. This ligament prevents posterior translation of the tibia relative to the femur, as well contributing to resistance of varus, valgus, and external rotation stresses. The most common mechanism of injury to the PCL is the so-called dashboard injury, in which a force strikes the shin backward while the knee is in a flexed position, or in athletes, when an athlete falls onto a hyperflexed knee with a plantarflexed foot. Hyperextension or rotation injuries associated with varus or valgus force can also result in PCL tears. Due to the significant forces required to cause damage to the PCL, it is relatively rare to see isolated PCL tears. Most PCL tears are seen in combination injuries that also involve damage to the ACL, medial collateral ligament, medial meniscus, or posterolateral corner structures.[4]

History/exam: Patients with an acute PCL tear typically report diffuse knee pain, with tenderness both posteriorly as well as over the anterior tibia or area that received the impact force. Swelling is usually present, but often less than the typical hemarthrosis effusion observed with ACL tear. A Posterior Drawer test demonstrating posterior tibial subluxation is considered one of the most accurate signs of PCL injury.[2] The similar posterior sag test can demonstrate posterior subluxation of the tibia relative to the femur due to gravity in the absence of an intact PCL, with the auadriceps active test being used to reveal the ability of active quadriceps contraction to move the sagging tibia anteriorly, back into position.

Imaging: Standard plain radiographs are useful to rule out other boney injuries of the knee, such as avulsion of the PCL's tibial attachment, while cross-table lateral views may show a radiographic sag sign compared to the unaffected side. MRI is helpful to confirm the diagnosis and evaluate for other, frequently associated injuries.

Treatment: Optimal treatment of a PCL tear will depend on the injury characteristics. Surgical reconstruction of the PCL is somewhat controversial, and is typically reserved for high-grade PCL tears associated with other knee injuries. Many PCL tears have a good prognosis with nonoperative, rehabilitation treatment. Unlike ACL tears, PCL injuries are considered to have the potential for intrinsic healing, which has been attributed to superior blood supply of the PCL compared to the ACL. However, individuals who have suffered injury to the PCL do appear to be at increased risk of developing degenerative arthritis of the knee, particularly of the patellofemoral compartment, related to changes in knee kinematics.[5]

Medial and Lateral Collateral Ligament Injuries

Anatomy/pathology/epidemiology: The medial collateral ligament (MCL) and lateral collateral ligament (LCL) are integral in restraining valgus and varus angulation of the knee, respectively. The MCL is made up of both superficial and deep portions, and is augmented by the medial capsular ligament at the deepest layer. The fibers of the superficial MCL originate proximally from the posterior aspect of the medial femoral

condyle, and insert distally onto the medial tibia deep into the pes anserinus, approximately 5 cm distal to the joint line, while the deep fibers originate from the medial joint capsule, and insert directly onto body of the medial meniscus via the meniscofemoral and meniscotibial ligaments. The LCL originates from the posterior lateral femoral epicondyle and inserts onto the fibular head, and, unlike the MCL, does not fuse to the capsular ligament nor attach onto the lateral meniscus.

History/exam: The MCL is the most commonly injured ligament in the knee, with damage most often caused by a direct blow to the lateral aspect of the knee, resulting in an overwhelming valgus stress and external tibial rotation, though, noncontact twisting injuries can result in MCL sprains as well. Isolated LCL injuries are rare, and typically result from a varus or twisting injury, with associated damage to the posterolateral structures frequently stemming from a hyperextension mechanism due to a blow to the anteromedial tibia. With either MCL or LCL sprains, patients typically complain of pain directly over the injured ligament complex, and the sensation of the knee giving way into valgus or varus with walking or pivoting. On examination, localizing the point of maximal tenderness may assist in determining whether a tear has occurred proximally, mid-substance, or distally, which may have treatment implications. The varus and valgus stress tests, performed at 30° knee flexion to relax the stabilization component from the cruciate ligaments, suggest LCL or MCL injury, respectively, when the patient has pain (in low-grade sprains), or pain with ligamentous laxity in the form of excessive opening of the joint line compared to that of the opposite knee (in higher grade sprains). Joint opening with varus or valgus stress in a knee at full extension is highly concerning for concomitant cruciate ligament or posterolateral corner injuries.

Imaging: Knee radiographs in the evaluation of suspected MCL or LCL injuries are frequently normal, but useful in ruling out other bony injury. Some may occasionally demonstrate a small bony fragment if the injured collateral ligament is avulsed from the epicondyle acutely, though those with mid-substance tears will not. Radiographs of chronic MCL injuries may reveal calcification at the MCL origin, known as Pellegrini-Stieda syndrome. MRI is not necessary to confirm the diagnosis but can be helpful in delineating the degree of disruption of the collateral complex, determining whether the injury is proximal, mid-substance, or distal, as well as in evaluation for frequently associated meniscal or cruciate tears.

Treatment: Conservative management of almost all MCL sprains with hinged knee bracing and progression to early motion and rehabilitation is usually highly successful, though surgical repair may be considered in some complete tears, particularly if there are other associated injuries.

Patellar Instability

Anatomy/pathology/epidemiology: Patellar instability includes patellar subluxation and dislocation. Patellar subluxation describes abnormal tracking of the patella while it remains within the trochlear groove of the femur, while patella dislocation refers to events in which the patella is displaced completely from the sulcus. Patellar dislocation should not be confused with a potentially limb-threatening "knee dislocation." Acute patellar dislocations almost always occur with the patella displacing laterally from the trochlea. The typical inciting mechanism involves a valgus or twisting movement with internal rotation of the femur associated with a strong quadriceps contraction, often occurring in soccer, gymnastics, and hockey, or from a direct blow to the patella knocking it out of position. Patella dislocation occurs most often in adolescents and young adults, with a number of anatomic risk factors, including patella alta, genu valgum, trochlear dysplasia, and increased Q-angle, predisposing some individuals to instability.

History/exam: Patients who suffer a patellar dislocation typically describe sudden severe pain followed by falling to the ground, and often note an obvious, visibly deformed knee. This deformity may be described medially, in which case it likely represents the appearance of the uncovered medial femoral condyle, or be described as laterally, due to the patella sitting lateral to the trochlea, where it remains until it is reduced. Reduction is usually achieved easily by passively extending the knee with gentle pressure applied along the lateral patellar edge, and rarely requires anesthesia. First-time dislocations of the patella are associated with rapid, dramatic swelling from an acute hemarthrosis. On examination, maximal tenderness typically overlies the injured medial restraint that has failed, most commonly, the medial patellofemoral ligament avulsing off its femoral attachment,[6] or according to more recent research, off its patellar attachment.[7] Tenderness over the lateral femoral condyle and medial facet of the patella may represent osteochondral fractures sustained during the dislocation event. A classic finding of patellar instability is patellar apprehension, in which the patient reports pain and anxiety as the examiner gently attempts to manually sublux the patella laterally while holding the relaxed knee in approximately 30° of flexion. Aspiration of the knee effusion following a patellar dislocation typically demonstrates hemarthrosis and may reveal floating fat globules, particularly in the setting of associated osteochondral fractures.

Imaging: Radiographs rarely demonstrate patellar dislocation, as positioning the knee extended on the x-ray table usually results in its reduction back into the trochlear groove. However, radiographs may reveal large osteochondral fractures of the lateral femoral condyle or patella, or anatomic features predisposing an individual to patellar instability, such as patella alta or trochlear dysplasia with a hypoplastic lateral condyle. Including an axial patellar image, such as the merchant view, is recommended to evaluate patellofemoral congruity. MRI is useful to demonstrate damage of the medial supporting structures associated with acute dislocation, as well as bony edema or osteochondral injuries to the lateral femoral condyle and/or medial patellar facet.

Treatment: Acute patellar dislocations and subluxation events are typically treated nonoperatively with brief immobilization

only as needed for symptoms, followed by early, extensive rehabilitation and functional patellar bracing with lateral support. Patellar dislocations associated with a loose fracture fragment in the joint, however, may require surgical intervention. Unfortunately, up to 44% of patients will experience recurrent episodes of patellofemoral instability.[8] Surgical correction of an underlying extensor mechanism mal-alignment is rarely required but may be considered as a last option in cases of recurrent instability despite appropriate rehabilitation.

Quadriceps Tendon and Patellar Tendon Ruptures

Anatomy/pathology/epidemiology: The extensor mechanism of the knee can generate substantial forces that can result in rupture of the quadriceps tendon or the patellar tendon (occasionally known as the patellar ligament). These injuries typically occur due to direct blunt trauma or excessive tension being applied through the extensor mechanism, such as with a fall onto a partially flexed knee as the quadriceps is forcibly contracting. The quadriceps tendon is the largest tendon in the body, and connects the quadriceps femoris to the superior aspect of the patella, technically a sesamoid bone within the extensor mechanism of the knee. The fibers of the quadriceps tendon traverse the patella and condense inferiorly to form the patellar tendon (or ligament), which inserts onto the tibial tubercle. Quadriceps tendon ruptures are more common in patients over age 40,[9] and are more likely to occur in patients with a history of multiple corticosteroid injections, diabetes, gout, and certain other underlying conditions. The use of anabolic steroids has also been associated with quadriceps rupture. Patellar tendon ruptures are comparatively less common, typically occurring in patients under age 40,[9] and are frequently associated with sports activities involving jumping, such as basketball and volleyball. Patellar tendon ruptures are frequently found in the setting of underlying patellar tendinosis. In the skeletally immature, young athlete, similar mechanisms of forceful quadriceps contraction against a partially flexed knee can result in a patellar sleeve fracture, an avulsion injury in which the distal patellar pole and articular surface pull free with the tendon.

History/exam: Patients often report feeling a pop at the time of injury and are unable to walk due to the loss of active knee extension, though knee flexion is preserved. Patients with partial tears may retain the ability to partially extend the knee but may lack full extension. On examination, ecchymosis and a large effusion are common, and a tender, palpable defect may be demonstrated in the injured tendon. With complete rupture, patients are almost always unable to perform a straight-leg raise or extend the knee against gravity.

Imaging: Radiographs may reveal a small avulsion from either the superior patella or inferior patellar pole, depending on the site of injury. Radiographs, particularly the lateral knee image, may demonstrate either a high-riding patella, known as patella alta, after patellar tendon rupture, or a low-riding patella, or patella baja, after complete quadriceps rupture. MRI is often not necessary but may be used to confirm the diagnosis, particularly in partial tears, and assist with surgical planning.

Treatment: Prompt surgical repair is indicated for complete tears of either tendon. Delayed surgical treatment beyond 1–2 weeks can prevent attainability of end-to-end suturing in otherwise appropriate cases, and is associated with poorer outcomes.[9] Partial tears of the quadriceps or patellar tendons with normal patellar height and preserved active extension may be treated nonoperatively with immobilization in extension for 3–6 weeks, followed by gradual range of motion and quadriceps-strengthening exercises.

Acute Chondral Injuries

Anatomy/pathology/epidemiology: Articular cartilage, the glistening, white hyaline cartilage that caps the end surfaces of bones making up synovial joints, is made up of chondrocytes and an extracellular matrix consisting of water, proteoglycans, and Type II collagen. This layer functions to provide a low-friction, highly lubricated contact area between articulating surfaces, while distributing contact pressure to the underlying subchondral bone. These features can allow joints to tolerate repetitive compressive loading and shear forces for many decades. However, direct trauma to the knee, including ACL tears, meniscal injuries, and patellar dislocations, can frequently result in focal damage to the articular cartilage, known as acute chondral injury. Classification systems of chondral injuries are based on the depth of injury, from mild, superficial fissuring to more severe lesions extending through the articular cartilage into the underlying subchondral plate. Once damaged, articular cartilage cannot repair itself, and over time, elevated joint contact pressures at the site of damage will predispose the knee to developing symptomatic osteoarthrosis.

History/exam: Symptoms of an acute focal chondral injury may be subtle, and may overlap with or be overshadowed by symptoms stemming from other associated injuries; thus, a high index of suspicion is required for diagnosis. Crepitus, giving way, intermittent locking, persistent localized pain, and recurrent effusions may all be associated with a chondral injury.

Imaging: Knee radiographs may reveal large osteochondral defects extending into the subchondral bone; however, typically MRI is necessary to evaluate more subtle subchondral bone and cartilaginous injuries, particularly in surgical planning and selection of the procedure of choice.

Treatment: Treatment of focal chondral injuries of the knee can include conservative management in patients preferring to avoid surgery, or those with advanced degenerative arthritis deemed inappropriate for articular cartilage restoration procedures. Nonoperative interventions in the treatment of chondral defects typically include NSAIDs, judicious use of corticosteroid injections, and use of oral or injectable

chondroprotective agents, such as viscosupplementation injection. Surgical intervention options are principally based on the size of the defect, are typically considered as palliative (typically arthroscopic debridement and lavage), reparative (such as microfracture techniques to stimulate fibrocartilage repair), or restorative (including autologous chondrocyte implantation and osteochondral allografting).

ACUTE SHOULDER INJURIES

Evaluation of an acute injury in the shoulder begins with the patient's history, as this will almost always narrow the differential diagnosis. In addition, it is often possible to stratify injuries by age and sport to assist in the evaluation.

Acromioclavicular Joint Injury

Anatomy/pathology/epidemiology: Injuries to the acromioclavicular (AC) joint represent between 40% and 50% of athletic shoulder injuries.[10] It can result from a direct or an indirect blow to the shoulder. AC joint injuries are commonly seen in sports such as football and hockey but can also be seen in many contact sports including mountain biking and mixed martial arts.

The severity of injury can be quantified by the Rockwood classification system.[11] This system divides AC joint injuries into six different types. Types I, II, and III involve progressive degrees of injury to the AC joint capsule and coracoclavicular ligaments. Type I involves isolated injury to the AC joint capsule. Type II involves a greater degree of injury, with disruption of the AC joint capsule in addition to some degree of incomplete tearing of the coracoclavicular ligaments. In a Type III separation, both the AC joint capsule and coracoclavicular ligaments are completely disrupted often with significant superior displacement of the clavicle relative to the acromion. Types IV and VI, in which the clavicle is displaced posteriorly and inferiorly, respectively, are extremely uncommon. Type V is an exaggerated Type II injury, in which there is considerable additional injury to the envelope of surrounding soft tissue, the deltotrapezial fascia. The increased severity of this injury leads to a greater degree of displacement that can be appreciated both clinically and radiographically with vertical joint displacement between 100% and 300%.

History/exam: Depending on the time-out from injury, there can be evidence of bruising and swelling in the anterior shoulder and deformity at the AC joint. Patients will often be able to localize the pain to the AC joint. In addition, the pain and muscle spasm will often radiate up into the trapezius and down into the deltoid fascia.

Imaging: Optimal radiographs for evaluating these injuries include an anteroposterior (AP) view of both AC joints on a single film; if possible, an axillary view to assess AP displacement and evaluate for intra-articular fracture; and the 15° cephalic tilt view (Zanca) with under-penetration to visualize the AC joint specifically.

Although some in the past have advocated a weighted view to differentiate between Type II and Type III injuries, it typically does not change the treatment and therefore is not necessary.[10]

Treatment: Over 85% of acromioclavicular joint injuries represent Type I–III injuries.[10] These, for the most part, may be treated nonoperatively by conservative measures and then gradual return to play when symptoms allow. Conservative measures include rest, sling, and gradual mobilization with a strengthening program and possible injection into the acromioclavicular joint if necessary. There remains some controversy as to how to treat Type III injuries in the overhead throwing athlete and perhaps some overhead laborers but the best evidence at this time still supports the role of nonoperative management.[12] Types IV–VI are generally treated with surgical intervention.

Anterior Shoulder Dislocation

Anatomy/pathology/epidemiology: The shoulder is the most commonly dislocated joint in the body. Risks factors for shoulder dislocations include overall ligamentous laxity and history of previous dislocation. Anterior shoulder dislocations far exceed posterior shoulder dislocations and represent over 90% of instability events.[13] More common in contact and collision sports such as football, rugby, and hockey, the instability event usually results from application of a strong external rotation or extension force to the vulnerably positioned arm. The arm is most vulnerable in abduction and external rotation.

History/exam: On visual inspection of the acutely dislocated shoulder, the patient will usually hold the arm at the side in slight abduction and external rotation. The deltoid loses its rounded contour and often a sulcus can be appreciated beneath the acromion. It can be difficult to examine the patient if they have a large body habitus.

It is important to perform a neurovascular exam at the time of injury. It is estimated that there is an incidence of axillary nerve contusion or injury in 9%–20% of anterior shoulder dislocations.[13] The neuropraxia usually resolves with time but may take several weeks.

Imaging: Minimum radiographic views should include a true AP view, perpendicular to the plane of the scapula rather than the thorax, and an axillary lateral view. Additional views may be helpful in determining additional bony pathology.

Treatment: It is best to attempt to reduce the dislocation as soon as possible. The longer that it is out of position allows the body to produce greater muscular spasm. This makes it increasing difficult to reduce without anesthesia. If there are any concerns that on-the-field reduction cannot be done without causing further injury, then reduction should be delayed until radiographs are obtained.

There are a number of maneuvers that have been described for reducing the shoulder. Some reduction techniques include those described by Stimson, Hippocrates, and Milch. After

reduction or in cases of difficult reduction, it is important to evaluate the shoulder neurovascularly and radiographically. It is important to again note the status of the axillary nerve.

The recurrence rate for anterior shoulder dislocation varies between 17% and 96% and is directly related to age.[14] Patients younger than 20 years have the highest incidence for recurrent dislocation. CT scans are usually reserved for dislocations that are irreducible, chronic, or associated with fracture. MRI has little value in the acutely dislocated shoulder but can demonstrate soft tissue, muscular, and labral pathology in the subacute or chronic setting.

Immobilization with a sling for comfort and then gradual return to a functional strengthening program is usually recommended for first-time dislocations. However, as a result of the high recurrence rates up to 90% among young adults and adolescents, some advocate primary surgical stabilization in this group of athletes.[14]

Posterior Instability

Anatomy/pathology/epidemiology: Posterior dislocations account for just 4% of all glenohumeral joint dislocations and may present as acute or chronic.[15] Approximately 50%–80% of posterior dislocations are unrecognized at the time of initial presentation.[15] In athletes, a direct blow to the anterior shoulder or a posteriorly directed force to a flexed, internally rotated, and adducted shoulder is the typical mechanism of injury. Posterior subluxation can be related to a specific traumatic event or repetitive minor traumatic episodes. Athletes participating in swimming or overhead activities may be subject to tensile failure of the posterior capsule from repetitive microtrauma, thereby precipitating symptoms of posterior instability.

History/exam: Unlike anterior dislocations, most acute posterior dislocations reduce spontaneously. Patients with an acute posterior dislocation usually present with the arm in an adducted, internally rotated position. The coracoid is typically prominent, and the dislocated humeral head creates a posterior fullness. Although the presentation may be subtle, a lack of external rotation and inability to supinate the forearm are the hallmarks of diagnosis.

Imaging: Radiographic evaluation should consist of a three-view trauma series. The axillary view will reveal an empty glenoid with the humeral head displaced posteriorly. CT may be helpful for identifying impaction fractures or bone loss. The more common presentation of posterior instability includes pain, instability, or both when the arm is placed in the provocative position of flexion, adduction, and internal rotation. Patients may describe crepitus or clicking in certain positions.

Reproduction of the instability should be attempted during physical examination. Stability tests include the posterior drawer test, load and shift test, and jerk test.[15] Instability testing more frequently elicits symptoms rather than produces a discernable translation that can be appreciated by the examiner.

Rotator Cuff Tear

Anatomy/pathology/epidemiology: While the majority of rotator cuff tears are degenerative, the rotator cuff can be torn from a single traumatic injury. These types of tears tend to happen more in people under age 50 following an acute trauma or repetitive overhead work or sports activity. The rotator cuff includes the tendons of supraspinatous, infraspinatous, teres minor, and subscapularis. The majority of rotator cuff tears occur in supraspinatous tendon.

History/exam: An acute tear often involves the history of a fall onto an elbow or hand with forces transmitted through the arm to the shoulder. In a significant sized tear there can be ecchymosis present, although not usually. Testing for rotator cuff injuries involves the empty can test (supraspinatus), strength with internal and external rotation with the arm at the side at 90° of forearm flexion (testing supraspinatus/infraspinatus and subscapularis, respectively). Other tests for rotator cuff function involve the Napoleon's "Bear Hug" or lift-off test for subscapularis and the "horn blower" sign for infraspinatous.[16] Inspection and palpation of the biceps tendon and the bicipital groove are also important as a rotator cuff injury may also involve the bicipital sling.

Imaging: Radiographs are helpful in evaluating for other associated findings including fracture, dislocation, slope of the acromion, presence of osteoarthritis, and other factors that may have predisposed the patient to this injury. However, MRI is the imaging modality of choice for a rotator cuff tear. Contrast is not necessary in the setting of an acute injury.[16]

Treatment: Most full thickness rotator cuff tears require surgical intervention. Older patients who present with a small tear on MRI imaging may be treated initially or definitively with physical therapy. Should these patients fail a course of formal physical therapy focusing on the rotator cuff, scapular stabilizers surgical intervention may be warranted. Younger patients with acute large rotator cuff tears or those athletes who present with rotator cuff tear and instability may be considered for surgical intervention earlier. Younger patients with small tears and no evidence of instability may also trial physical therapy.

Clavicle Fractures

Anatomy/pathology/epidemiology/exam: Clavicle fractures are caused by direct trauma. Localized pain along the clavicle, deformity, crepitus, and swelling are consistent findings. Mid-shaft clavicle fractures are the most common and represent over 80% of all clavicle fractures.[17] Clavicle fractures of the distal third represent 10%–15% of clavicle fractures.[17] They can be further characterized into Types I through III. These types represent minimal displacement, fracture medial to the coracoclavicular ligaments, and fracture that extends into the AC joint, respectively. Distal clavicle fractures have a high incidence of non-union but most of these are asymptomatic, and only a small number of these will be severe enough to require surgery.

Clavicle fractures of the medial third are relatively rare and represent less than 5% of clavicle fractures. These can be successfully managed with nonsurgical intervention, with the exception of a posteriorly displaced fracture that may threaten underlying neurovascular structures.

Uncommon associated injuries with clavicle fractures include ipsilateral scapula and rib fractures, pneumothorax and neurovascular injury.

Treatment: Treatment involves use of supportive measures such as a sling and analgesics rather than attempts at reduction. The sling may be utilized for up to 4 weeks; however, range of motion exercises must be instituted starting approximately 48 h post injury to prevent joint contractures. Fortunately, most mid-shaft clavicle fractures will heal, although there are some characteristics that place some patients at risk for nonunion and decrease in function. These include "Z" pattern fractures and those with greater than 2.0 cm of shortening. These fractures may be considered for surgical management.[17]

Imaging: The clavicle is best visualized with an AP view and a view with the beam aimed 30° cephalad. The serendipity view may be used to visualize the sternoclavicular joint and medial clavicle fractures. This is a 40° cephalic tilt view focusing on the sternoclavicular joint.

Pectoralis Muscle Injuries

Anatomy/pathology/epidemiology: Ruptures of the pectoralis major muscle were thought to be uncommon but are being reported with increasing frequency. Interestingly, almost all documented cases of rupture are in male athletes.[18] Most ruptures are complete and involve the sternal head at or near the humeral insertion site.

History/exam: The most common mechanism of injury is during the eccentric loading of the pectoralis major tendon while weight lifting. This typically involves the arm in a position of abduction, extension, and external rotation, as seen in flat or decline bench press. However, rupture has also been reported in wrestling, water skiing, rugby, and other sports. Swelling and ecchymosis often complicate the initial diagnosis of this injury and, while not optimal, it is not uncommon for a patient to have a delay in diagnosis. The presentation of a male athlete with a history of an acute eccentric event and a large amount of ecchymosis, especially in the anterior chest wall and biceps region, should lead one to be highly suspicious for a pectoralis major muscle rupture. Inspection of the anterior axillary fold will likely have an abnormal contour as compared to the contralateral side. The absence of the pectoralis major contour in the axilla can be accentuated when asking the patient to forward flex the arm to 90°, with the elbow also bent at 90°, and asking the patient to resist shoulder adduction. Many of these patients will be able to relate to this maneuver, as it is similar to the "pec deck" in weight lifting. Medial retraction of the pectoralis major muscle may create abnormal bulging of the anterior chest wall.

Imaging: While the physical examination is the mainstay in diagnosis, radiographs may be helpful to evaluate for an avulsed bony fragment. MRI also can aid in earlier detection of the injury when physical examination findings are inconclusive and it may also aid in the identification of partial tears. It is important to specify the diagnosis in question for the MRI so that the anterior chest wall and insertion site of the pectoralis major on the humerus can be imaged. Most standard shoulder MRI protocols do not extend distally enough to visualize the pectoralis major tendon insertion.

Treatment: Nonsurgical treatment is appropriate for incomplete tears or the rare muscle belly injury. Surgical treatment is advocated for both athletes and in most patients. The ideal time for intervention is less than a month from injury to minimize the effects of tendon retraction and scar tissue. However, repair has been reported at 2 years out from injury with good results.[18] The benefits of surgical intervention include improved cosmesis and restoration of strength. Peak torque strength has been shown to return to 99% after repair versus 56% with nonsurgical treatment.[18]

ACUTE FOOT AND ANKLE INJURIES

Anatomy/pathology/epidemiology: Injuries to the foot and ankle are among the most common ailments experienced by the athlete. Adherence to the RICE mantra, as well as early protected weight bearing, remains the mainstay of treatment for most injuries. While most of these injuries are mild and self-limiting, several injuries to this anatomical region require special attention, due to either their relative frequency of occurrence or to make sure rarer, more severe injuries requiring specialized treatment are not misdiagnosed and undertreated. While a complete listing of these injuries is beyond the scope of this chapter, several such injuries are outlined in the following.

History/exam: Perhaps more importantly than any other anatomical region, careful attention to specific location of pain or dysfunction on history and exam can be diagnostic for the foot and ankle injury. Commonly, patients are quite general in regards to their pain and its location; the clinician may find it helpful to ask the athlete to point to his or her area of worst pain with a single finger. This can sometimes be difficult, however, as multiple concomitant injuries can occur. Further, it is not uncommon for one to experience an acute-on-chronic injury, making it hard to sort a mild injury from one more severe. Careful attention to areas of edema and questions about prior history of trauma also aid the clinician in accurate diagnosis. Mechanism of injury can often be helpful as well, such as in the common inversion mechanism seen with most ankle sprains.[19]

COMMON INJURIES

Ankle Sprains

Anatomy/pathology/epidemiology: In combination with benign muscular strains, ligamentous ankle sprains make up the majority of injuries to the foot and ankle—14.9% of

all injuries in the NCAA population.[20] Most sprains involve the lateral ligamentous complex of the ankle.[21] The anterior talofibular ligament (ATFL) connecting the anterior distal fibula to the talus is the most commonly sprained ligament, followed closely by the calcaneofibular ligament (CFL). This ligament connects the inferior fibular tip to the lateral calcaneus.[21]

History/exam: Swelling over this area is common with ankle sprains. Patients commonly report an inversion mechanism of injury.[19] When asked about the area of maximal pain, the athlete will point to a region just anterior to the fibula or just distal to its tip. Recurrent ankle sprains can become a common problem after a severe ankle sprain, with recurrent sprains occurring 10% of the time.[21]

Ligamentous laxity, either generalized or posttraumatic, may predispose the patient to recurrent sprain. Side-to-side exam of the affected ankle compared to the contralateral normal ankle may demonstrate increased anterior translation of the calcaneus compared to the tibia when an anterior pressure is applied to the posterior heel. This anterior drawer test signifies laxity of the ATFL. Similarly, a positive talar tilt test where the calcaneus is firmly tilted via varus stress while stabilizing the tibia signifies CFL laxity.

Treatment: Regardless of whether the sprain represents a grade I, II, or III injury, initial treatment consists of RICE and protected weight bearing, with gradual return to full weight bearing and play. Common treatments for recurrent sprains involve either ankle bracing or taping, muscular strengthening about the ankle, and most importantly, proprioception exercises. Proprioception is the body's ability to sense its position in space; retraining ankle proprioception via balancing exercises such as a trampoline or wobble board has been shown to be helpful in preventing recurrent ankle sprains.[22] Rarely, in severe recurrent sprains surgery may be indicated.

High Ankle Sprain

Anatomy/pathology/epidemiology: One specific type of ankle sprain deserving special mention is the high ankle sprain, which makes up 1% of all ankle sprains.[23] Unlike the common ankle sprain, which involves the lateral ligamentous complex, the high ankle sprain involves injury to a confluence of tissue connecting the tibia to the fibula termed the syndesmosis. By definition, this injury occurs above the ankle joint.

History/exam: Pain is typically more vague and hard to locate than with common sprains and swelling is minimal or nonexistent. Pain is worsened by activities where the tibia is stabilized and the foot/ankle is externally rotated. On physical exam, recreation of this mechanism or pain with the squeeze test, i.e., compression of the tibia and fibula by squeezing of the calf, will exacerbate pain.[23]

Imaging: Essential radiographs include three views of the ankle and a full length tibia/fibula radiograph in the AP and lateral planes.

Treatment: A non-displaced high fibular fracture with no evidence of ankle mortise incongruency may be treated nonoperatively with non-weight bearing in a short leg cast. Recovery time for this injury depends on severity and can average from 2 to 3 weeks to 6 weeks or longer.[23] Rarely, for severe unstable injuries surgery is indicated.

Ankle Fractures

Anatomy/pathology/epidemiology: While not as common as ligamentous sprains, ankle fractures are also quite common and differentiation from sprains is necessary as fractures require radiological imaging and medical consultation. Many sprains, on the other hand, are self-limiting and easily self-treated.

History/exam: Mechanism of injury is typically more severe than with sprains, and maximal pain is typically located directly over bony prominences rather than the soft tissue surrounding them. With obvious fracture and deformity, the ankle should be splinted in position and the patient should be made non-weight bearing with crutches until medical evaluation with radiograph is available. More subtle injuries can be difficult to distinguish from ankle sprains. If any doubt exists as to the diagnosis, radiologic imaging should be performed.

Imaging: The Ottawa ankle rules were designed to help decide when imaging may or may not be indicated.[24] These rules state that radiographs are only needed when there is pain over the posterior aspect of the bony prominence of the distal fibula, the same area over the distal tibial malleolus, or when the patient cannot bear weight both initially and at the time of physical exam. These rules are nearly 100% sensitive for fracture, although only modestly specific. Therefore, very few fractures are missed using these rules, while they can reduce the number of unnecessary radiographs taken by 30%–40%.[25]

Treatment: Unstable ankle fractures are treated surgically involving non-weight bearing for 6–12 weeks depending upon the severity of the injury. For non-displaced or isolated fibular fractures, weight bearing may be started immediately; however, pain may limit full weight bearing and crutch assist may be warranted until pain resolves—approximately 2–3 weeks post injury. A supportive walking boot may aid in allowing early weight bearing.

Peroneal Tendon Injuries

Anatomy/pathology/epidemiology/exam: While pain over the soft tissue about the anterior or distal fibula is consistent with ankle sprain, and pain directly over the bone is suggestive of fracture, pain over the soft tissue just posterior to the fibula suggests injury to the peroneal tendons or musculature. While it is quite common to experience peroneal muscular strains, either in an isolated manner or secondary to another injury process, occasionally injuries to this area are more severe. The superior retinacular tissue holding the tendons in place can become injured, allowing subluxation or frank

dislocation of the tendons out of the bony groove behind the fibula.[26] The soft tissue surrounding the area can become quite boggy, and pain or instability can be maximized by performing resisted ankle eversion with the ankle in plantarflexion.[27] Further, peroneal tendon tears can occur as the tendons reverse directions about the distal end of the fibula, especially tears of the peroneus brevis.

Treatment: Treatment with RICE and protected weight bearing are first-line treatment, but if the injury fails to resolve, advanced imaging in the form of MRI or ultrasound is indicated, followed by the occasional need for surgery.

Osteochondral Lesions

Anatomy/pathology/epidemiology: Osteochondral lesions of the ankle most commonly involve the talar dome. These lesions are essentially a chip of bone attached to cartilage of varying size that comes off of the host bone.

History/exam: Varying symptoms according to size and location of the lesion may occur, sometimes involving locking and catching of the ankle due to the loose body formed. More often, the lesions are small and without mechanical symptoms. Pain location is usually ill defined and deep; as a result, delayed diagnosis is more the rule than the exception. Ankle swelling commonly occurs, especially after impact activities such as running or jogging.

Imaging: Although these injuries can sometimes be seen on x-ray, more often MRI or CT scan is required for diagnosis.

Treatment: Treatment may involve ankle injections and physical therapy or surgical intervention, and is best managed by orthopedic referral.

SPECIFIC INJURIES

Achilles Tendon Rupture

Anatomy/pathology/epidemiology: Injury to the Achilles tendon most commonly occurs with an eccentric muscular load, which involves aggressive contraction of the gastrocnemius-soleus complex while simultaneously lengthening the muscle and tendon.[28]

History/exam: Patients commonly report a feeling of being kicked or shot in the back of the leg. An inability to bear weight on the affected extremity is common initially. A palpable gap may be apparent in the tendon just superior to its insertion on the posterior calcaneus. With full tears, an inability to actively plantarflex the foot can occur, although the exam may be complicated by compensation with the remaining foot flexors and the peroneus longus. The Thompson test involves laying the patient prone and squeezing the posterior calf muscles. With this motion, the ankle should passively plantarflex. A lack of plantarflexion is consistent with a full Achilles tear.

Imaging: Although x-rays are often ordered to rule out bony involvement, the diagnosis of Achilles rupture remains a clinical rather than a radiographic diagnosis, and MRI is rarely needed.

Treatment: Achilles ruptures can be treated either surgically or nonsurgically.[29] Orthopedic consultation to discuss treatment is indicated as the optimal management of this injury must be tailored to the individual patient.

Calcaneus Fracture

Anatomy/pathology/epidemiology/exam: Calcaneus fractures usually involve a severe injury or fall from a height. A large amount of severe heel pain, bruising, and inability to bear weight are found.

Imaging: X-rays and potentially CT scans are indicated to rule out this diagnosis when one is suspicious of this injury.

Treatment: Non-weight-bearing status should be maintained with crutches until this diagnosis is ruled out if one suspects a calcaneus fracture. Calcaneus fractures are indicated for surgical intervention if a displaced intra-articular fracture involves the posterior facet, the anterior process of the calcaneal cuboid articulation is involved >25%, the calcaneal tuberosity is displaced, and selected open fractures.

Jones Fractures

Anatomy/pathology/epidemiology: Injury to the lateral midfoot and pain isolated to the base of the fifth metatarsal bone should suggest the potential for a Jones fracture or one of its variants. A Jones fracture is a fracture at the base of the fifth metatarsal near its metaphyseal–diaphyseal junction.[30] Unlike its variants, including an avulsion of the tip of the bone or a proximal fracture found within only the diaphyseal shaft, a true Jones fracture is notable due to its tendency for prolonged difficulty in healing.[30] The reason for this problem is due to the poor vascularity of this bone, with its predominate blood supply coming in a retrograde manner from distal to proximal.

Treatment: Because of its difficulty in healing, either prolonged casting with non-weight-bearing status or primary surgical fixation with a screw is indicated. Therefore, after radiographic diagnosis, orthopedic consultation is indicated.

LisFranc Injuries

Anatomy/pathology/epidemiology/exam: Injuries to the midfoot are often termed mid-foot sprains, or LisFranc injuries. Most mid-foot sprains are benign and self-limiting injuries that respond to RICE.[31] However, with severe injury, large amounts of mid-foot edema, or inability to bear weight, a full LisFranc injury should be ruled out. This involves tearing of the ligaments attaching the tarsal to the metatarsal bones, and most specifically the LisFranc ligament attaching the base of the second metatarsal to the medial cuneiform.[31] If fully torn, the normal arch of the foot is lost and instability of the midfoot joints occurs. Prolonged delays in diagnosis may result in early posttraumatic mid-foot arthritis, a difficult problem to treat effectively in the active athletic population.

Imaging: Initial weight-bearing x-rays are taken to look for bony gaping. Further, stress views of the foot in abduction or MRI are also usually indicated.[32,33]

Treatment: Strict non-weight bearing and elevation should be initiated. Referral to a foot and ankle specialist is indicated if this diagnosis is made or suspected.

Turf Toe

Anatomy/pathology/epidemiology/exam: Pain after a vigorous hyperextension of the great toe with tenderness mainly at the metatarsophalangeal (MTP) joint is suggestive of turf toe.[34] The injury occurs most commonly on artificial playing surfaces, and involves an injury to the plantar capsular structures of the joint.[35]

Imaging: X-rays are often indicated to rule out associated fracture.

Treatment: RICE and protected weight bearing are the initial treatments, followed by return to full weight bearing over several days to weeks depending on injury severity. Extended carbon fiber turf toe plates may be used in shoes to help prevent joint hyperextension for severe or recurrent injury. Recovery often takes 3–4 weeks. If symptoms are recurrent and not cared for properly, the condition can progress to arthritis of the MTP joint over time. This condition is termed hallux rigidus.

ACUTE HIP INJURIES

Sports-related injuries have been reported to account for approximately 2.6 million visits to the emergency room by children and adolescents yearly.[36] However, hip injuries are less commonly encountered in sports, accounting for only 5% and 9% of injuries.[37] Injuries to the hip/large-weight-bearing joints have gained recent increased attention as these injuries may significantly impact short- and long-term sports performances resulting in increased morbidity.[38,39] The hip is estimated to transfer up to eight times body weight loads during jogging or vigorous sports activities.[40] Among the most commonly encountered injuries are hamstring/quadriceps strains/avulsions, hip dislocation, and rarely fractures of the proximal femur. This chapter will define these injuries including anatomy/pathology/epidemiology, history/exam, initial treatment, and return-to-play guidelines.

Hamstring or Quadriceps Strains or Avulsions

Anatomy/pathology/epidemiology: Muscle strains are some of the most common hip injuries in athletics and of hip muscle strains, the hamstring bone–tendon unit is among the most commonly injured.[41] The most common avulsion fractures of the pelvis include the ischial tuberosity in approximately half of all cases, anterior inferior iliac spine, and anterior superior iliac spine.[42]

History/exam: The diagnosis is made when the patient complains of pain at the muscle insertions, rarely in the muscle belly itself, and is usually found in muscles crossing two joints.[43] Most commonly encountered is groin or medial thigh pain following an eccentric muscle contraction, for example, soccer players experience strain of the iliopsoas muscle due to eccentric hip flexion.[44]

Treatment: Initial treatment should involve RICE principles, i.e., rest, ice, compression, and elevation of the limb along with nonsteroidal anti-inflammatory medications.[45] Absent motion of the affected joints or a palpable defect should prompt referral to an emergency room as these may indicated grade III strains or complete ruptures and or avulsions at the insertions of the affected muscles.

Return-to-play guidelines: Avulsions are more commonly encountered in the skeletally immature athletes and may be managed nonoperatively in certain cases; however, referral to an orthopedic surgeon is essential to confirm treatment.[41,46] Return to play is allowed when pain-free range of motion and strength returns.

Hip Dislocation

Anatomy/pathology/epidemiology: Hip dislocation is defined as displacement of the femoral head outside the acetabular confines. True dislocation is uncommon in athletes. The most commonly encountered traumatic closed hip dislocation pattern is posterior, usually the result of large forces directed across the flexed knee into the femoro-acetabular joint[47] such as in collisions in skiing or contact sports.

History/exam/imaging: The diagnosis is confirmed radiographically on a plain AP pelvis radiograph, however a posterior dislocation should be suspected when a collision results in an athlete complaining of hip or groin pain and the leg held in a flexed, adducted, and internally rotated for posterior dislocations.[48] The patient will be unable to bear weight and is typically in extreme pain.

Treatment: A closed hip dislocation is best treated with closed reduction as quickly as possible due to the fragile vascular supply to the femoral head, in which osteonecrosis may occur in up to 20% of patients.[49] The patient should be transferred to an emergency room quickly and reduction of the hip performed within 6 h to decrease incidence of osteonecrosis of the femoral head.[50] Prior to transfer, the patient should be examined carefully for neurovascular deficits such as sciatic nerve palsy or vascular injury. The patient is treated with touchdown weight bearing for approximately 6 weeks with hip precautions consistent with the dislocation pattern (posterior or anterior).

Return-to-play guidelines: Return to play is allowed after 6 weeks and when the hip has a full range of motion that is pain free and strength is regained to symmetrical with the contralateral hip.[37]

Proximal Femur Fracture

Anatomy/pathology/epidemiology: Fractures of the proximal femur are an extremely rare entity in athletics. Case reports

have been described for intra-capsular proximal femur fractures in sports such as skiing.[51] These fractures are considered surgical emergencies due to the resultant risk of osteonecrosis of the femoral head, which has been cited upward of 38%–100% in Delbet Type I transphyseal fractures.[52] The mechanism of injury is similar to hip dislocation but typically involves a high velocity or force.

History/exam/imaging: The hip is typically held in a flexed shortened, abducted, and externally rotated position. The diagnosis should be suspected in high energy trauma with the patient unable to bear weight and complaining of groin or hip pain.[48] The diagnosis of hip fracture—physeal, nonphyseal, and intra- or extracapsular is confirmed radiographically and subsequent treatment guided based on type of fracture, displacement, and skeletal maturity of the patient.

Treatment: Immediate referral to an emergency room via ambulance transport is prudent as long bone fractures are serious injuries and can be life threatening. Immobilization of the athlete in a position of comfort is essential.

Return to play: Return to play is not allowed until the fracture is healed and range of motion with strength returns.[50]

ACUTE HAND, WRIST, ELBOW INJURIES

Hand, wrist, and elbow injuries occur acutely in many sports and athletic activities with an incidence between 9% and 29% reported for upper extremity injuries. Commonly encountered injuries include distal radius fractures and tendinous/ligamentous injuries in the hand/digits such as jersey, mallet, and gamekeeper's thumb. Elbow dislocations are also commonly encountered both simple and in combination with various fractures.[53,54] This chapter will serve to define these injuries including anatomy/pathology/epidemiology, history/exam, initial treatment, and return-to-play guidelines.

HANDS: JERSEY, MALLET, GAMEKEEPER'S THUMB

Mallet Finger

Anatomy/pathology/epidemiology: Mallet finger is an eponym utilized to describe a finger that following injury is unable to be actively fully extended at the distal interphalangeal joint.[55] The mallet injury is secondary to a discontinuity and disruption of the extensor tendon at the insertion site of the dorsal distal phalanx. Mallet injuries may be bony with an avulsion fracture at the extensor digitorum communus insertion on the dorsum of the phalanx. Mallet fingers may also be completely tendinous ruptures at the insertion site in the absence of bony injury.

History/exam: The injury mechanism of closed mallet fingers is forced flexion of the distal interphalangeal joint against an extended finger.[56] The athlete will be unable to extend the distal phalanx of the affected digit.

Treatment: Initial treatment guidelines include gross reduction of the finger and the distal interphalangeal joint to an extended position and maintenance of this position via splinting. Commonly employed techniques include a dorsal finger splint via aluma foam or a tongue depressor secured to the digit extending from the proximal phalanx to the tip of the finger. Care must be taken to ensure perfusion of the digit tip is maintained following splinting by assessing capillary refill, color, warmth, and sensation. The patient should be referred to an orthopedic hand surgeon for close follow-up visits and to assess for need of surgical intervention. Healing of a nonoperative injury may take up to 12 weeks with the initial 6 weeks spent in a splint at all times.

Return-to-play guidelines: The patient is allowed to return to play if the athlete may safely participate with a splinted digit and comfortably performs activities required by the sport.[57]

Jersey Finger

Anatomy/pathology/epidemiology: Jersey finger is an eponym utilized to describe an injury at or to the volar distal phalanx of the hand creating a discontinuity of the flexor digitorum profundus tendon at its insertion site. Jersey injuries may be bony fractures or purely tendinous avulsions.

History/exam: The mechanism of injury is forced extension of the distal interphalangeal joint against a flexed digit tip.[58] The patient will be unable to flex the distal phalanx of the affected digit.

Treatment: Initial treatment guidelines are to place the digit into a flexed position at the distal interphalangeal joint and splint the phalange. Care must be taken after splinting the finger to ensure adequate digit tip perfusion is maintained by assessing the skin temperature, capillary refill, color, and sensation. The patient should be referred to an orthopedic hand surgeon in order to maintain close follow-up and assess need of surgical fixation—of note the necessity is of higher incidence than that of mallet injuries.[59]

Return-to-play guidelines: The athlete is not allowed to return to play until the tendon is well healed, functional, and painless range of motion regained. Operative intervention is probable; thus, the average return-to-play timeline is approximately 6 months.[57]

Gamekeeper Thumb

Anatomy/pathology/epidemiology: Gamekeeper thumb is an eponym utilized to describe an injury to the ulnar collateral ligament of the thumb at the metacarpal–phalangeal joint.[53,67] The mechanism of injury is forced abduction or a valgus force directed against the thumb. The force sprains the ulnar collateral ligament and may be graded in standard fashion as v1, 2 or 3. The injury may be purely ligamentous or may also result in an avulsion fracture from the base of the thumb proximal phalanx.

History/exam: The patient will complain of thumb pain, occasionally directly pointing to the insertion of the ulnar collateral ligament. The thumb is typically swollen and may be ecchymotic. Physical exam maneuver may include stress testing with the metacarpal phalangeal joint in 90° of flexion and extension applying ulnar stress. Should a firm endpoint not be felt, the patient should be considered as having sustained an ulnar collateral ligament rupture until further assessment.

Treatment: The treatment should involve immobilization of the thumb in a thumb spica splint. Most injuries have successful nonoperative outcomes.[60] However, following nonoperative management should the metacarpal–phalangeal joint remain unstable on stress testing, surgical intervention may be warranted.

Return-to-play guidelines: The athlete may return to play in a thumb spica cast if conducive to the sport. If a cast cannot be worn safely, return to play is delayed until the ligamentous sprain or disruption is healed and full painless motion and strength are restored to the hand. Most UCL sprains graded 2 or 3 are treated in a thumb spica cast for approximately 6 weeks.[57,60]

DISTAL RADIUS FRACTURES

Anatomy/pathology/epidemiology: Distal radius fractures are among the most common fractures of the upper extremity in the United States with greater than 450,000 occurring annually[61] and approximately 8% secondary to sports.[62] The injury is characterized as involving the intra-articular surface or the extra-articular surface.

History/exam: The mechanism of injury most commonly encountered in sports is a fall onto an outstretched hand aka FOOSH injury. Diagnosis of a distal radius fracture is confirmed radiographically but should be suspected with pain, swelling, or gross deformity at the wrist.

Treatment: The limb should be assessed for neurovascular status and placed into a padded volar splint.[61] The patient should be referred immediately to an orthopedic surgeon or an emergency room for initial treatment on the day of injury. Assessment of fracture type and further treatment plans including definitive management will be based upon fracture characteristics as delineated on anterior–posterior wrist radiograph, oblique views, and the lateral view.

Return-to-play guidelines: Depending upon the type and severity of the fracture, the return to play will be allowed once the fracture is healed (average 8–12 weeks) and painless full range of motion restored to the wrist.[57,63]

ELBOW DISLOCATION

Anatomy/pathology/epidemiology: Elbow dislocation involves incongruency of the joint surfaces of the ulnotrochlear articulation, radiocapitellar articulation, or the radio-ulnar joint proximally. Elbow dislocations are estimated to constitute 10%–25% of elbow injuries in adults.[64]

History/exam: The mechanism of injury is typically a fall onto an outstretched arm. The diagnosis is often obvious with notable gross deformation of the elbow. The most common pattern of dislocation is posterior or posterolateral accounting for approximately 90% of simple elbow dislocations.[65] Careful assessment of the neurovascular status of the arm is paramount.

Treatment: Gentle reduction of the dislocated elbow should be attempted utilizing traction and flexion of the forearm. Following closed reduction, the neurovascular status should again be assessed and gentle range of motion of the joint performed.[66] If the elbow is stable the arm should be placed into a sling, referral to an orthopedic surgeon made, and range of motion exercises initiated at 48 h following reduction. Unstable elbow injuries may require operative intervention.[61]

Return-to-play guidelines: Simple stable elbow dislocations may return to play once painless range of motion and strength are restored.[57]

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64 Concussion in Sport

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CONTENTS

Introduction 789
Epidemiology and Injury Risk 790
Effect of Age 790
Effect of Sex 790
Effect of Sport 791
Genetics 791
Concussion Evaluation 791
On-Field Assessment 792
Sideline, Locker-Room Evaluation 792
Emerging Evaluation Tools 792
Concussion Management and Resolution 792
Initial Management 792
New Management Technologies 793
Return to Play 794
Other Considerations 794
Same-Day Return to Play 795
Potential Concussion Complications 795
Post-Concussion Syndrome 795
Second Impact Syndrome 795
Concussion Prevention 795
Protective Equipment 795
References 796

INTRODUCTION

A concussion is a neurological injury sustained by forces from a blow to the head or transmitted to the head (e.g., from the body). The definition of concussion is not wholly agreed upon, but the basic premise is that force causes the brain to undergo a complex pathophysiological process, resulting in chemical changes in the brain that affect its function [1]. The cell membrane may become more permeable after injury, with resulting electrolyte imbalances, hyperglycolysis, and impaired oxidative metabolism, resulting in a functionally impaired cell [2]. The cellular impairments account for the functional, not structural, neurological problems we see in concussed athletes. Symptoms such as headache, dizziness, confusion, and others represent the injury.

Until the last few years, many medical and lay people considered concussion to be a fairly inconsequential injury. Whether referred to as "getting dinged" or "getting your bell rung," concussion was thought to be a normal part of many sports that did not interfere much with ability to play or have any long-term effects. New concerns about the long-term impact of sport-related concussion has come about, largely driven by media focus on professional athletes who have struggled to recover from brain injuries or on athletes who have died with a recent history of concussion [3]. In addition, there are emerging reports of potential long-term brain injury from concussion, in the form of chronic traumatic encephalopathy (CTE), in professional football and college football players [4–6]. The publicity generated from high-profile cases has resulted in a trend toward attitude change regarding concussion identification and management, with rule changes designed to mitigate concussion risk being implemented in many sports. In addition, federal and state legislation directed at improving concussion education, recognition, and care has been implemented in many parts of the United States.

With the new focus on concussion in sport, many questions remain unanswered.

What is the risk for concussion in sport? How should a concussion be managed? What is "normal" concussion recovery? What is the long-term risk of having a concussion? While we currently know some about concussion risk, there is probably more we *don't* know about the injury itself, how to assess recovery, and what to advice about long-term risk for injury.

We know more concussions are being sustained than previously recognized. Estimates in the 1990s put concussion incidence at 300,000 sport-related injuries per year [7], but more

recent estimates indicate incidence is likely to be between 1.6 and 3.6 *million* injuries yearly [8]. Several studies have shown the problem of concussion underreporting, which makes the real incidence difficult to pinpoint [9–11]. In any case, sports involvement at every age is increasing, with over 30 million children and adolescents participating in organized sports in the United States (US) [12]. Concussion rates are increasing in most high school sports, whether due to actual increased injuries or better detection/reporting [13]. As all types of injuries, including concussion, will logically increase as more people are involved, the knowledge of concussion risk, prevention, appropriate assessment and management if sustained, and outcome is more important than ever.

EPIDEMIOLOGY AND INJURY RISK

Effect of Age

Children up to age 18 account for the majority of sport-related concussions [14]. The pediatric population is of particular interest, since the brain is still rapidly forming and changing through adolescence, with potential for devastating effects if brain injury is sustained during development. In fact, the ongoing rapid brain development in children may actually increase their injury exposure [15]. Because children have anatomic and physiologic factors that make them more susceptible to injury and more difficult to assess, risk for injury is thought to be higher than that of adults. Increased forces are generally needed for clinical concussion symptoms to appear, due to head size and geometric differences (compared to adults) in the skull and brain [15,16]. Compared to adults, the brain undergoes a larger amount of force, with potentially more damage, to result in symptoms, which may help explain why children often take longer to recover than do adults. Lastly, cognitive function assessment in a developing brain is more difficult, and it is harder for children to accurately describe symptoms of concussion.

Given the increased risk for injury and problems with recovery, it is not surprising that a study of 100 U.S. high schools and 180 U.S. colleges showed that concussions were a greater proportion of all injuries sustained by the high school athletes (8.9%) compared to the college athletes (5.8%), even though the college athletes had a higher rate of concussion [17]. In other studies, high schoolers had both a higher concussion incidence and higher proportion of injury [18,19]. Reasons for increased injury risk are not clear, but potential causes, in addition to differences in brain structure and function, include skill of younger players compared to older, more highly selected players, protective equipment quality and condition, and increased injury exposure due to more playing time at younger ages [18].

Effect of Sex

When reviewing data on injury rates between sexes, it is important to acknowledge that there may be reporting bias that cannot be readily measured. Women have been shown to be more concerned about how their injury could affect future health [20], and they have also been shown to more honestly report injury. Sporting culture has long endorsed a mentality that men (and not women) should play certain sports (e.g., football), should play even while hurt, and should not report injuries that may keep them from playing. While these trends are slowly changing, this culture has also created a more protective environment for women, and it may be indeed easier for women to report injuries than men. As women continue to become more involved in sport and more involved in sports traditionally reserved for men, one of two things may happen: either men will become more comfortable with injury reporting, or women will become less comfortable. Hopefully our culture will continue to support what is becoming apparent with concussion; that getting an injury cared for is not only important for continuing sport play but is equally important for overall health.

Several studies have shown female athletes to be at higher risk for concussion than men in comparable sports (e.g., soccer, basketball). In a 2011 prospective study of high school sport injuries, women's high school basketball athletes had a 1.7 injury rate ratio compared to men; softball had a 1.9 rate ratio, and women's soccer had a 2.1 rate ratio.

This amounts to about twice the risk of men [13]. A 2009 critical review of sport concussion by gender [21] showed 9 of 10 studies reporting higher absolute injury rates for woman compared to men. Notably, even comparisons on absolute injury rates in ice hockey, where checking is illegal in the women's game, showed higher rates for women. In the review, mechanism of injury differed, with men having more concussions with player contact and women having more concussions with ball or surface contact. An NCAA-focused study over three seasons (1997–2000) [22] showed female soccer and basketball players to have higher concussion incidence than their male counterparts. There was no injury difference in lacrosse, softball, baseball, or gymnastics. The study did find, however, that women had a higher injury rate in games, while men had a higher injury rate in practices. Lastly, in 2007, a large study of high school and college athletes showed high school and college women to have higher concussion rates than men in the same sport [17]. The authors also note there were differences in how concussions were sustained; for example, in soccer, more girls were injured defending, while more boys were injured goalkeeping. This reminds us that how a sport is played potentially affects injury risk. In softball, pitching style is very different from that in baseball; accordingly, boys have been shown more likely to sustain a concussion being hit by a pitch than are girls.

There are theories on why women may have higher risk for concussion than men. In particular, differences in head size and shape and neck strength are thought to affect injury risk. While this is not definitive, it at least makes some sense. Women have been shown to have less head-neck mass, neck girth, and less neck muscle strength than men in several studies [23,24]. In soccer heading, increased head mass has been shown to decrease linear and angular head acceleration [25].

Given these parameters, it would follow that men are able to better control their heads and necks in sport, possibly resulting in less force transmitted to the brain, from any potential injurious situation. We understand that forces sustained by the brain are essential in the concussive injury, that those forces lead to the pathophysiological cascade of neuronal dysfunction and energy crisis that is at the center of the injury. If force can be mitigated by better head and neck control, then concussions may be reduced, especially in women [26]. Unfortunately, there is not much proof in this argument so far. Only one small prospective study has been done [27]; although 8 weeks of cervical strength training increased neck girth and some strength measures in 19 collegiate women, force application was not affected, and the study was too small to follow concussion incidence.

Effect of Sport

In the United States, football athletes have long had the highest number of concussions sustained. This is in large part due to the number of athletes playing the sport. A large study of high school injury rates confirmed that football had the highest number of concussions, but the percentage of total injuries sustained in the sport was less than women's soccer and basketball. Overall, football accounted for 40.5% of concussions. Women's soccer (21.5% of concussions), men's soccer (15.4% of concussions), and women's basketball (9.5% of concussions) followed football [17]. The most recent published study of high school concussion incidence showed football having the highest incidence and accounting for more than half of all concussions. Baseball and cheerleading had the lowest incidence of concussion [13]. Intuitively, one would think that higher contact sports would have higher exposure rates, and this has held true. Higher impact sports such as football, lacrosse, and soccer had the highest rates. However, there is concussion risk in all sports, and that should be conveyed to participants.

Knowledge of where children most often sustain concussions is helpful, since they account for so many injuries. Sport participation resulted in about a quarter of concussions sustained in a 3 year prospective study in Australia. Over half of all injuries were related to a fall. About a quarter of injuries occurred at home, and about a fifth of injuries occurred at school. Surprisingly, concussions classified as severe were sustained by children and adolescents participating in organized sports a rate *six times higher* than those participating in leisure physical activities [20]. In an emergency department study of visits for concussion, about half the concussions were sport related, and a quarter of those injuries were during organized sport [29].

Genetics

Limited research has been done on genetic influence of the ApoE protein and ApoE promoter gene on concussion risk, given association seen in some moderate-severe brain injury studies. A significant association was shown between the ApoE-TT promoter genotype and concussion in college female soccer and male football athletes in a recent retrospective study [30].

CONCUSSION EVALUATION

Despite the explosion of concussion research during the past decade, the diagnosis and management of concussion is still primarily made based on clinical assessment with the aid of supplementary tools such as symptom checklists, motor and neurocognitive evaluation, and imaging (when indicated) [1]. Current consensus guidelines recognize that concussion evaluation and management strategies are "works in progress" due to the rapid evolution of our understanding of concussion injuries themselves and expanding recognition of both their short and long-term sequelae [1,31–33]. Because of the inconsistency of presentation of concussive injuries between and within individuals and the variability of symptoms and deficits over time, many of these injuries are still unrecognized and underreported by athletes themselves, coaches, parents, and medical staff alike [10]. A high index of suspicion and consistent evaluation methods must be employed.

The evaluation process for concussion needs to begin during the preseason [34]. The pre-participation evaluation allows for an excellent opportunity to identify high-risk individuals and to provide educational opportunities regarding the signs and symptoms of a concussion to the athlete, coaches, medical staff, and parents. Athletes should be questioned on the number of previous concussions, length and type of previous symptoms, time missed from school and athletic participation, and any current problems or concerns. Knowing the athlete's concussion history is imperative to future management. Several "formal" tools have been widely utilized to aide in concussion management [1,31]. The Standardized Assessment of Concussion (SAC), Acute Concussion Evaluation (ACE), Standardized Concussion Assessment Tool (SCAT), or newly published updated version SCAT2, are a few of the many instruments that may be utilized to evaluate baseline athlete function as well as monitor post-injury progression [34]. Similarly, baseline cognitive testing during the preseason and prior to injury is being more widely implemented at all levels of athletic participation [35]. Post-injury assessments may then be compared to the individual's baseline levels to aid in return to play decisions. The implementation of computer-based neuropsychological testing has allowed for more formalized testing to a widespread audience in a cost-effective and efficient manner. Post-injury tests can then be compared to the individual's baseline performance. Attention should be given to examine preseason test results as up to 15% may be unreliable [36]. The regular use of postural or motor testing has also been gaining acceptance. Use of these and other concussion assessment tools are enhanced by obtaining baseline testing and should be considered as part of a larger concussion management policy or strategy. Many athletic governing bodies have recommended the use of one or more of these tools or

have developed/implemented policies or procedures requiring their availability as part of a structured concussion management policy. Medical providers should verify with their organization, league, state statues, or their athletic governing body as to what are their local obligations and requirements for managing concussed athletes. An emergency action plan should also be prepared and rehearsed to prepare for future injuries of this nature [37].

On-Field Assessment

The on-field evaluation of the injured athlete should focus on standard emergency response protocols including primary assessment of airway, breathing, and circulation [34,38]. Because concussions can occur concurrently with other injuries such as the cervical spine, these potential accompanying injuries need to be considered and evaluated before a decision is made on the injured athlete's immediate disposition (emergency transport versus transfer to the sideline for further evaluation). The athlete's mental status, neurologic status, and the potential for cervical spine involvement must be obtained in a judicious manner. Emergency protocols need to be enacted as necessary based on the providers' immediate assessment. Athletes with prolonged loss of consciousness should be transported emergently. Once concurrent catastrophic injuries have been excluded, the athlete can be removed from the field of play to continue the assessment process either on the sideline or ideally in a more private location such as the locker room. It is understood that practical limitations such as the number and training of the on-site medical providers and the location and proximity of the athletic contest will influence the feasibility of evaluation methods. Athletes who are acting inappropriately, or vary from their recognized baseline such as running the wrong plays, missing assignments, performing poorly, or identified by teammates should also be evaluated for a possible concussion.

Sideline, Locker-Room Evaluation

The sideline evaluation should be a continuation of the on-field assessment [38]. Less time restrictions would allow for a more in-depth assessment of athlete's function, symptoms, and mechanism of injury. Did the athlete lose consciousness? If yes, for how long? Is there associated antegrade or retrograde amnesia? What was the mechanism of injury? Loss of consciousness, historically considered a hallmark of concussion, actually is a rare finding occurring in approximately 10% of concussive injuries. Amnesia and dizziness have been associated with more severe injury and longer resolution of symptoms.

A complete neurologic assessment should be conducted. Evaluation for confusion, orientation, cranial nerve function, abnormal eye movements and pupillary response, strength of all major muscle groups, sensation of all limbs and trunk, and reflexes should be performed. Any abnormal or asymmetric finding should warrant further evaluation. A cognitive assessment should be performed to evaluate memory, the ability to perform calculations, speed, and concentration. Use of a standardized assessment tool and the availability of preseason baseline assessments allow for more appropriate interpretation of test results. An assessment of motor/postural function should also be performed when immediately possible. Single leg stance, stork test, and testing of tandem gait may be helpful in an immediate setting until a more formalized balance assessment may be performed. Comparison to the athletes' baseline data is ideal. Finally, a standardized symptom checklist should be performed post-injury and repeated serially as appropriate. Comparisons can be made with the preseason assessment to improve interpretability. Commonly reported symptoms are often reported in the somatic, cognitive, and emotional domains. Changes in athlete's behavior and personality post-injury are not uncommon and should be recognized by the medical team. Knowing the individual athlete can provide some insight into what may otherwise be subtle changes. Because concussions are dynamic injuries that evolve over time, serial assessments must be performed to monitor for deterioration or changes in status. The frequency of these evaluations will depend on the severity of injury, comfort level of the medical providers, athletes, and supervising adults. Any athletes with worsening symptoms, focal neurologic findings, or neurological deterioration may require more immediate assessment and intervention including emergent transport.

Emerging Evaluation Tools

Many new technologies are currently being evaluated for their contribution to the diagnosis and management of concussed athletes. The role of these tools is currently undefined. Software for handheld cognitive assessment, the use of biomarker from lumbar puncture and serum tests, various modalities to quantify reaction time, evaluation of the vestibular system, are some of the more common [35]. While currently considered investigational in nature, further research may emerge to justify their routine use to help guide our clinical assessment of the concussed athlete.

CONCUSSION MANAGEMENT AND RESOLUTION

Initial Management

Once an athlete is suspected of suffering a concussion, they should be immediately removed from competition [12]. Currently, many states have either enacted or are considering laws related to concussion identification and management. Many of these laws clarify who has the legal responsibility and authority to remove a suspected injured athlete from competition and who has the authority to return them to competition [39]. In addition, many athletic governing bodies have developed specific policies, protocols, or recommendations that outline an athlete's return to play. The purpose of these statements is to provide as much as possible, a uniform,

safe return to competition for the injured athlete without undue pressures from outside influences. Communication of the injury status of the athlete with the athlete themself, team medical staff, and coaches is crucial [40]. When possible, the athlete should be removed from the sideline for the remainder of the competition. An adult supervisor, ideally someone familiar with the particulars of the situation and concussion management, is recommended to monitor the injured athlete for the initial 24–48 h post-injury for any change in status or worsening of symptoms. Collection of an injured athlete's helmet or other medical equipment at the time of injury and diagnosis will help to ensure that they do not unintentionally return to competition [41]. Serial evaluations should be performed by the medical staff to monitor for changes in symptoms. When appropriate, a final disposition must be rendered as to the individual diagnosis (concussion or suspected concussion) and if the patient is considered safe to return home or travel with adult supervision, or will require more urgent evaluation. Signs and symptoms that would trigger a more immediate evaluation include worsening headache, seizure, focal neurologic signs, lethargy, repeated vomiting, slurred speech, unable to recognize person or places, increasing confusion, behavioral changes, or irritability, weakness or numbness in arms or legs, neck pain, or prolonged loss of consciousness [42].

Management of the acutely concussed athlete should include education of the signs and symptoms of concussion as well as communication with their adult supervisor. The injured athlete should *discontinue all physical activity* and limit extraneous or extracurricular daily activities as much as possible. The term cognitive rest has all been developed to describe similar limitations for activities that require higher brain function. Symptomatic athletes should limit all cellphone, Internet, and video game play. If they are attending school, considerations should be made regarding school attendance and limiting school work [43]. The purpose of these recommendations is to provide the athlete with a period of rest and recovery without provoking or worsening symptoms. Communication of these recommendations to the athlete's teachers, or counselor is important. The athlete should discontinue driving or operation of heavy machinery. They should be instructed to discontinue any use of alcohol and illegal substances. The use of any and all medications should be discussed with the medical provider to avoid masking of symptoms. An appropriate plan for follow-up should be developed and communicated [37,44].

A host of new treatment options are being explored in the management of acute concussion and post-concussion symptoms. Unfortunately, few well-conducted randomized controlled trials have been performed to support their use. Most of these current uses are considered off label. It is unclear as to what role these will play in the future, or which patients will be more optimally managed given their administration. Most of these drugs or supplements are theorized to treat particular symptoms, especially in athletes with more severe difficulties or prolonged symptoms. Some of the more widely used medications include amitriptyline, gabapentin, amantadine, methylphenidate, seizure medications, "triptans," muscle relaxants, anti-inflammatory agents, and SSRIs [45–50]. Various supplements such as fish oil, flax seed oil, DHA, omega-3, and antioxidants have been theorized to improve recovery of lessen the amount of injury. One important point to recognize is that, if medication is being used to manage an athlete's symptoms, it should be noted that they should not be considered asymptomatic. The risk of returning an athlete to play while taking medication to suppress symptoms is unknown. Other emerging treatment modalities have been implemented in an effort to facilitate recovery from a concussion. Heart rate–based rehabilitation programs are being implemented to stress an athlete at subthreshold levels. Vestibular rehabilitation programs can be utilized to help manage dizziness and postural difficulties. Manual techniques can help manage headache associated with cervical strain often occurring concurrently with a concussion. The exact role and timing for implementation of these therapies is still being investigated; however, they provide alternative measures to help treat more complicated injuries.

The decision on whether or not to image an acutely concussed athlete is dependent on several factors: the presentation of the athlete, symptoms, and changes in symptoms, presence or absence of any aforementioned "red flags," the comfort level and experience of the medical provider in managing concussions, and the comfort levels of the athlete themselves, their parent, or supervisor. In general, a CT scan is the imaging modality of choice to evaluate for underlying pathology that may mimic a concussion in an acutely injured athlete due its speed, cost, and availability [12]. While helpful to assess for a competing diagnosis, a negative CT scan does not "rule out" a concussion. Concussive injuries are not considered to cause visible structural defects on a standard CT image. MRI may also be considered to evaluate patients with more long-standing, severe, or worsening symptoms. Similar to CT, standard MRI sequences generally do not reveal abnormal structural changes induced by a concussive injury; however, newer sequencing techniques and enhanced resolution may provide additional insight than current standard imaging protocols [12]. Many other more advanced imaging techniques are being developed but are not widely available or considered the standard of care at this point in time (fMRI, MRI spect) [51–53].

New Management Technologies

Innovative tools are also being explored for the routine management of concussion. While these tools are currently considered investigational at this time due to their lack of standardization, cost, and availability, further research may justify their use in management of future concussed athletes. Some of the more promising technologies include ocular motor/vestibular testing, genetic studies such as Apo E4 and other genes, and biostatistical techniques to identify at-risk individuals [30,54,55]. Research continues in the area of protective equipment such as improved materials for helmets

and head gear, improved helmet fit, and design [56–58]. The use of helmet or mouthpiece-based accelerometers may help medical providers identify individuals at high risk of injury [59]. Additional assessment tools of reaction time and neurologic function such as EEG, MEG, ERP, and EP may help in both the diagnosis and management of injuries. Biochemical techniques such as use of CSF markers such as AB, APP, Tau, NF-L, GFAP, S100B, CK-BB, IL-1B, and IL-6 are being explored for their diagnostic and predictive value [60–64].

Similarly, serum markers such as AB, amyloid A, CRP, retinol-binding protein 4, neuron-specific enolase (NSE), myelin basic protein (MBP), Tau, CK-BB, GFAP, IL-1B, IL-6, and S-100B may contribute to future concussion management. While these technologies are promising, the use of these additional evaluation methods is still exploratory at this point and considered in the context of well-designed research trials only.

RETURN TO PLAY

One of the most difficult decisions in all of sports medicine is to decide when a concussed athlete is safe to return to play [65]. There have been more than 40 different return to play guidelines published over the last few decades, none of which were outcomes based. All of these former guidelines have since been abandoned. The current trend in concussion management has called for a more conservative return to play approach than outlined in historical reports. The current best medical consensus opinion was outlined by the Concussion in Sports (CIS) Group and updated in 2008. The CIS is an international panel of experts that has been meeting regularly to review the current medical evidence regarding the management of sports concussion. Their current recommendation acknowledges the need for an individualized assessment of the injured athlete followed by a gradual return to physical activity in a graded nature once symptoms have completely resolved. Before an athlete is returned to play, he/she is required to have a completely normal physical and neurocognitive exam. Athletes can be progressed from one step to the next if they remain symptom-free with a minimum of 24 h recommended between steps. If symptoms recur, the athlete should drop back to the previous step where they were asymptomatic. The progression is noted next [1]:

1. Rest (until asymptomatic)
2. Light exercise (walking, stationary bike)
3. Sport-specific activity (i.e., skating in hockey)
4. Noncontact drills
5. Full-contact drills
6. Game play

The use of supplementary assessments in addition to an athlete's reported symptoms has become more widely implemented. Specifically, the addition of a more formal cognitive assessment and postural testing has been found to complement assessments by symptoms alone. Broglio et al. [66] has reported on the value neurocognitive and postural assessment and that 89%–96% of athletes had abnormal finding on assessments at 24 h after injury. Unfortunately, it is still unclear if the tracking of reported symptoms, neurocognitive performance, postural testing, or a combination of these three domains truly mimic physiologic recovery. Each of these areas has its own limitations. Symptom assessment has been the mainstay of concussion management programs for decades; however, concerns of underreporting and denial of symptoms, or concomitant medical conditions necessitate that more objective measures be utilized in managing these athletes. Symptom recovery has been shown to take longer in children (greater than 1 month) compared with adolescent athletes [67]. Collegiate athletes reported a faster recovery compared to high school athletes with most recovering in 1–2 weeks [68,69]. Cognitive impairment has also been associated with concussive injury [69,70]. These often tend to resolve quickly in most individuals (5–7 days) [69], although resolution may precede or persist after symptom resolution [66]. Neurocognitive assessments have been shown to have their own limitation with "gaming," environmental factors, motivation, and fatigue affecting the results [71,72]. Finally, postural or balance testing is also gaining favor as an assessment tool given that it also may precede or show persistent deficits after symptom resolution [73]. Further investigation as to the ideal use and interpretation of these tools is necessary to optimize patient care [74].

Other Considerations

Several other factors should also be considered in guiding return to play decisions. While many of these are difficult to presently quantify, consideration should be given for a more conservative approach:

1. Age of the athlete—Children have been shown to have biochemical and structural differences that may influence recovery [75,76]. Symptom recovery has been shown to be slower in children versus adolescent athletes, as well as in high school versus collegiate athletes; thus a more conservative return to play may be reasonable [65,67,69,77]. The CIS group recognized these issues and applied their guidelines to children >10 but also noted that younger athletes may require a more conservative approach [15].
2. Concussion history—Athletes with a history of multiple concussions, prolonged symptoms, amnesia, or short interval between injuries may be at risk for repetitive head injury and require a more conservative approach [78].
3. Abnormal brain—Athletes with a previous history of neurologic disease (seizure disorder), learning disability, ADHD, etc., may be at increased risk for concussion [79].
4. Gender—Female athletes have reported more severe symptoms and a more prolonged recovery compared to male counterparts in the same sport [22].

5. Sport—The risk for concussion varies by the nature of sports, position, and possibly protective equipment. High-risk individuals returning to high-risk sports may require a more gradual return.

Same-Day Return to Play

Currently, the same-day return to play of a concussed athlete remains controversial. While common practice at some level of sports, the trend is clearly moving toward a more conservative nature. The National Football League reported that 51% of concussed players in 1990s to early 2000s returned to the same game [80,81]. Recent updates to league policy and new proposed updates regarding concussion no longer allow this practice. The CIS group guidelines from Prague initially did not allow for any same day return to play, but these were softened for adults in their Zurich update [1,31]. Currently, only the NATA guidelines allow for the same day return of an athlete in limited circumstances. Despite these differences, all guidelines agree that no symptomatic athlete at any level should be returned to play.

POTENTIAL CONCUSSION COMPLICATIONS

Post-Concussion Syndrome

Post-concussion syndrome (PCS) is a diagnosis that represents a delay from the expected healing from concussion. Simply put, patients who have concussion symptoms that last longer than we think should have PCS. The problem lies in the moving target that is concussion resolution. We do not know, with certainty, when symptoms should resolve. As noted earlier in the chapter, there are many issues that potentially affect concussions, such as age, gender, and genetics. There is controversy about when the diagnosis of PCS should be made, but there has been a trend toward earlier diagnosis, sometimes as early as 3–4 weeks after initial injury. *The Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, states three or more symptoms of concussion must persist for at least 3 months after injury to make a diagnosis of PCS.

PCS is important to identify, as the symptoms (cognitive, psychological, somatic, psychosocial) may start to dramatically affect the athlete's life. Every aspect of life can be altered, including social, sport, school, and work. The risk of PCS varies with comorbidities and treatment, and the exact incidence is not known, but it has been estimated to occur in 10% of concussion cases [82]. The diagnosis is often missed; a British study demonstrated that only 60% of general practitioners were able to recognize PCS on the basis of symptoms [83].

Radiographic imaging (e.g., CT, MRI, fMRI) is not currently used to make the diagnosis of PCS, as imaging techniques are not yet sensitive enough to demonstrate the injury. However, other cranial abnormalities can be identified or excluded by these techniques. The diagnosis of PCS should include evidence of neuropsychological test performance deficits, in addition to clinical symptoms. Neuropsychologists can assist with academic and work accommodations appropriate for present cognitive deficits and can help follow cognitive progress as the patient progresses.

Treatment of PCS is outside the scope of this chapter; however, realize that treatment can be very complex, with managing multiple symptoms over a long period of time. Managing headache, sleep, and neuropsychological symptoms may involve medication and psychotherapy, in addition to academic, work, physical, social, and other life accommodations.

Second Impact Syndrome

A much rarer, but more catastrophic, condition associated with concussion is second impact syndrome (SIS). SIS can occur when an athlete sustains a second concussive injury before symptoms from the first concussion have resolved. The brain is thought to lose ability to regulate its blood supply, and brain herniation occurs [84]. The second impact may be comparatively minor, but unfortunately, the vast majority of these cases are fatal. Reported cases in the literature almost exclusively involve high school aged athletes.

CONCUSSION PREVENTION

Protective Equipment

Although helmets were initially introduced into sport to prevent catastrophic head injuries, such as epidural hematomas and skull fractures, recent attempt has been made to decrease concussion incidence through helmet technology. It is difficult to separate concussion from all head injuries in many studies, but there are data showing skiers and snowboarders wearing helmets have risk reduction of head injury [85,86], as do bicyclers [57]. Almost all of the concussion-specific research has been done in American football. Some helmet designs have shown decreased force transmission, but definitive decrease in actual injury has not yet been demonstrated [56]. A methodologically flawed study in high school football athletes did show a 31% reduced relative concussion risk with a helmet designed to reduce head and face contact forces [77].

Rugby and soccer headgear have been introduced into their respective sports to decrease concussion risk. The intention is good; if headgear compatible with the game as currently played can reduce concussion, the sport is improved. No randomized controlled trials have been done in soccer. One large non-randomized study of youth soccer athletes [87] demonstrated those not wearing headgear had more concussions than those who did, but symptom self-report was used in this study that defined concussion as the presence of any concussion symptom (e.g., headache, fatigue), posing a real problem with methodology. In rugby, two randomized controlled trials have not found that protective headgear decreased concussion incidence [1,88].

The addition of protective equipment to sports not currently using it (e.g., helmets in women's lacrosse) may decrease concussion risk, but this is only theorized. Continued

injury epidemiology is important to understand where most injuries occur and to direct injury prevention toward those mechanisms.

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65 Scientific Basis for the Use of Modalities in Sports Medicine

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CONTENTS

Cryotherapy 799
Superficial Heat 801
Hydrotherapy 802
Ultrasound 803
Phonophoresis 806
Iontophoresis 806
Electrotherapy 808
Pain Control 809
Strengthening 810
Tissue Healing 812
EMG Biofeedback 812
Laser Therapy 813
Summary 813
References 813

Time away from sports participation for an injured athlete has physical, mental, and financial sequelae. Therapeutic modalities have the ability to impact these iatrogenic effects and improve the healing environment. Thermal and electrotherapeutic interventions do not directly accelerate biologic healing; however, when manipulated, they can maximize the effectiveness of rehabilitative care. This chapter provides the health care professional with an overview of the scientific basis for the use of therapeutic modalities. Superficial application of heat and cold, ultrasound, phonophoresis, iontophoresis, electrotherapy, and the emerging practice of laser application are discussed.

CRYOTHERAPY

Cryotherapy is one of the most commonly used modalities in sports medicine [1]. There is strong evidence for the efficacious use of cryotherapy in the treatment of acute inflammatory conditions and muscle soreness. Decreasing tissue temperature through the use of cryotherapeutic interventions can assist with decreasing pain [2,3], spasm [4], and swelling [4,5], caused by acute injury. Overall, cryotherapy decreases tissue temperature by removing heat "conduction" from the surrounding tissues. Conduction occurs at the interface between the cold modality and the skin as well as between superficial and deeper tissue layers. In the animal model, the therapeutic goal for reducing cellular metabolism without cellular damage is cooling tissue to 10°C–15°C; this may be considered in limb salvage, but the optimal temperature goal in cold use for rehabilitation in humans is unknown [6]. In general, human skin surface temperatures are between 30°C and 35°C before treatment, and the cold-induced analgesia begins as 13.6°C [3]. Temperatures during or after treatment should not be reduced below 10°C to preserve cell integrity [6]. Cryotherapy has been shown to decrease nerve conduction velocity and increase pain threshold and tolerance. In one study, nerve conduction velocity was shown to decrease 0.4 m/s for each 1°C decrease in temperature [7]. Diminished nerve conduction velocity is likely responsible for the decrease in pain associated with the use of cryotherapy.

A number of cold therapy application methods exist including ice bag, gel packs/chemical cold packs, cold or ice water immersion, ice massage, and commercial circulating and/or compressive cold devices. The goal in each of these devices is to reduce the tissue temperature, and each offers different advantages to the user. Ice gel and other chemical ice substitutes are reusable, do not melt or drip, and can mold to the target surface area especially at bending joints. These ice substitutes can reach temperatures in the freezer of –5°C to –15°C compared to ice at 0°C, creating a higher risk for tissue damage at the time of application [8]. Ice massage allows for local cooling combined with a therapeutic goal of

tissue friction while commercial circulating units combine the motion of ice chilled immersion with the convenience of a dry, contained apparatus easy to use in the home setting. Compression coupled with ice has the added benefit of increasing contact area and possibly limiting rewarming from surface air [9].

In 2000, Barber compared two cryotherapeutic interventions on 87 patients following anterior cruciate ligament (ACL) reconstruction. The study found continuous-flow cold therapy (commercial circulating unit) to be more beneficial than bagged crushed ice in terms of lowering pain, reducing the use of pain medication, increasing knee flexion, and improving functional ratings [10]. In this study, the patients were instructed to use the cold modality constantly for 3 days and as needed for days 4 through 7. The group using crushed ice was instructed to replace the ice when it melted. One must question the impact of compliance in the use of the crushed ice constantly for 3 days due to the challenges inherent with melting, dripping, and waking from sleep to add ice; a circulating unit avoids these challenges. Although compliance was not measured in this study, the convenience of commercial circulating units is likely to increase adherence to wearing schedules when long periods of cooling are suggested. In 2007, Kennet et al. compared 20 min application of four commonly used cold modalities (crushed ice, gel pack, frozen peas, and ice water immersion). Crushed ice and ice water immersion were found superior to gel pack and frozen peas at decreasing tissue temperature, 17°C–19.5°C drop compared to 13°C–14.5°C drop. The investigators also cautioned that the low pre-application temperature of both the gel pack and the frozen peas may place the tissue at risk and therefore the skin should be protected and routinely monitored with their use [11].

Compliance in ice therapy is an important factor for effective use. Warren et al. [12] studied skin and intra-articular temperature changes in the knee during and following a 60 min treatment of ice compared to a chilled water cryotherapy device. The authors concurrently recorded pain levels on a visual analog scale (VAS) with the two devices. Ice was more effective at reducing both skin and intra-articular temperatures compared to the cryotherapy device at all time frames measured; skin/intra-articular decreases at 30 min ice (21.4°C/3.3°C) and cryo (14.8°C/2.2°C); 60 min ice (26.2°C/12.8°C) and cryo (16.7°C/7.1°C); 90 min ice (12.3°C/15.2°C) and cryo (8.2°C/9.7°C); and 120 min ice (5.8°C/11.2°C) and cryo (4.4°C/5.7°C). However, while measuring visual analog pain (scale of 0–10 cm), the authors found that the ice group had clinically significant higher pain (0.7 cm and 2.2 cm on VAS) at the 30 and 60 min time frame respectively when compared to the cryotherapy group (2/10 cm). As you can see by the average temperature reductions at different time periods, the intra-articular region benefited from cooling for 60 min compared to 30 min; however, higher associated pain may have implications on compliance. Research should continue to combine time, especially the multiple 10–30 min bout cycles, with pain reports to find the most tolerable yet clinically valuable cryotherapy parameters.

Compression has been proposed to assist with cooling and reducing tissue temperature. Tomchuk et al. compared 30 min of ice bag using an elastic wrap with a commercial wrap (Flex-i-Wrap, Cramer Products Inc, Gardner, KS) to no compression. They found that superficial temperature decreases were greater with compression (elastic and commercial) than without while intramuscular tissue temperature decreases were greater using the elastic compression versus the commercial wrap. Overall, [13] supported the use of elastic wraps for compression with acute injuries. Ice massage is an effective means of providing maximal tissue cooling more quickly than other cryotherapy methods and is most beneficial for a localized treatment area [14]. Ice massage performed for 5 min to a 4 in. × 6 in. area of the posterior thigh was found to decrease superficial tissue temperature by 13.5°C, tissue 1 cm deep by 8.8°C, and tissue 2 cm deep by 4.1°C [15]. A systematic review by MacAuley [18] on the literature available on tissue cooling concluded that many studies lack sufficient information to directly compare all cooling methods to determine the best method of cooling; however, they found that the literature routinely supports that standard ice packs applied directly to the target tissue through a wet towel are effective in achieving an optimal tissue temperature reduction of 10°–15°.

Depth of penetration of tissue cooling has also been studied. Merrick et al. looked at the thermodynamic properties of three methods: ice bag, ice in cloth lining "wet-ice," and frozen gel pack (Flexi-Cold), comparing the tissue temperature changes at three depths (skin surface, superficial adipose layer +1 cm, and superficial adipose layer +2 cm). They concluded that ice-based treatments (ice bag and wet-ice) were more effective at lowering superficial skin temperature and the superficial adipose layer +1 cm depth compared to frozen gel packs (Flexi-Cold). However, at a depth of the superficial adipose layer +2 cm, there was no significant difference between the treatments [16]. The authors conclude that tissue temperature decreases are not commonly seen at a depth of 2 cm below the subcutaneous adipose layer [16,17] and superficial skin temperature changes are not a predictor of deeper intramuscular tissue temperature changes (2 cm below subcutaneous adipose layer; [17]). Future studies must continue to measure temperature changes at multiple depths to provide meaningful information about tissue response to cryotherapy.

Longer time frames may be needed to cool deeper tissues. Since deeper tissue will conduct heat toward the more superficial layers as they cool, deeper layers can continue to become cooler over time [18]. Although evidence regarding the optimal duration of treatment is lacking, considering the average tissue depth, [8] performed a systematic review on time periods from 5 to 85 min of ice application and concluded that the first 10 min after cold application provided the greatest therapeutic effect, and much smaller and slower changes, if any, occurred after that time period. To maximize this effect, the author recommends repetitive application

bouts of 10 min to achieve lowered tissue temperature of both superficial and deeper structures [8]. Human studies looking at the influence of subcutaneous fat suggested that the time frame of cooling when an individual has less than 1 cm of adipose was optimally 10 min; however, if dealing with athletes with greater than 2 cm of adipose, their recommendation was to increase the cooling time to 20–30 min [19]. In combining data, the evidence recommends repetitive 10–30 min bouts for cryotherapy application; the optimal rest or off time between bouts is unknown.

Tissue damage can occur when cold modalities are incorrectly applied or not monitored. For that reason, one needs to consider the precautions and contraindications associated with the use of cold modalities. There are several precautions to using ice including diminished sensation, active infection, near or over eyes, and tissue that is at risk for damage [20]. Contraindications include impaired circulation (active deep vein thrombosis [DVT]), cold hypersensitivity (cold urticaria, Raynaud's disease), over-regenerating nerves, chronic wounds, and anterior neck and carotid sinus damage [20]. A layer of protection should be applied between the cold therapy and the skin with the exception of ice friction massage. Special attention should be paid for gel and chemical packs as their initial pre-application temperature is lower than ice, so skin should be monitored more closely with their use. Circulating cold units provide continued cold to the skin, and although they have a nylon cover holding the fluid, the skin should still be monitored as burns can occur (see Figure 65.1). When compression is added to these devices, it can also create pressure spots of increased cold density, and they should routinely be unwrapped and skin inspected.

Since cold has the ability to impact nerve conduction and cellular metabolism, an athlete should adequately warm up after receiving cryotherapy prior to participation in activity. The impact of cryotherapy on joint position sense is variable, but if altered, this loss of proprioception may place the cooled area or an adjacent area at risk for injury. Joint position sense was found to be altered at the knee following application of ice using a circulating device for 15 min [21] and at the ankle after a 15 min ice immersion treatment [22]. However, [23] found that an ice bag applied for 30 min did not impair shoulder joint position sense in healthy individuals. Muscle strength [24] and performance [25] have also been shown to be diminished after receiving cryotherapy. Clinicians need to take all of these physiological effects into account as precautions when using cryotherapy before an activity as the athlete may be more susceptible to injury during the first 30 min following ice treatment [8].

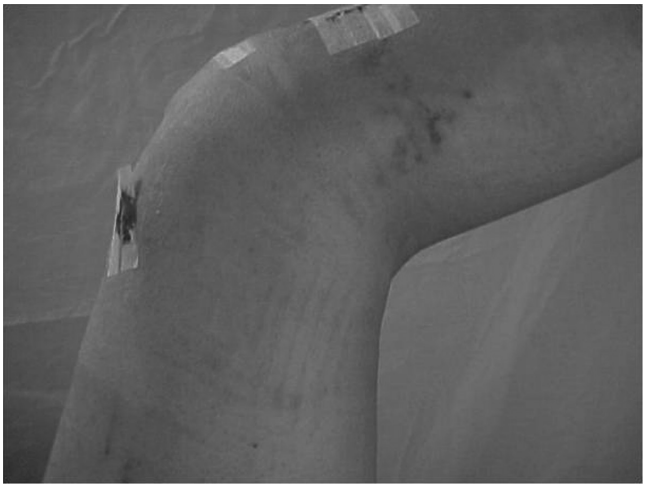


FIGURE 65.1 Example of burns following prolonged use of a commercial circulating cold device.

Ice may not always be readily available to an athlete or their therapist especially during travel activities. A prospective, randomized, double-blinded controlled study by [26] demonstrated the efficacy for use of a cold gel for minor, acute soft tissue injuries. The gel was made with 3.5% menthol and 8% ethanol as the primary cooling agents. The gel was applied four times a day for 14 days following sports-related soft tissue injury. Pain was monitored throughout the experiment and continued for an additional two weeks. Pain decreases were significant when compared to placebo group at 7, 14, and 28 days. Clearly, the most effective cooling agent is one of the cold modalities previously discussed; however, these findings may indicate that a cold gel is better than nothing when ice cannot be accessed.

Cryotherapy is a safe modality with few contraindications. The only danger occurs with long-duration applications at low temperatures. The evidence for effectiveness of cryotherapy in the treatment of acute musculoskeletal injuries is strong in theory and practice and therefore can be an inexpensive, effective modality.

SUPERFICIAL HEAT

Superficial heat, in the form of hot packs (moist or dry), hydrotherapy, infrared heat lamps, and over-the-counter commercial heat wraps, is most frequently used in sports medicine as an adjunct to rehabilitation training and/or conditioning. The therapeutic effects of increased circulation and muscle relaxation occur as a direct result of tissue warming while the corresponding pain relief is largely attributable to the muscle relaxation. In order to achieve a physiological response, tissue temperature must be elevated to 40°C–45°C [27–30]. Heating prior to activity or after activity or both are common in the sports medicine community.

The evidence is largely theoretical, but clinically, superficial heat is often used before stretching superficial muscles. Because heating increases blood flow, the increased tissue temperature rapidly dissipates after removal of the heat source. To maximize tissue extensibility, performing the stretch either concurrently with superficial heat or immediately following removal of the heat would minimize heat loss and theoretically increase the effectiveness of the stretch. However, recent studies suggest that the muscle flexibility changes seen with the combination of superficial heat and stretching did not outperform stretching alone [31,32].

Knight et al. [33] evaluated the combination of different types of heating coupled with a stretching program of ankle dorsiflexion (runner's stretch) performed three times weekly for 6 weeks on ankle dorsiflexion range of motion. The greatest gains in ankle dorsiflexion were seen in the group with 7 min of deep heat modality (ultrasound) prior to stretching compared to control with no stretching, static stretching only, active heel raises prior to static stretching, or superficial moist heat prior to static stretching. All groups outperformed controls at 2 and 4 weeks; however, the deep heat group outperformed the other experimental groups only at 2 weeks; neither deep nor superficial heat outperformed stretching alone after the 2 week time period. In general, superficial heating may feel better, but it does not appear to yield greater increases in tissue length, and the added benefit of deep heat may be short-lived.

The medium through which heat flows can also influence the tissue response. Petrofsky et al. studied the impact of 15 min of infrared heat lamp applied with either a wet towel (moist heat) or a dry towel (dry heat). He concluded that moist heat increased blood flow by 386% and skin moisture by 44% while dry heat increased blood flow by 282% with no corresponding increase in skin moisture [34]. Moisture present during the transfer of heat is a more effective medium than air. Dry heat must contend with air contact between the skin and the heating element slowing the rate of heat transfer [35]. Since the heat transfer is slowed, dry heat can be safely applied over a longer period of time.

The time needed to transfer heat can be influenced by body fat as it functions as an insulator preventing heat penetration. Petrofsky et al. measured the skin temperature and the temperature 25 mm below the skin surface under three conditions: warm whirlpool (40°C), moist hot packs with eight layers of towel (73°C), and dry heat with a chemical dry pack (42°C) [36]. He followed the treatment times most commonly used, 15 min for both the moist hot pack and whirlpool conditions and 6 h for the chemical heat pack (commercially available in drugstores to be worn throughout the day). Petrofsky et al. determined that body fat did not influence penetration depths of heat with the dry heat modality applied for 6 h. The thin and overweight subjects showed significant superficial heating increase (6°) by 30 min and the heating remained relatively stable for the 5–6 h; a lesser increase in deep muscle heating peaked at 2 h (2°) and continued until hour 6. The moist heat modalities applied for a shorter period of time (15 min) had rapid superficial changes of 6° within 5 min; however, the deep muscle was less responsive (1°) and all responses were diminished in the overweight group [34]. The authors concluded that a slower dry heating modality may be most effective in those overweight patients with higher adipose. The clinical goal of heating may also be beneficial over a longer period of time, for example, throughout a golf outing, and the use of these commercial self-stick heat packs can be considered when prolonged effectiveness and depth of penetration are important.

In a 3 year claims review, hot pack burns were identified as the second leading cause of malpractice claims in physical therapy behind traumatic fractures [37]. Fyfe [38] investigated the relationship among subject's first perception of warmth, skin temperature, and skin color following application of moist hot packs with eight layers of toweling (standard amount of toweling to protect the skin) to the lumbar spine. Warmth was first perceived by 99% of the individuals within 1 min of application and maximal heating occurred within 9 min of their first perception of warmth. The subject's skin temperature was recorded, the therapist was also asked to clarify the color of the skin (unchanged, slightly pink, pink, and very pink/red), and the subject was asked to report their sensation (slightly warm, definitely warm, very warm, hot). Interestingly, in those patients whose skin color was recorded as very pink/red, 7% rated the sensation as slightly warm, 28% as definitely warm, and only 30% felt the skin was hot. This lack of correlation between perception and the clinical indication of skin color means that asking a patient how they feel about the temperature is insufficient to ensure protection. The therapist should both visually inspect and verbally question a patient to ensure they are protected during the first 10 min of the treatment [38]. Reports of discomfort and visual color changes of an extreme nature warrant use of more toweling at a minimum or cessation of the modality.

Lying supine on hot packs is discouraged because the weight of the body on the hot pack can cause greater transfer of heat in prominent areas especially in areas where the pressure restricts blood flow and higher risk of burns exists. Additionally, special care should be taken when heat is applied over bony prominences even in non-weight-bearing positions. Less dense tissue can heat more quickly, and if pressure impedes blood flow, the heat dissipation can be retarded leading to higher burn risk. If sensation or circulation is impaired, gentle heating should be used and the skin should be monitored for signs of distress. Superficial heat should not be used over areas of acute inflammation, active infection or hemorrhage, or known malignancy. In the case of vascular insufficiency or absence of sensation, heat is not a viable treatment option. Use of heat should be avoided if the individual cannot communicate effectively to convey possible distress. Lastly, heat should not be used in conjunction with application of topical liniments or heat rubs as there could be an accumulation of heat that yields an adverse reaction. If liniments have been applied, the skin should be thoroughly washed prior to using any form of heat. Superficial heat can be used to increase temperature, increase circulation, and decrease muscle spasm.

HYDROTHERAPY

Hydrotherapy, including cold water immersion (CWI), hot water immersion (HWI), and contrast water therapy (CWT), is used to directly treat athletic injuries or as a form of recovery from athletic participation. Typically,

the water temperature for HWI is between 39°C and 41°C, and CWI is 13°C–16°C. The physiological effects of these applications are similar to those discussed in superficial heat and cold application with water serving as the medium. When agitation and movement in the water occur, the layer of insulation around the body continually erodes and the rate of temperature transfer is accelerated utilizing convection [39].

CWT, repetitive application of heat and cold in an alternating fashion, has been widely used in the treatment of athletic injuries and more recently attempting to contribute to recovery after rigorous exercise. Two systematic reviews of CWT by Stanton et al. [40] and Hing et al. [41] demonstrate that despite anecdotal evidence that CWT is beneficial, there is very little scientific evidence to support or refute its clinical value mainly due to the poor methodology of published articles on the topic. Additionally, it has been theorized that CWT produces a "pumping action" as the alternating between hot and cold creates vasodilation and vasoconstriction, respectively. Several have questioned the legitimacy of this theory, since intramuscular temperature changes were not significantly improved with the use of contrast therapy [41] and the lymphatic system is not capable of contracting to contribute to the removal of edema through this "pumping action."

Great variation in the literature exists regarding the parameters used in CWT only adding to the challenges in determining its efficacy. The 10–15 min treatments of 3:1 or 4:1 ratio (minutes in hot water compared to time in cold water) were the two most commonly utilized protocols in the literature, yet the ratio range was 1–10:1–5 and the total duration was 6–31 min [41]. Stanton et al. [99] found that the range of water temperature was 41°C–45°C for hot and 8°C–16°C for cold while [41] found the range to be more narrow for the hot water (38°C–40°C) and similar for the cold water (10°C–15°C). If the clinical goal is to cool or heat, contrast bath before the intended modality has no additive benefit and its role in assisting with swelling is unsupported.

Several recent studies have attempted to evaluate functional recovery to activity. Ingram et al. [42] found 2 min × 5 min of CWI (10°C) was superior to both CWT consisting of three alternating episodes of 2 min cold (10°C) and warm/hot (40°C) when assessing complaints of muscle soreness 24 h after exercise. Additionally, CWI demonstrated improved return to baseline strength when looking at leg extension and flexion. Vaile et al. [43] investigated four conditions (and control) for endurance cyclists randomly assigned following five consecutive days of high-intensity exercise. CWI (15°C for 14 min) and CWT (seven cycles of 1:1 cold at 15°C and warm at 38°C) were found to assist recovery as a result of seeing improvements with time trial performance and sprint performance when compared to decreases in performance noticed following HWI (38°C for 14 min) and passive (14 min sitting with minimal movement) interventions.

Anaerobic performance measured by maximal isometric voluntary contraction and maximal 30 s rowing test was found to have slightly improved recovery following both cold modalities of CWI and CWT [44]. CWI has been used by athletes with multiple competitive bouts in a day as a means to decrease delayed-onset muscle soreness (DOMS) or exercise-induced fatigue [45]. There is evidence to suggest that both cold modalities improve postexercise swelling, dynamic jump performance, and isometric force compared to no treatment at all. It is unclear if these outperform other forms of cold application; however, in general, cold treatment after exercise appears to have some potentially beneficial effects when available [42].

Full body water immersion techniques, "ice bath," have been used in an effort to accelerate the recovery period following successive bouts of strenuous exercise (e.g., tournaments when athletes have to compete multiple times in a short time frame) and are becoming a more popular trend. In a systematic review by Bleakley and Davison [46], cardiovascular, respiratory, temperature, metabolism, and biomechanical responses to short bouts of CWI (<15°C) were reviewed. Although physiological changes were seen in heart rate, blood pressure, respiratory volume, metabolism, and cerebral blood flow and biochemical changes in peripheral catecholamine, oxidative stress, and free radical formation, the studies were all performed on healthy individuals leaving the generalizability to recovery to athletic activity unanswered.

Hydrotherapy provides an environment for the entire limb to be immersed in water, increasing surface area coverage. Exercises can be performed simultaneously. The main disadvantage of whirlpools is that the limb is dependent. When swelling is a concern, whirlpool may not be an optimal therapeutic option. The decision to warming or cooling a limb is dependent on the intended therapeutic goal, and hydrotherapy can be considered as an application of these thermal agents. The new trend of whole-body ice immersion or "ice bath" has little scientific evidence to support or refute its usefulness while potential dangers exist. More high-quality efficacy and safety evidence on this intervention is needed.

ULTRASOUND

Ultrasound is the propagation of sound waves through soft tissue causing vibration of molecules and subsequent production of heat. The ultrasound sound head contains a piezoelectric crystal that creates the wave and is responsible for transmitting energy to the target tissue. The tissue density dictates the dissemination of ultrasound waves from the piezoelectric crystal to the targeted tissue. Dense tissue predominantly composed of protein absorbs ultrasound energy most effectively (i.e., tendon, cartilage, and bone) [47].

Ultrasound frequency, intensity, and mode can be altered to reach a variety of tissue depths for the desired

therapeutic effect. Ultrasound waves travel in a sinusoidal oscillatory pattern. The frequency is defined as the number of oscillations per second and dictates the depths of structures targeted within a treatment session [48]. Frequency is inversely proportional to the depth of penetration. Therefore, administration of 1.0 MHz ultrasound targets deeper tissues (up to 5 cm deep) such as the quadriceps or gastrocnemius muscle bellies, whereas 3.0 MHz ultrasound targets more superficial structures (1–2 cm deep) such as the patellar tendon [49]. If 1.0 MHz is used to heat superficial structures such as patellar, Achilles, or peroneal tendons, the underlying bone will absorb the ultrasound waves, creating discomfort due to overheating of the periosteum. At 3.0 MHz, the depth of ultrasound penetration is shallower, more energy is absorbed in the superficial soft tissue structures, and less energy is absorbed by bone, thus decreasing the risk of discomfort during ultrasound administration [50,51]. Clinically, if your targeted tissue is <2 cm deep, 3.0 MHz is the most appropriate frequency to utilize, while 1.0 MHz should be used if the targeted tissue is 2–5 cm deep.

Intensity refers to the strength (watts) of the ultrasound wave produced by the transducer with respect to the size (cm^2) of the transducer measured in watts per square centimeter (W/cm^2). As the ultrasound intensity increases, the rate of tissue temperature rises [49]. Tissue temperature increases between 1°C and 4°C have been shown to produce changes in soft tissue. Mild heating (1°C temperature increase) accelerates metabolic rate of tissue. Moderate heating (2°C–3°C temperature increase) reduces muscle spasm, pain, and chronic inflammation and increases blood flow. Vigorous heating (4°C temperature increase) alters the extensibility of collagen fibers allowing a clinician to stretch soft tissue [52]. Table 65.1 reflects the degree of tissue temperature increase expected at various intensities and treatment durations [47,53].

TABLE 65.1
Tissue Temperature Changes Related to Ultrasound Intensity and Time

Tissue Temperature Change at 1 MHz

	Time (min)			
Intensity (W/cm^2)	2.5	5.0	7.5	10
0.5	<0.5°	<0.5°	<0.5°	0.5°
1.0	<0.5°	1.0°	1.25°	1.75°
1.5	1.0°	1.75°	2.5°	3.5°
2.0	1.25°	2.25°	3.25°	4.0°

Tissue Temperature Change at 3 MHz

	Time (min)			
Intensity (W/cm^2)	2.5	5.0	7.5	10
0.5	0.75°	1.5°	2.0°	3.0°
1.0	2.5°	3.5°	5.0°	5.75°
1.5	2.75°	5.0°	***	***
2.0	4.0°	***	***	***

***Treatment was terminated due to subject discomfort.

Continuous-mode ultrasound is administered with an uninterrupted flow of energy whereas pulsed-mode ultrasound refers to the administration of ultrasound with periodic breaks in energy flow. Pulsed-mode ultrasound is defined by a duty cycle that describes the duration of energy flow during a single pulse period. For example, in a 20% duty cycle, the ultrasound is active 20% of the time and inactive 80% of the time. A 100% duty cycle is considered continuous mode. When pulsed-mode ultrasound is utilized, the amount of energy transmitted to the targeted tissue is described as the spatial average temporal intensity (I_{SATA}), which accounts for the peak intensity (I_{SATP}) chosen as well as the duty cycle. The following equation demonstrates how to calculate spatial average temporal intensity [47,53]:

$$I_{SATA} = I_{SATP} \times \text{Duty cycle}$$

Both pulsed and continuous modes have been shown to produce thermal effects in soft tissue. Gallo et al. [54] researched the thermal heating capabilities of pulsed versus continuous ultrasound when controlling for spatial temporal average intensities. The two conditions included continuous mode, 3 MHz, 0.5 W/cm^2 for 10 min, and pulsed mode, 3 MHz, 1.0 W/cm^2, 50% duty cycle for 10 min. The results of the study revealed no statistically significant difference in the rate or extent of tissue temperature increase. Under both conditions, Gallo discovered approximately 2.8°C temperature change in the gastrocnemius muscle. Therefore, in a clinical setting, either pulsed- or continuous-mode ultrasound can be utilized to effectively increase tissue temperature while accommodating to the comfort of the patient.

The ability for ultrasound to heat the underlying tissue is well established in the literature. Some clinicians believe that pairing ultrasound with other modalities such as superficial heat or cooling enhances the effectiveness of ultrasound. Draper et al. [55] investigated the deep heating ability of continuous ultrasound on skin at room temperature compared to precooled tissue. The use of a cold modality was thought to widen the temperature gradient before administering ultrasound, thus accelerating the rate of tissue temperature rise. Tissue temperature was taken at a depth of 5 cm, and ultrasound was administered for 10 min at 1 MHz frequency and 1.5 W/cm^2 intensity. The results demonstrated a 4°C temperature increase from baseline in the room temperature skin group and a 1.8°C temperature increase from baseline in the precooled tissue group. Draper concluded that the use of a cold modality prior to administering ultrasound did not enhance the thermal effects of ultrasound, and individuals receiving ultrasound alone demonstrated tissue temperature increase twice that of the experimental group. These findings suggest that application of ice prior to administering ultrasound decreases the efficacy of ultrasound when the clinician intends to heat subcutaneous structures. Conversely,

Draper et al. [56] also investigated the ability of moist heat to assist the thermal effects of ultrasound on target tissue. Participants were randomized to receive a 15 min moist hot pack treatment or a 15 min room temperature pack treatment prior to 10 min of 1.0 MHz continuous ultrasound at 1.5 W/cm^2 intensity. The moist hot pack had an additive thermal effect on soft tissue by targeting superficial structures (1 cm deep), while the 1 MHz ultrasound heated deeper soft tissue structures (3 cm deep). Based on the results of these studies, when ultrasound is paired with a second modality, moist heat is preferential over cold due to its additive thermal effect on soft tissue.

Ultrasound application requires the use of a coupling agent because ultrasound waves do not effectively travel through air. Coupling agents provide a medium for ultrasound waves to travel from the transducer through the skin. On primarily flat even surfaces such as the quadriceps, a water-based gel will provide adequate direct contact for the ultrasound waves to penetrate the skin [57,58]. Indirect contact coupling agents such as underwater or gel pads are warranted for use over uneven surfaces. For example, when treating the peroneal tendons, bony landmarks such as the lateral malleolus will prevent uniform contact between the ultrasound head and the skin. Draper et al. [59] found that use of water as an indirect coupling agent greatly reduced the ability to heat soft tissue, suggesting that indirect coupling methods required a greater treatment intensity to achieve the same thermal effects as direct method. However, Merrick et al. [60] explored the efficacy of gel pads and water-based ultrasound gel in heating underlying soft tissue and demonstrated similar heating capabilities of each method when ultrasound parameters were controlled. The research design focused only on the deep heating capacities of two different mediums used with continuous mode at a frequency of 1 MHz; therefore, the results of this study cannot be generalized to pulsed-mode or superficial heating at 3 MHz, and the clinician should always adjust treatment parameters in response to the patient's comfort level.

The effective radiating area (ERA) refers to the size of the ultrasound head used to administer the modality. The treatment area should be limited to 2× the ERA to allow for adequate thermal effects to occur [47]. Therefore, if the area of your ultrasound head measures 5 cm^2, the treatment area should not exceed 10 cm^2. When considering this concept, clinicians should be aware of the transducer size relative to the treatment area. A 5 cm^2 ultrasound head can treat a 10 cm^2 area of the low back or quadriceps; however, treating areas larger than this limit would be ineffective. The area needs to be limited to treatable sizes and smaller areas should be treated with small ultrasound heads.

When ultrasound is administered, it is important to recognize and understand the beam nonuniformity ratio (BNR) of the piezoelectric crystal, which produces areas of increased intensity from the ultrasound head. These areas produce "hot spots" and result in patient discomfort. The spatial peak intensity (I_{SP}) represents the greatest power of the ultrasound beam produced by the piezoelectric crystal. The spatial average intensity (I_{SA}) represents the average power of the ultrasound beam within the ERA. BNR can be calculated by dividing the spatial peak intensity by the spatial average intensity:

$$\text{BNR} = \frac{I_{SP}}{I_{SA}}$$

If an ultrasound head has a spatial peak intensity of 12 W/cm^2 and a spatial average intensity of 2 W/cm^2, the BNR is 6:1. A more uniform ultrasound beam is reflected in a smaller BNR. Ultrasound units with a BNR <6:1 are acceptable for therapeutic use. Despite the BNR, the variable energy produced by the piezoelectric crystal within the transducer creates a nonuniform delivery of energy; therefore, it is strongly recommended that the ultrasound head move constantly during application to avoid localized tissue damage and discomfort due to overheating [61].

In multiple research studies, the speed of ultrasound head movement has been controlled to within 2–4 cm/s to standardize the influence of speed on the thermal effects of ultrasound. However, Weaver et al. [62] assessed the difference in heating capacities when ultrasound was applied at 2–3, 4–5, and 7–8 cm/s and found no statistically significant difference in the tissue temperature increase among the three groups when intensity, frequency, and the treatment area were controlled. Weaver noted that therapists had a tendency to increase the treatment area when the ultrasound head is moved more quickly. This behavior disperses the thermal benefits of ultrasound across a larger surface area, thus reducing the degree of tissue temperature rise. This theory helps provide rationale supporting the previous literature stating suboptimal heating effects when the ultrasound head is moved at a faster speed. In a clinical setting, the speed of ultrasound head movement is not the most important treatment factor. The treatment area should be limited to 2× the ERA and the movement of the ultrasound head should be in overlapping circular or longitudinal movements [47].

The data supporting precautions and contraindications to ultrasound are not strong at this time. Therefore, it can be difficult to differentiate which conditions allow a clinician to proceed with caution or warrant discontinuation of the modality. Use of ultrasound over cardiac pacemaker is an absolute contraindication due to the ability of the acoustic power to alter the electrical activity of the cardiac device. Ultrasound also has the potential to disrupt cardiac activity and cause arrhythmias when used directly over the thoracic cavity. Ultrasound use for obstetric purposes has a significantly lower power; therefore, use of therapeutic ultrasound over the abdomen of a pregnant woman is not recommended due to potential risk. Avoid use of therapeutic ultrasound over reproductive organs due to the risk of excessive heating, which may lead to infertility. Although research has failed to provide strong evidence to support increased cell proliferation with therapeutic

ultrasound, use of ultrasound over malignant tumors, myositis ossificans, and heterotopic ossificans is generally not recommended. Due to the risk of increased bone formation, ultrasound may accelerate the growth of pathologic bony lesions. Proliferation of malignant cancer cells may allow for greater tumor growth or metastasis. Use of ultrasound over epiphyseal growth plates is not recommended; however, ultrasound is likely to create periosteal pain due to absorption of the ultrasound waves before stimulation of bone growth can occur. It is generally recommended to avoid therapeutic ultrasound over immature growth plates. Vibrations associated with ultrasound waves could dislodge blood clots; therefore, use of ultrasound over known regions of DVT is contraindicated. It is not recommended to use ultrasound over areas of active bleeding, infection, or acute injury because increased blood flow is the body's natural response to increased tissue temperature. Use of ultrasound will likely worsen these conditions [63].

Therapeutic ultrasound is primarily utilized as a deep heating modality in the sports medicine setting and is well supported in the literature for its thermal effects in soft tissue up to 5 cm deep. However, research fails to confirm nonthermal ultrasound effects such as pain reduction and facilitation of healing in musculoskeletal conditions. Shanks et al. [64] performed a literature review assessing the effectiveness of therapeutic ultrasound on lower extremity injuries such as heel pain, Achilles tendon pain, ankle sprains, and knee injuries. Six placebo-controlled studies showed no statistically significant benefit between sham and therapeutic ultrasound and failed to demonstrate strong evidence to support the use of ultrasound for musculoskeletal injuries. A recent Cochrane review analyzed the efficacy of ultrasound for the treatment of acute ankle sprains [65]. Five placebo-controlled trials met the inclusion criteria and were critiqued for their ability to improve pain, range of motion, swelling, and functional disability, and there was little evidence to support the use of ultrasound on acute ankle sprains. The limited information available on optimal treatment parameters warrants the need for more randomized placebo-controlled trials.

In general, ultrasound is effective as a superficial and deep heater. If the specifics of parameters are observed, both pulsed and continuous ultrasound can produce thermal effects. The ultrasound head should be moved in circular or longitudinal motions to avoid burns due to the BNR, and the nonthermal effects of pulsed ultrasound are not supported as a treatment guideline at this time.

PHONOPHORESIS

The properties of ultrasound can be manipulated to deliver medication transcutaneously, and this procedure is called phonophoresis. Ultrasound uses sound energy to theoretically alter the permeability of the skin to allow for medication placed on the skin surface to be absorbed into the underlying soft tissue. The goal of phonophoresis is to deliver medication through the skin directly to injured tissue to assist an athlete with recovery. Anti-inflammatory medication such as dexamethasone and hydrocortisone and analgesic medication such as lidocaine are commonly used in the form of a cream, gel, or ointment with phonophoresis. The use of phonophoresis to administer medication theoretically allows for a more direct route of transmission by placing the medication at the targeted site avoiding depletion of the medication due to digestion with oral ingestion. Oral medication enters the digestive tract and liver, which metabolize the medication and reduce the amount that enters the system and target tissue [66].

Cagnie et al. [67] compared the body's ability to absorb ketoprofen, a medication used to decrease pain and inflammation combined with a gel coupling agent, creating Fastum gel. The researchers observed patients with knee pain who were scheduled to undergo arthroscopic knee surgery under three treatment conditions. Group A was given ketoprofen gel with 1 MHz continuous ultrasound at an intensity of 1.5 W/cm^2, Group B was given ketoprofen gel with 100 Hz pulsed ultrasound (20% duty cycle), and Group C received ketoprofen gel with sham ultrasound. Adipose and synovial tissue samples were taken 47–77 min following phonophoresis to assess local penetration of ketoprofen, and blood samples were taken 2 h after application to assess systemic penetration of ketoprofen. Significantly greater amounts of medication were detected in synovial tissue in the groups using ultrasound, A and B, compared to sham ultrasound, group C. Minimal ketoprofen was detected in plasma or adipose tissue under all three conditions. The study demonstrated that phonophoresis was able to administer the medication locally without a systemic response; however, no therapeutic benefit of the treatment (change in pain or effusion) was observed in the groups. A list of commonly used medications complied by Ciccone is found in Table 65.2. More research is needed to further determine the usefulness of phonophoresis in a clinical setting.

IONTOPHORESIS

Iontophoresis is an electrotherapeutic modality that delivers medication transcutaneously with the purpose of decreasing pain or inflammation. Direct current produces an electrical field that repels ions and drives medication through the skin to reach the targeted tissue [68]. Ions are charged particles. Anions are negatively charged and cations are positively charged. When administering iontophoresis, the medication must be ionized to allow for electromigration of particles through the skin. The ionized medication is driven through the skin via repulsion of the like-charged particles with direct current [68]. A delivery electrode and a return electrode are used to administer iontophoresis. The medication is applied to the delivery electrode and the return electrode is placed on the skin to complete the circuit. The polarity of the medication dictates whether the delivery electrode is the cathode or anode. The cathode is utilized to deliver negatively charged medication and the anode is utilized to deliver positively charged medication.

TABLE 65.2
Common Medications Used for Iontophoresis and Phonophoresis

Drug	Principal Indication(s)	Treatment Rationale	Iontophoresis	Phonophoresis
Acetic acid	Calcific tendinitis	Acetate is believed to increase solubility of calcium deposits in tendons and other soft tissues	2%–5% aqueous solution from negative pole	—
Calcium chloride	Skeletal muscle spasms	Calcium stabilizes excitable membranes; appears to decrease the excitability of peripheral nerves and skeletal muscle	2% aqueous solution from positive pole	—
Dexamethasone	Inflammation	Synthetic steroidal anti-inflammatory agent (see Chapter 29)	4 mg/mL in aqueous solution from negative pole	0.4% ointment
Hydrocortisone	Inflammation	Anti-inflammatory steroid (see Chapter 29)	0.5% ointment from positive pole	0.5%–1.0% ointment
Iodine	Adhesive capsulitis and other soft tissue adhesions; microbial infections	Iodine is a broad-spectrum antibiotic, hence its use in infections, etc.; the sclerolytic actions of iodine are not fully understood	5%–10% solution or ointment from negative pole	10% ointment
Lidocaine	Soft tissue pain and inflammation (e.g., bursitis, tenosynovitis)	Local anesthetic effects (see Chapter 12)	4%–5% solution or ointment from positive pole	5% ointment
Magnesium sulfate	Skeletal muscle spasms; myositis	Muscle relaxant effect may be caused by decreased excitability of the skeletal muscle membrane and decreased transmission at the neuromuscular junction	2% aqueous solution or ointment from positive pole	2% ointment
Hyaluronidase	Local edema (subacute and chronic stages)	Hyaluronidase appears to increase permeability in connective tissue by hydrolyzing hyaluronic acid, thus decreasing encapsulation and allowing dispersion of local edema	Reconstitute with 0.9% sodium chloride to provide a 150 mg/mL solution from positive pole	—
Salicylates	Muscle and joint pain in acute and chronic conditions (e.g., overuse injuries, rheumatoid arthritis)	Aspirin-like drugs with analgesic and anti-inflammatory effects (see Chapter 15)	10% trolamine salicylate ointment or 2%–3% sodium salicylate solution from negative pole	10% trolamine salicylate ointment or 3% sodium salicylate ointment
Tolazoline hydrochloride	Indolent cutaneous ulcers	Tolazoline increases local blood flow and tissue healing by inhibiting	2% aqueous solution or ointment from negative pole	—
Zinc oxide	Skin ulcers, other dermatologic disorders	Zinc acts as a general antiseptic; may increase tissue healing	20% ointment from positive pole	20% ointment

The method in which the medication travels through the skin is not clearly understood; however, there are two main proposed theories. Some researchers believe that medication travels through the skin via sweat and sebaceous glands and hair follicles. It is also theorized that electrical current changes the permeability of the skin's surface, allowing for greater transmission of the medication through the skin. Mild skin irritation and small blister-like vesicles are common skin reactions in response to the local alteration of pH due to the chosen medication and these typically resolve within minutes to hours after conclusion of the treatment [53].

Dosage can vary based on amplitude (milliamperes) and duration (minutes) of the treatment and measured in mA · min. Research suggests that the optimal dosage response to iontophoresis ranges from 40 to 80 mA·min [68] and a greater delivery of medication is achieved with increasing treatment durations [69]. The dosage can be calculated by multiplying the intensity (milliamperes) by the treatment duration (minutes):

$$40\ \text{mA} = 1\ \text{mA} \times 40\ \text{min or } 2\ \text{mA} \times 20\ \text{min}$$

$$\text{or} \quad 4\ \text{mA} \times 10\ \text{min}$$

$$80\ \text{mA} = 2\ \text{mA} \times 40\ \text{min} \quad \text{or} \quad 4\ \text{mA} \times 20\ \text{min}$$

Anderson et al. [69] compared the absorptive capabilities of dexamethasone under three treatment conditions each totaling 40 mA·min dosage: 4.0 mA/min for 10 min, 4.0 mA/min for 10 min followed by 400 min of passive absorption of medication (leaving the iontophoresis delivery electrode in contact with the skin without electrical current), and 0.1 mA/min for 400 min. The results of the study revealed deeper penetration

of medication when a prolonged treatment time was utilized. Both 400 min of passive absorption of medication and 0.1 mA/min for 400 min demonstrated the ability to penetrate a small percentage of medication up to 12 mm whereas the medication administered at 4.0 mA/min for 10 min penetrated only 2 mm below the surface of the skin. The results of this study indicate the most important treatment parameter when using iontophoresis in a clinical setting is time. The longer treatment duration allows for deeper penetration of medication into underlying soft tissue. New technology has created iontophoresis patches that do not require wires or an external unit to provide the direct current. The newer patches allow a therapist to apply iontophoresis and allow it to run throughout the day without the patient present in the clinic. This new technology will allow for longer treatment durations and maximize the pharmacological benefit of iontophoresis.

Dexamethasone is one of the most commonly used corticosteroids utilized to decrease inflammation. Neeter et al. [70] researched the effects of dexamethasone on acute Achilles tendon pain. Participants were randomized to receive either four 20 min treatments with 3 mL of dexamethasone or saline. Both groups improved at 1 year follow-up; however, the dexamethasone group demonstrated larger improvements in pain level during and after walking, stair climbing, and physical activity. Nirschl et al. [71] also demonstrated short-term benefits of dexamethasone on acute epicondylitis. Patients received six dexamethasone or sodium chloride treatments 1–3 days apart over the course of 15 days. At 1 month follow-up, each patient completed a questionnaire regarding any change in symptom severity and received a phone call to discuss any adverse events concerning their epicondylitis. Post hoc analysis found that subjects receiving the six designated treatments within a shorter period of time (<10 days) demonstrated greater pain relief. For acute conditions, early and frequent application of anti-inflammatory medication appears to effectively reduce a patient's pain and disability.

Although some researchers have found iontophoresis an efficacious treatment intervention, several other researchers failed to identify strong evidence to support the use of this modality. Gurcay et al. [72] compared the use of iontophoresis with betamethasone, phonophoresis with betamethasone, and night splints in a patient with carpal tunnel syndrome. No treatment proved to be more effective in reducing severity of symptoms or improving function. However, the iontophoresis dosage did not fall within the recommended 40–80 mA min treatment, which may account for the inability to distinguish a superior treatment method in this study. In treatment of plantar fasciitis, Cleland et al. [73] found that soft tissue mobilizations and joint mobilizations were superior to iontophoresis and ultrasound interventions.

Japour et al. [74] researched the effectiveness of acetic acid iontophoresis on the conservative management of heel pain. Patients reporting chronic heel pain were recruited for the study and received iontophoresis with 5% acetic acid solution, at 2–3 mA for 15–20 min, 2–3 times/week for 3 weeks. Prior to initiation of treatment, the patients' average numeric pain rating score (0–10) was 7.5 out of 10. After the course of iontophoresis, the average numeric pain rating score was 1.8, demonstrating a clinically and statistically significant difference in heel pain. First-step pain is a common impairment affecting patients with heel pain. Participants in this study experienced a resolution of first-step pain with 2.8 weeks of acetic acid iontophoresis treatment whereas the other 11 cited studies averaged 7.8 weeks of conservative treatment for similar symptom response. The research design failed to utilize a control group, and success of the intervention was compared to other studies that utilized various methods of conservative treatment (i.e., orthotics, shoe modification, oral medication, injections, rest, physical therapy, etc.), which limits the clinical usefulness of this study.

Iontophoresis appears to be an effective treatment intervention when a therapeutic dosage is administered, and the appropriate medication is chosen for a given musculoskeletal pathology. Dexamethasone is an anti-inflammatory agent. Some clinicians utilize dexamethasone on tendinosis pathologies that no longer possess an inflammatory process. In these instances, if improvements in pain or function are achieved, it is unclear if this was due to medication or potential benefits of electrical stimulation. On the other hand, failure to improve is expected when the medication administered is not appropriate for the given pathology. In general, anti-inflammatory medications should be administered in acute conditions immediately following the acute inflammatory phase in order to allow for initiation of the healing response to occur.

Table 65.2 summarizes commonly used medication for iontophoresis and phonophoresis [75].

There are very few contraindications to iontophoresis. Allergy to the administered drug is a relative contraindication for use of iontophoresis. Discussing the drug allergy with the prescribing physician and pharmacist may allow the patient to receive an alternate medication and still gain benefit from this modality. The electrical current used to deliver the ionized medication can alter the electrical output of pacemakers, bladder stimulators, and phrenic nerve stimulators; therefore, iontophoresis is an absolute contraindication in these circumstances. Electrotherapeutic agents have the potential to cause skin burns; therefore, it is recommended that the patient have intact sensation. However, in the absence of sensation, frequent skin checks can prevent adverse reactions to iontophoresis [66].

ELECTROTHERAPY

Electrical stimulation is frequently used in the rehabilitation of athletic injuries to reduce pain, muscle spasm, and disuse atrophy and promote strengthening and tissue healing. Electrical stimulation appears to have impacts on biological tissue in a myriad of ways depending on the target condition and parameters utilized. This modality is versatile and effective when used in rehabilitation for recovery and return to sport.

PAIN CONTROL

Pain is the most frequent complaint of those seeking medical care. Pain is a complicated phenomenon that includes both a sensory (pain location and intensity) and an affective-motivational component (unpleasantness). Pain assessment will generally take both of these components into consideration, and information collected during the athlete interview may help direct the therapist to the source of the patient's pain complaint. Acute pain is typically seen in the athletic population and is in response to current or impending tissue damage. This information can be protective in nature; for example, if an athlete has suffered a fracture of the fifth metatarsal, running and even walking can be painful. If the pain is removed too early, the athlete may consider returning to activity and risk further injury or delay healing. It is important to be sure that if pain is treated when it is providing a protective function, another protective mechanism must take its place, such as a walking boot, to ensure that the healing structures receive sufficient protection. Chronic pain does not provide the same protective information as acute pain and routinely outlasts tissue healing time frames. This pain is less informative and can inhibit recovery and return to sports participation.

Pain rating scales such as a VAS are generally 10 cm lines numbered 1–10 or 1–100 with anchors such as No Pain to Worst Imaginable Pain or anchors related more to unpleasantness such as Pleasant to Extremely Unpleasant. These scales are very reliable when the athlete places a mark along the line representing their current pain level [76]. Less reliable but commonly used is the verbal rating scale when the athlete reports their level of pain (0–10) on a scale of 11 [77]. These scales can provide data on current levels of pain but may be more useful when changes in pain levels from pre- to post-intervention are measured and calculated. Measuring the change in pain level before and after or during the use of electrical stimulation can give the therapist evidence needed to decide if the treatment should be continued or be modified.

Electrical stimulation for pain control is generally characterized by four levels: subsensory level, sensory level, motor level, and noxious level. All of these types of stimulation are classified as transcutaneous electrical nerve stimulation (TENS) since they utilize surface electrodes applied to the skin. The parameters for each of these types of stimulation are seen in Table 65.3. Microcurrent electrical nerve stimulators have very short pulse durations and current amplitudes. There has been some emerging evidence in the use of this modality in wound healing [78,79]; however, in most studies, microcurrent does not demonstrate a better effect than sham [80,81]. Currently, there is insufficient evidence to support the use of electrical stimulation below sensory threshold for pain management.

Sensory-level stimulation above the sensory level but below the motor threshold is commonly used and studied as a pain control modality. Although sensory stimulation can still occur when muscular contractions are present, they are often unneeded or can interfere with the intended action of the stimulation treatment. Muscular contractions can move a painful joint or create a protective response from the athlete in the presence of acute or significant pain and are often undesirable. Patients are educated to tolerate increases in the amplitude of sensory stimulation until they perceive comfortable paresthesia. This is often described as tingling, buzzing, or even an intense crawling feeling. The pain relief that develops during the use of sensory stimulation is likely due to a block of pain signal transmission in the periphery or central inhibition of pain transmission by large-diameter nerve fibers [82]. The stimulation is most effective when the unit is on and has little lasting effect once the stimulator is turned off [83]. Sensory-level stimulation has been found to be as effective as acetaminophen with codeine in controlling the pain associated with acute traumatic conditions such as sprains, contusions, fractures, and lacerations [84]. Denegar and Perrin [85] found that electrical stimulation significantly reduced the pain associated with induced DOMS compared with sham stimulation and no treatment.

TABLE 65.3
Commonly Used Stimulation Parameters Associated with the Four Clinical Levels of Stimulation for Pain Control

Mode of Stimulation	Amplitude Adjusted to Produce	Phase/Pulse Duration	Frequency (pps, bps)	Duration of Treatment	Duration of Analgesia[a]
Subsensory level	No perception of stimulation	Not specified	<3	Not specified	Not known
Sensory level	Perceptible tingling ("pins and needs")	2–50 μs	50–100	20–60 min	Short none to few minutes
Motor level	Strong visible muscle contraction	>150 μs	2–4	30–45 min	Long hours
Noxious level	Painful sensation	≤1 ms	1–5 or <100	Seconds to few minutes	Long hours

pps, pulse per second; bps: bursts per second.

[a] Both the time to onset of analgesia and the duration of analgesia have not been clearly established in the literature for the majority of commonly encountered pain syndromes that may be managed with TENS interventions.

Electrode placement in sensory stimulation is generally over the painful site or surrounding the painful site. There is no specific pad location most effective for a body region such as the low back or ankle; instead, the clinician should systematically rule in or out locations based on the location of the pain, the size of the area, and most importantly, the response of the patient to the treatment. There is some evidence that placement of pads in areas remote from the pain but related such as trigger points or acupuncture points may also provide relief [86]. Hidderley and Weinel [87] found that pain relief with sensory stimulation applied to acupuncture points outperformed stimulation over unrelated sham acupuncture points.

Electroanalgesia can be produced through sensory-level stimulation. Typically higher frequencies (>100 pulses/s) and pulse durations (>50 μs) are used with close pad placement to create interelectrode analgesia [80,82]. Small electrodes in close proximity will increase the corresponding current density in the area coupled with high-intensity current to create a local analgesic response. This stimulation can be used to calm a superficially irritated structure or reduce discomfort to allow for another procedure to be performed (i.e., joint or scar manipulation). Manal [88] advocate the use of high-intensity electrical stimulation to control pain in noncontractile tissue [89]. The area to be treated must be localized and palpable. Parameters for the stimulation are classic Russian current; 2500 Hz AC current (400 μs pulse duration), 50 bursts/s, 12 s on, 8 s off. See Figure 65.2 for setup. The current is increased to the maximal tolerable level (beyond comfort level). Interelectrode analgesia occurs quickly generally within the first 5 min. The treatment can be stopped at 5 min or be increased to 10–15 min depending on tolerance. The improvement from pretreatment pain levels is generally immediate and long lasting. If no response is seen to an initial treatment, intensity and time can be increased in the next session; if still unsuccessful, the patient may not be responsive to this intervention.

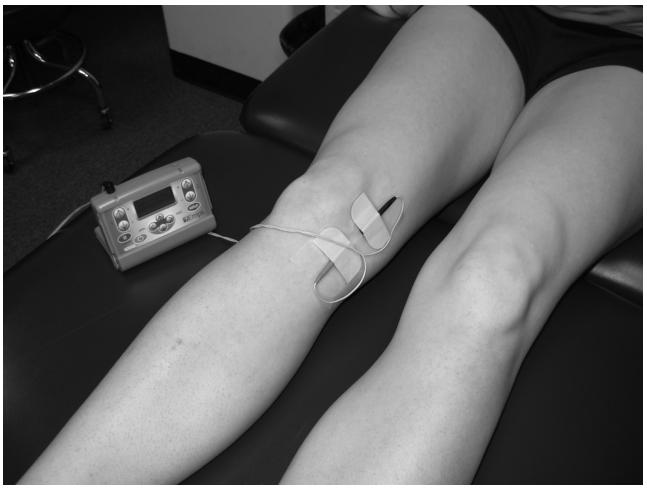


FIGURE 65.2 Electrode setup for administering high-intensity electrical stimulation.

Motor-level stimulation is used most often in chronic pain. The goal in motor stimulation is a visible muscle response. Pulse durations are longer (>150 μs) in order to generate a strong contraction while frequency is shorter (2–4 pps) to create rhythmic contractions. This has also been called strong, low-rate frequency motor TENS or acupuncture-like TENS [90]. Since muscle contraction and "jumping" of the muscle is expected, patients should be prepared for this response and their target tissue or limb should be supported so movement will not aggravate or worsen their condition. Electrodes can be placed over areas of muscular hypersensitivity or often a local point stimulator with a remote dispersive pad can be used. In ultrasound/electrical stimulation combination units, the ultrasound head (with the sound modality turned off) serves as the stimulation applicator. Interelectrode analgesia is slower under these conditions so treatment times are longer and performed more frequently.

Noxious-level stimulation is intended to create a painful stimulus at or remote from the site of pain, causing a rapid hyperstimulation analgesia followed by an endorphin-mediated response [91]. The choice for noxious-level stimulation is generally made after failure of other types of stimulation due to the inherent nature of discomfort; however, in the athletic population it may be utilized more often.

Research on the benefits of TENS for pain is challenging. The Cochrane Report on the value of TENS for chronic pain states that "The published trials do not provide information on the stimulation parameters which are most likely to provide optimum relief, nor do they answer questions about long-term effectiveness" ([92]: p. 2). The variety of parameters and lack of clarity in written papers make reproduction in a clinical setting challenging and provide conflicting results. Studies are emerging to address dose–response for frequency; however, other characteristics lack study [93].

STRENGTHENING

The desire to enhance athletic performance beyond the level attainable through an intensive volitional training program has led to the investigation of electrical stimulation as a strength supplement. Studies of clinical stimulation have examined the most effective electrode size [94], pad placement [95], stimulators [96], and wave form [97] and frequency [98] in hopes of generating the most efficacious electrical stimulation parameters to give athletes a training advantage and competitive edge.

Neuromuscular electrical stimulation (NMES) has been used with success to strengthen the abdominal muscles [108], trunk extensors [100,101], latissimus dorsi [102], and the quadriceps [103–106]. The exact mechanism by which electrical stimulation improves strength of the target muscle is unknown. It has been theorized that electrical stimulation can preferentially recruit large-diameter type 2 fibers (fast-twitch) compared to smaller-diameter type 1 (fatigue-resistant) fibers. Early in the postoperative or injury phase, it may be difficult if not impossible for an athlete to recruit

these fibers due to reduced activity and effort level. It has been theorized that activation of these fibers when they may otherwise be underutilized may help delay the consequences of disuse. Delitto et al. [107] utilized high-intensity electrical stimulation for quadriceps training on an elite weight lifter; biopsies before and after the stimulation protocol demonstrated a reduction in type 1 fibers and an increase in type 2 fibers, suggesting a conversion of fiber type in response to stimulation. High-force contractions can also increase the available actin and myosin in muscle allowing for increased number of cross bridges and correspondingly increased force-generating capability. This may also contribute to increases in force production capabilities seen with electrical stimulation strengthening regimens.

Alon et al. [108] compared NMES alone with NMES plus volitional exercise on the strength of abdominal muscle training three times weekly for 4 weeks. The contractions utilized a symmetrical biphasic waveform with maximal intensity for 5 s on and 5 s off. The on time was lengthened each week from 5–7.5 to 10–12.5 coupled with an increase in repetitions by 20% weekly to increase the stimulation dosage. Electrical stimulation plus volitional exercise produced greater strength gains than electrical stimulation alone.

In the lumbar spine, training programs utilizing low-frequency stimulation and high-frequency stimulation have both demonstrated increases in muscular endurance while [101] demonstrated that subjects receiving electrical stimulation to the lumbar paraspinals developed increased isometric back extensor strength compared to a group performing exercise alone. Electrical stimulation to the lumbar spine has been performed in a quasi-isometric fashion by stabilizing the pelvis to the table in the prone position over pillows. Once the hips are stabilized, the patient attempts an anterior pelvic tilt and the pelvis is considered stable if little to no movement occurs. Small 2 cm × 2 cm electrodes are configured in two channels, each on the right and left sides of the spine at the target spinal levels. Parameters vary among studies—pulse duration: 250–400 μs, on time 15 s, off time 30–50 s, ramp time 0–5 s, total treatment duration 15–30 min. Intensity of the stimulation is increased to maximal tolerable by the patient; however, a visible muscle contraction should be apparent and in some cases a strong contraction creating pelvic movement on the stabilizing belt is expected [109].

Electrical stimulation of the latissimus dorsi muscle of swimmers resulted in isometric, concentric, and eccentric improvements in peak torque coupled with improved pool performance swimming times [102]. Similar parameters as described in lumbar spine have also been utilized to supplement recovery and strengthening of the posterior rotator cuff of the shoulder [110]. Isometric stabilization can be achieved by strapping the arm across the patient's stomach in an elbow flexed position. A more rotational neutral position can be achieved using pillows between the trunk and the arm and anteriorly to support the arm at the side. Electrodes are placed over the muscle belly of the target muscle, most often the infraspinatus or supraspinatus or both, which can be palpated during a resisted isometric contraction.

A recent systematic review of the role of NMES of the quadriceps after anterior cruciate ligament reconstruction reviewed eight randomized controlled clinical trials and concluded that although there was variability in the parameters (see Table 65.4), electrical stimulation coupled with volitional exercise exceeded strength recovery when compared to volitional exercise alone [104]. This conclusion agrees with two prior literature reviews also concluding that electrical stimulation plus exercise outperforms exercise alone in quadriceps recovery after anterior cruciate ligament reconstruction [117,118]. Although variations exist, the majority of the study stabilized the leg in a mechanical device with straps at a flexed knee angle of 60°–90° or in full knee

TABLE 65.4
Summary of Neuromuscular Electrical Stimulation Treatment Parameters

Author	Frequency (Hz)	Pulse Width (μs)	Duty Cycle	Intensity	Treatment Course[a] (Duration)	Treatment Sessions[b]	Follow-Up Time[c]
Sisk [111]	40	300	10 s on, 30 s off	MTL	1st–6th week (6 week)	38	7th week
Delitto [112]	50	400	15 s on, 50 s off	MTL	2nd or 3rd–6th week (3 week)	15	6th week
Wigerstad-Lossing [113]	30	300	6 s on, 10 s off	65–100 mA	1st–6th week (6 week)	18	6th week
Draper [114]	35	N/A	10 s on, 20 s off	MTL <50 mA	1st–6th week (6 week)	105	6th week
Snyder-Mackler [105]	75	400	15 s on, 50 s off	MTL	3rd–6th week (4 week)	12	6th week
Paternostro [115]	30	200	5 s on, 15 s off	MTL	1st–6th week (6 week)	38	6th week
Ross [116]	50	200	15 s on, 35 s off	MTL	1st–6th week (6 week)	26	6th week
Fitzgerald [103]	75	400	10 s on, 50 s off	MTL	3rd–14th week (11 week)	21	12th–16th week

MTL, maximally tolerated level; N/A, not available.

[a] Start and end of treatment in the postoperative weeks.

[b] Estimated number of treatment sessions (treatment a week multiplied by the number of weeks).

[c] Time point after anterior cruciate ligament reconstruction when outcome measures were taken.

extension supported on a table. Electrodes are placed on the quadriceps, one proximally and one distally, and the electrical stimulation parameters found in Table 65.4 provide a summary of acceptable options. Electrical stimulation has been shown to improve strength in healthy muscle as well as muscle impaired by injury or disuse. Whether strength gains result from retraining the nervous system, recruiting more motor units, or changing recruitment pattern or fiber type, the outcome is improved function.

TISSUE HEALING

Electrical stimulation can assist in wound healing through a variety of mechanisms. Fibroblast proliferation and collagen synthesis both contribute to wound healing and respond favorably to electrical stimulation. Bourguignon et al. [119] utilized high-voltage pulsed current (HVPC), a form of interrupted direct current also called "hi-volt," on fibroblast cells at 150 pps at 50–150 V. Under the anode, fibroblasts proliferated and increased DNA production and collagen synthesis. These positive changes have implications in wound healing as well as soft tissue, such as tendon and ligament healing. Scientists are looking at the value of electrical stimulation on healing rates of animal tendon and ligaments to provide preliminary guidelines and efficacy data to be applied later in future human population studies. Daily treatment for 2 weeks with anodal current via implanted electrode in rat Achilles tendon increased tensile strength after surgical tenotomy [120]; similar results were seen in the Achilles tendon and patellar ligament in rabbits [121,122]. The transfer of this success to human tendon and ligament is currently not available.

A 44% increase in vascular perfusion (angiogenesis) is also seen in venous ulcers in response to monophasic pulsed current (pulse duration 140 μs, 64–128 pps, 30 min daily for 38 days) accompanied by an 82% increase in oxygen delivery to the wound site [123]. The use of low-intensity direct current and HVPC both appears to have the ability to inhibit the growth of bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* but do not kill formed bacteria colonies [124]. Most studies suggest that the bacteriostatic effect occurs under the cathode, but recent evidence demonstrates a positive effect under both the cathode and the anode with HVPC at 250 V, 100 pps, 1 h daily for 3 days [125].

Electrostimulation is also used to promote bone healing in fractures with delayed bony healing, including those most likely to present with a nonunion after fracture such as the distal tibia and scaphoid. Three methods of stimulation have been applied to fracture sites: a percutaneous direct current bone stimulator [126] is partially invasive, allows for patient mobility, and can be used with a magnetic fixation device but does require an operation for implantation and is contraindicated in the presence of infection. An implanted direct current stimulator is fully invasive and has similar challenges as the percutaneous stimulator. An external pulsed electromagnetic field stimulator is noninvasive and can be utilized in the presence of infection [126,127]. No bone stimulators are effective in the presence of a synovial pseudoarthrosis where scar tissue and fluid prevent the approximation of the healing ends or a sizable gap of another cause exists. It may be of value to note that bone stimulators are not routinely covered by insurance carriers unless certain requirements are met such as failure of healing for at least 3 months' duration, a fracture gap of 1 cm or less and patient compliance with non-weight bearing, one or more previous failed fusion, or fresh fractures in distal tibia or scaphoid due to the high incidence of nonunion.

The most common adverse reactions from electrical stimulation are skin irritation, rash, and burning sensation [128]. Contraindications include patients with a demand-type pacemaker, placement of electrodes over medical stimulators, monitors or leads; over damaged skin, malignancies, arterial or venous thrombus, or carotid sinus; over phrenic or vagus nerve, eyes or transcranially. Precautions include skin irritation after prolonged use; consultation is suggested for use with pregnant women, and monitoring of vital signs during use is suggested in patients with cardiac disorders. Careful monitoring is recommended when electrical stimulation is used in an area with decreased sensation.

EMG BIOFEEDBACK

Electromyographic (EMG) biofeedback involves the use of a voltmeter to make electromyographic measurements. EMG biofeedback is used to improve motor recruitment to generate stronger voluntary muscular contractions and to inhibit muscular contractions to promote relaxation of overactive muscles. Biofeedback is not as useful for eliciting muscle contraction in patients with spastic neuromuscular disease as it is with those with an intact central nervous system.

EMG biofeedback can be used over any superficial muscle. The purpose is to provide the patient or athlete with immediate feedback regarding performance regardless of whether the desired outcome is to increase or decrease muscle activity. Studies have demonstrated strength gains [129,130], improved motor learning, and neuromuscular reeducation [131,132].

Draper et al. [129] compared exercise with biofeedback and exercise with electrical stimulation to exercise alone for quadriceps strengthening after ACL reconstruction. EMG biofeedback outperformed both groups, electrical stimulation plus exercise and exercise alone. Interestingly, when comparison is made between the contraction intensities used in the electrical stimulation arm of this study, the intensity was below what would be expected to generate large strength gains [133]; therefore, the lack of gains with electrical stimulation appears suspect due to insufficient treatment application. However, regardless of the performance of the electrical stimulation wing of the study, it is still evident that EMG plus exercise was better at improving quadriceps strength than exercise alone. So although electrical stimulation is still the preferred method, when not possible, EMG biofeedback with exercise should be considered an alternative to exercise alone. The added benefit of electrical stimulation and exercise plus biofeedback has not been studied.

Levitt et al. [130] concluded that biofeedback with exercise improved extensor torque and quadriceps muscle recruitment after knee arthroscopy while Krebs [134] found a similar response in patients following meniscectomy. EMG biofeedback can assist the postoperative patient with muscle recovery especially in the quadriceps. A similar improvement in neuromuscular control of muscles has been demonstrated following EMG biofeedback training in the shoulder in patients with recurrent dislocations. Young [135] demonstrated that patients had improved function and reduced occurrence of instability after training.

In some cases, the desired action of the athlete is not a stronger contraction but rather decreased muscular activity to promote relaxation. Rokicki and associates [136] found that biofeedback-assisted relaxation training led to decreased incidence of headaches in patients with tension headaches, and similar results have been demonstrated in the management of temporomandibular joint dysfunction [137]. EMG biofeedback has been used successfully to promote relaxation of the quadriceps during anterior tibial translation testing of the cruciate ligaments [138] and can assist with hamstring relaxation during stretching at end range of knee extension in a stiff knee. Reducing compensations such as decreasing substitution of the upper trapezius muscle during shoulder elevation can provide clinical value. Since voluntary muscle contraction is a necessity during sports and other daily activities, it seems obvious that providing feedback during the performance of the desired movement pattern would lead to improved motor learning by reinforcing the correct movement. The use of EMG biofeedback provides information about the strength of contraction and can help improve control and eliminate over- and underuse as well as muscular substitution.

LASER THERAPY

Laser therapy has been commonplace in the medical office for many years. It is utilized for hair removal, vision correction, and dermatological care. The term "low-level laser" or "cold laser" has been used to describe lasers of the red beam or near-infrared of wavelength of 600 and 1000 nm power from 5 to 500 mW. Surgical lasers are much stronger in the 300 W range. To date, there are no uniform dosages, number of treatments, or treatment length specification for laser. Low-level lasers produce no sensation and do not burn the skin. The mechanism of action is proposed to be a photochemical response of cells to the laser light although the exact action is not known. One leading theory is that cytochrome c in intercellular membrane mitochondria is a photoreceptor causing excitation and bonding with oxygen resulting in cytochrome c oxidase, an ATP building block [139]. There are many possible biochemical factors stimulated by the use of laser that may influence pain and edema in tissue; however, to date their contribution remains theoretical.

Many currently published studies are on laser with lower dosages than are currently recommended and lack sufficient sample size and scientific rigor to make definitive clinical efficacy determinations. The American Pain Society of the American College of Physicians [140] reviewed low-level laser for the treatment of low back pain, and four trials found laser superior to sham up to 1 year after treatment while another high-quality study disagreed [140]. The authors noted that treatment parameters, wavelength, dosage, and dose intensity were variable and the preferred parameters are elusive.

A Cochrane systematic review by Brosseau et al. [141] reexamined the role of laser as a treatment for rheumatoid arthritis (RA). Six studies of 220 aggregate patients were included, but the variability of the application of the modality made comparisons difficult, and the authors lamented that negative trials may have been suppressed and never published, skewing the data pool. Nonetheless, authors concluded that some positive effect may be present; however, sufficient conflict in results suggests that a determination on the added value of low-level laser in the RA population cannot be made. Currently, laser is not reimbursed by commercial insurance and is considered by them to be investigational for musculoskeletal pain. The future will determine if this is an emerging practice or fad.

SUMMARY

We have reviewed the scientific basis and evidence for the use of thermal agents and electrotherapy in rehabilitation of sport injuries. The evidence ranges from theoretical to strong with the best evidence in cryotherapy, continuous ultrasound, iontophoresis, neuromuscular stimulation for strengthening muscle, and EMG biofeedback for muscle activity. Other agents that are commonly used in sports settings such as pulsed ultrasound, phonophoresis, superficial heating for flexibility, ice bath, and laser are supported by only weak evidence at best. An understanding of support in the literature for the use of these therapeutic agent and the parameters most likely to maximize the physiological response should allow for more effective treatments of athletes with musculoskeletal injuries.

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Part XIII

Obstetrics and Gynecology

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66 Preconception Care

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CONTENTS

Introduction 821
Age 822
Gynecologic History 822
Reproductive History 822
Medical History 823
  Hypertension 823
  Diabetes 823
  Seizure Disorder 823
  Mental Health 824
  Phenylketonuria 824
  Thyroid Disease 824
Medications 825
Family History 825
Social History 825
  Smoking 826
  Alcohol 826
  Substance Abuse 826
  Domestic Violence 826
  Environmental Exposures 826
Physical Examination 827
Counseling 827
  Diet and Nutrition 827
  Exercise and Body Weight 828
  Vaccinations 828
Conclusion 828
References 828

INTRODUCTION

Preconception care is a fundamental component of preventative medicine. Preconception care aims to promote the health of women before conception in an attempt to improve health outcomes for both the mother and her offspring and to reduce societal costs.[1]

While it is commonly recognized that access to prenatal care is associated with improved outcomes, there are now increasing data that preconception care is equally important. Today, we have more data and testing options in the field of genetics and have more knowledge on the effects of the environmental exposures and medical illness on fertility, as well as the effects of these on fetal growth and development. Unfortunately, very few women visit a health care provider for the express purpose of optimizing their health prior to pregnancy. In fact, in one study it was noted that only one in six obstetrician gynecologists or family physicians had provided preconception care to a majority of patients for whom they provided prenatal care.[1]

Since the rates of unplanned pregnancy in the United States approach 50%, coupled with the fact that it is increasingly common for women to receive primary health care and routine gynecologic care with a primary care physician, nurse practitioner, physician's assistant, or midwife, it is imperative that all providers who provide preventive care for women of reproductive age assess risk and provide appropriate counseling and management for those women for whom future pregnancy is planned. The 2006 Report of the CDC/Agency for Toxic Substances and Disease Registry (ATSD) Preconception Care Work Group and the Select Panel on Preconception care recommends that preconception care be an essential part of primary and preventive care. Components of preconception care include lifestyle counseling, identification of risks related to pregnancy, patient education regarding these risks, management options and alternatives, as well as the initiation of interventions that may lead to optimal pregnancy outcomes.[1]

AGE

Both extremes of reproductive age are associated with complications in pregnancy. Risk of chromosomal abnormalities increases with advanced maternal age, as does risk of gestational diabetes, preeclampsia, intrauterine growth restriction, and stillbirth. Some of this risk is attributable to increases in the prevalence of chronic medical conditions such as diabetes and chronic hypertension in older women. Older women should be counseled about these risks and, in the case of chromosomal abnormalities, options for screening tests or diagnostic testing such as chorionic villous sampling and amniocentesis should be offered when indicated during the pregnancy.

For adolescent patients, there is also an increase risk of preeclampsia and intrauterine growth restriction and stillbirth. However, in adolescents, the increased risks are likely associated with social factors including lack of prenatal care as well as a contribution from nutritional factors due to both poor diet and knowledge, as well as potential for competition for nutrients between the growing adolescent and her fetus.[2] Some of these can be mitigated with patient education, making resources available to patients, and lifestyle counseling.

While there may be different reasons and underlying causes for women at both ends of the reproductive age spectrum to be at higher risk during pregnancy, both groups can successfully carry healthy pregnancies to term. Clinicians should provide age-appropriate counseling and education and offer contraceptive education or preconception counseling.

GYNECOLOGIC HISTORY

A complete gynecologic history is of utmost importance in helping to identify potential factors that might affect future fertility and pregnancies. A menstrual history allows the assessment of ovulatory status and the potential for difficulty in conception. Patients who are attempting conception can be counseled about this issue, and some may seek fertility counseling and treatment earlier in the process. A history of a uterine anomaly may put patients at risk of spontaneous abortion or preterm birth. A history of tubal surgery puts women at risk for an ectopic pregnancy, and a prior uterine surgery such as a myomectomy may necessitate a c-section in a future pregnancy. Patients should be questioned about a history of abnormal pap smears. A history of high-grade cervical dysplasia, CIN II–III, requiring a cervical loop electrosurgical excision procedure or cone biopsy, puts some women at risk for cervical incompetence and preterm birth.[3]

Lastly, patients should be questioned about diethylstilbestrol (DES) exposure in utero. DES, a synthetic estrogen, was prescribed to pregnant women from the late 1940s to early 1970s to prevent pregnancy loss. This hormone was not effective and has been found to cause malformations of the female genital tract in utero. This has been linked to infertility, pregnancy loss, and premature delivery in women.[4] Women who have been DES exposed need an additional evaluation by an obstetrician with experience.

Eliciting a sexual history and history of risk factors for sexually transmitted infections (STIs) allows for screening and treatment for infection at a preconception visit. STIs have been associated with miscarriage, preterm labor, preterm birth, preterm rupture of membranes, and congenital infections. Untreated infections such as gonorrhea and chlamydia prior to pregnancy can lead to pelvic inflammatory disease, tubal scarring, infertility, and risk of ectopic pregnancy. A history of herpes with an outbreak or prodromal symptoms at the time of labor would necessitate a c-section due to the risk of transmission to the fetus. Women with partners who have a history of herpes are also at risk to contract herpes in pregnancy, and the risk of transmission to the neonate is greatest at the time of an initial outbreak. Women should be offered testing for gonorrhea, chlamydia, syphilis, HIV, and hepatitis B and C. HIV and hepatitis are chronic infections that can be transmitted to the fetus. If identified and managed by experienced providers prior to and during pregnancy, the risk of transmission to the fetus and overall health of the mother can be significantly improved.

REPRODUCTIVE HISTORY

Prior reproductive history is extremely important in identifying the risk for future complications in pregnancy. A thorough reproductive history includes inquiry about prior miscarriages, terminations, ectopic pregnancies, and the details of any deliveries.

Approximately 20%–30% of all pregnancies result in pregnancy loss from spontaneous abortion. While 10% of these will be clinically recognized as a spontaneous abortion, another 20% will be only transient increases in human chorionic gonadotropin around the time of menses.[5] The majority of pregnancy losses occur in the first trimester. The rate of miscarriage increases with a maternal age of less than 18 years or an age of 35 years or more. One in five women will have a miscarriage. Two consecutive losses can occur in up to 5% of all reproductively active couples, and this percentage is higher in women 35 years of age or older. Recurrent pregnancy loss, defined as three or more losses, occurs in about 1% of patients trying to conceive.[6] While some providers will start a workup in patients with a history of two consecutive losses, many patients do not undergo evaluation until three losses.

Initial testing in the evaluation of recurrent pregnancy loss that may be considered part of a preventative health visit includes screening for underlying medical issues such as diabetes, thyroid disorders, and autoimmune disorders, all of which can lead to recurrent pregnancy losses. For women who have had three miscarriages and initial evaluation for underlying medical diseases is negative, referral to an obstetrician gynecologist for further evaluation is indicated.

While early losses before 10 weeks of gestation are common, losses occurring in the second trimester, especially after 15–16 weeks, are not. Women with late losses should be evaluated after one loss, and this should occur prior to another pregnancy. While the same etiology of recurrent

first-trimester losses may also cause a late pregnancy loss, other causes such as cervical insufficiency should be considered. Cervical insufficiency is characterized by painless dilation of the cervix due to a structural or functional defect. Patients at risk may have a history of cervical trauma or cervical surgery, but some women have no risk factors. Women who have a history consistent with cervical insufficiency should be advised to seek care with an obstetric provider early in their next pregnancy.[7]

Information about prior deliveries should include gestational age at delivery, mode of delivery, birth weight, health of the infant, and any complications that occurred in the pregnancy. Previous complications such as diabetes in pregnancy and preeclampsia indicate an increased risk of those complications in subsequent pregnancies and indicate an increase risk of medical complications even when not pregnant. Women with a history of gestational diabetes have an increase risk of developing diabetes later in life and preeclampsia increases a woman's risk of sudden cardiac death. Patients who have had a prior pregnancy complicated by neural tube defects (NTDs) have a 2% risk of recurrence, and folate supplementation at the level of 4 mg/day will reduce this risk.[8]

MEDICAL HISTORY

Identifying medical conditions, including mental health issues, prior to pregnancy allows the primary care provider the opportunity to modify medical care and medications as needed to optimize a woman's health and disease status prior to pregnancy. If needed, appropriate specialists can be consulted so women and their partners can be educated on the potential effects of medical conditions on a future pregnancy, as well as the effect of pregnancy on their medical conditions.

Hypertension

Chronic hypertension occurs in up to 5% of pregnant women. Chronic high blood pressure puts women at risk for preterm birth, fetal growth restriction, placental abruption, and cesarean delivery in pregnancy. There is also an increased risk in the development of superimposed preeclampsia. The incidence of these potential adverse effects is related to the degree and duration of hypertension and other organ system involvement or damage.[9,10]

During a preconception visit, the age of onset, results of previous testing, severity and duration of high blood pressure, medications used, and physical examination determine what testing should be done prior to pregnancy. Ideally, women with chronic hypertension are evaluated for potentially reversible secondary causes of hypertension and end-organ damage including serum creatinine, blood urea nitrogen, and 24 h urine evaluation for total protein and creatinine clearance. Depending on the duration and severity of disease, additional testing may include EKG, echocardiography, ophthalmologic examination, and renal ultrasonography. While most women with mild chronic hypertension are successfully managed in pregnancy, women with significant left ventricular hypertrophy on echocardiogram prior to pregnancy may have worsening of cardiac function in pregnancy and develop heart failure. Women with severe renal disease and a serum creatinine greater than 1.4 mg/dL may have a significant deterioration of renal function during pregnancy.[9]

Ideally, blood pressure is well controlled prior to pregnancy with diet and exercise as first-line agents. If medication is needed, beta-blockers and calcium channel blockers are considered safe in pregnancy. Angiotensin-converting enzyme inhibitors are contraindicated, as they are associated with significant fetal renal dysgenesis leading to fetal renal failure and death.

Diabetes

Preconception evaluation and planning are essential for optimizing both maternal and fetal outcome in women with pregestational diabetes mellitus. Glycemic control at the time of conception plays a key role in reducing fetal and neonatal complications. Offspring of women with pregestational diabetes are at increased risk for congenital malformations due to poor periconception glycemic control. Women with pregestational diabetes should be informed of the importance of glycemic control. Glycosylated hemoglobin (A1C) values above 8% have been linked to an increase in the risk of congenital anomalies as well as spontaneous abortion. One meta-analysis evaluating the relationship of periconceptional maternal A1C to congenital anomalies in the offspring found that for each one standard deviation unit increase in A1C above normal, there was an associated increase in congenital malformations by an odds ratio of 1.2.[11]

Preconception care for women with pregestational diabetes mellitus should aim to educate the patient and her partner regarding issues for the patient and her unborn child and how she can best achieve a healthy pregnancy. Interventions directed at improving diabetes care prior to pregnancy should strive for euglycemia with AIC levels less than 7% prior to conception. Studies evaluating the effect of preconception care on the risk of congenital anomalies have linked preconception care to a reduction in the risk of congenital anomalies.[12]

In addition to the risk of spontaneous abortion and congenital anomalies associated with glycemic control prior to pregnancy, poor glycemic control increases the risk of macrosomia and birth trauma. Pregestational diabetes mellitus has also been associated with increased risk of preeclampsia, intrauterine fetal demise, and worsening of maternal end-organ disease. Preconception counseling should educate women with preexisting diabetes in pregnancy about the importance of glycemic control and close follow-up for the entirety of their pregnancies.

Seizure Disorder

Women with seizure disorders are at increased risk for giving birth to infants with congenital anomalies, with 6%–8%

risk for women with seizure disorder at risk versus 2%–3% for women without a seizure disorder. Congenital anomalies seen more frequently in offspring of women with seizure disorders include cleft lip or palate, cardiac defects, NTDs, urogenital defects, and intrauterine growth restriction. Low folate levels are independently associated with congenital abnormalities in women with a seizure disorder. It remains unclear if these increased risks are associated with the use of antiepileptic drugs alone or the seizure disorder itself. In either case, there is compelling evidence that the use of folic acid supplementation prior to pregnancy reduces these risks.[13,14] Women with seizure disorders should be followed closely but reassured that with folic acid supplementation and preconception care, 90% of women will have a healthy pregnancy.[13]

In each woman planning a pregnancy, the need for antiepileptic drugs should be assessed, as some women may be successfully withdrawn from medication prior to pregnancy. The need for medication and the best medication to use should be tailored to each patient. Monotherapy with a single agent is preferred, as the risk for congenital anomalies is directly related to the number of antiepileptic drugs to which the fetus is exposed in the first trimester.[15] In general, as there is no consensus on which medication is best in pregnancy, the one that is most effective at stopping seizure activity in a given patient should be used. The exceptions to this are valproate and carbamazepine, which should be avoided if possible. Of the antiseizure medications, valproate has been shown to have the highest risk of teratogenicity and has increased levels in cord blood. Carbamazepine has been independently associated with major congenital malformations.[14]

Mental Health

For women with a history of psychiatric illness that predates pregnancy, a review of current psychoactive medications during a preconception visit is imperative. Advising a woman planning a pregnancy to discontinue psychiatric medications exchanges fetal or neonatal risks of medication exposure for the risks of untreated maternal illness. Untreated maternal psychiatric illness can result in significant complications including increases in alcohol and drug abuse, disruption of family environment, poor compliance in prenatal care, and poor maternal–infant bonding. Pregnancy and the postpartum period may also serve to exacerbate psychiatric illness. Ideally, shared decision making among obstetric and mental health clinicians and the patient should occur before pregnancy. A discussion of the risks and benefits of medication use, alternatives to medication, and therapy should involve the patient and her family support and occur within a multidisciplinary framework.[16,17]

The management of women with mental illness who are on medication should be individualized. For example, for those with mild depression or no symptoms for 6 months or longer, consideration can be given to tapering and discontinuing medication before becoming pregnant. However, for women who have psychosis, bipolar disorder, a history of suicide attempts, severe depression, or other major psychiatric illness, it may not be appropriate to taper or discontinue medications, and management should be done in partnership with a psychiatrist experienced in treating these disorders in pregnancy.[18]

Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive disorder of phenylalanine (Phe) metabolism characterized by a deficiency of the hepatic enzyme, phenylalanine hydroxylase (PAH). A deficiency of the PAH enzyme results in increased blood phenylalanine levels, which are toxic to the developing embryo. If untreated, PKU can result in fetal growth failure, microcephaly, seizures, and mental retardation. Children born to women with PKU on unrestricted diets have a 92% risk for mental retardation, a 73% risk for microcephaly, and a 12% risk for congenital heart defects. If phenylalanine levels are normalized before conception or by 8 weeks of gestation, there is evidence to suggest a significant reduction in the fetal sequelae of hyperphenylalaninemia. Although evidence suggests that women with PKU will benefit from remaining on a phenylalanine-free diet throughout their lives, many are not adherent to such a diet because of the unpalatable nature of many phenylalanine-free products. The failure of young women with PKU to adhere to dietary modification represents a significant public health challenge because of the significant fetal consequences of maternal hyperphenylalaninemia.[19] Women with PKU who are at risk of an unplanned pregnancy or are considering planning a pregnancy should be instructed to resume a phenylalanine-restricted diet.

Thyroid Disease

Thyroid disease is the second most common endocrine disorder in women of reproductive age. Both maternal hypothyroidism and hyperthyroidism can lead to complications in pregnancy. Inadequately treated maternal hyperthyroidism has been associated with a greater risk of fetal loss, preterm delivery, low-birth-weight infants, severe preeclampsia, and heart failure than in those with treated, controlled maternal hyperthyroidism. Poorly controlled maternal hypothyroidism has been associated with a slight increase in risk of preeclampsia, low-birth-weight infants, and fetal demise. Women with iodine-deficient hypothyroidism are at significant risk of having babies with congenital cretinism (growth failure, mental retardation, and other neuropsychological deficits).[20]

A euthyroid state should be achieved prior to conception with medications or surgery as appropriate. Maternal thyroid function should be followed in pregnancy due to the changes in maternal requirements throughout gestation. Currently, there is no evidence that identification and treatment of women with subclinical hypothyroidism improve maternal or infant outcomes, and therefore routine screening for subclinical hypothyroidism is not recommended during the preconception or prenatal period.[21]

TABLE 66.1
Partial Listing of Known Teratogens

Androgens
ACE inhibitors
Diethylstilbestrol
Diphenylhydantoin
Isotretinoin
Thalidomide
Warfarin

MEDICATIONS

An important aspect of preconception counseling is the review of a woman's medication list, including over-the-counter medications, prescription drugs, vitamins, and herbal supplements, in order to evaluate for potential risk to the developing fetus. Women with underlying health issues should continue medications needed to optimize their health, but providers should evaluate whether there is known teratogenic risk to these medications and whether alternate medications known to be safer in pregnancy are suitable. Women that are required to remain on teratogenic medications for their own health should be counseled about the risks of unplanned pregnancy and the use of a reliable method of birth control. While there are some medications known to be teratogenic (see Table 66.1 for partial listing), many medications have not been well studied in pregnancy. Providers should discuss with women the available data on the use of the particular medication in pregnancy, the risks of being off of the medication, and the alternative medications that may be available.

FAMILY HISTORY

Review of family history for the patient and her partner during a well-woman visit often reveals potential risks in pregnancy. A positive history in the patient or her partner for genetic diseases should prompt referral to a genetics counselor (Table 66.2).

In addition, in certain ethnic groups, even with a negative family history, patients are at an increased risk for having a child with a genetic disease. For example, in individuals of Eastern European Jewish (Ashkenazi) descent, carrier screening for cystic fibrosis, Tay–Sachs disease, Canavan disease, and familial dysautonomia should be offered. In addition, in this population, screening for mucolipidosis IV, Niemann–Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease may be considered. Tay–Sachs disease carrier screening should also be offered to individuals of French Canadian and Cajun descent.[22] In addition, individuals of African, Southeast Asian, and Mediterranean descent are at increased risk for being carriers of hemoglobinopathies and should be offered carrier screening (Table 66.3).[23]

TABLE 66.2
Genetic Diseases

Hemoglobinopathies
Sickle cell disease or known carrier status
Beta-thalassemia
Alpha-thalassemia
Hemophilia
Muscular dystrophy
Mental retardation
Unexplained
Fragile X
Cystic fibrosis or known carrier status

TABLE 66.3
Genetics Diseases by Ethnic Group

Disease	Ethnic Group at Highest Risk	Screening Test
Sickle cell anemia	African, Southeast Asian, Mediterranean, Caribbean	Hemoglobin electrophoresis
Beta-thalassemia	African, Indian, Mediterranean, Southeast and East Asian	CBC with indices
Alpha-thalassemia	African, Chinese, Filipino, Southeast Asian	CBC with indices
Tay–Sachs disease	Ashkenazi Jews Eastern European, French Canadian, Cajun	Assay for enzyme hexosaminidase A
Cystic fibrosis	Non-Hispanic Caucasian, Ashkenazi Jews	DNA analysis

TABLE 66.4
Rates of Cystic Fibrosis Carrier Status by Ethnicity

Ashkenazi Jewish	1/25
Non-Hispanic Caucasian	1/25
Hispanic American	1/46
African American	1/65
Asian American	1/94

While the carrier rates for cystic fibrosis are highest in the Ashkenazi Jewish population and non-Hispanic Caucasian population at rates of 1/25, it is becoming harder for patients to identify with a single ethnic group. Therefore, in 2005, the American College of Obstetrics and Gynecology Committee on Genetics recommended offering screening to all pregnant patients and to all patients considering conception regardless of ethnicity (Table 66.4).[24]

Providing these evaluations before pregnancy allows women and their partners greater control over their reproductive future. All screening for genetic disorders should involve informed consent. Patients may benefit from genetic counseling, especially in the Ashkenazi Jewish population.

SOCIAL HISTORY

The preconception period is an excellent time to educate patients on the risks posed by their lifestyle, behaviors, and environmental exposures. This counseling prior to pregnancy

gives the patient an opportunity to modify parameters under their control before exposing her fetus. In addition, many patients are more motivated to make positive changes if they are planning a pregnancy.

Smoking

Cigarette smoking is universally recognized to be harmful to both mother and fetus. Despite this, a 2004 survey found that in the United States an estimated 18% of pregnant women aged 15–44 years smoke cigarettes compared to an estimated 30% of nonpregnant women of the same age.[25]

In addition to the well-known health effects for the mother, smoking is associated with an increased risk of infertility, spontaneous abortions, preterm labor, low-birth-weight infants, stillbirth, placental abruption, and sudden infant death syndrome.[26,27]

While many women report they will stop smoking when pregnant, it is of greater benefit to the patient and the pregnancy to stop prior to pregnancy. Smoking cessation at any point in pregnancy leads to health benefits. Providers should specifically address the reproductive health risks of smoking to patients as part of any preventative health visit for women who are smokers and are of reproductive age. For nonpregnant women, the U.S. Preventive Services Task Force concluded that the combination of counseling and medications is more effective at increasing smoking cessation rates than from either alone. For nonpregnant women, however, they found inadequate evidence to evaluate the safety or efficacy of pharmacotherapy that is continued during pregnancy and so recommend only pregnancy-tailored counseling.[28] For patients who are pregnant, the use of nicotine replacement products or alternative smoking cessation agents should be undertaken with close supervision and with clear counseling of the patient in regard to the risks and benefits of smoking cessation and the risks and benefits of the agents being used.

Alcohol

Alcohol consumption in pregnancy may lead to fetal alcohol syndrome (FAS). FAS is characterized by growth deficiencies, abnormal facial features, and central nervous system abnormalities. FAS falls under the spectrum of adverse outcomes caused by prenatal alcohol exposure called fetal alcohol spectrum disorders (FASDs). In the United States, it is estimated that the rate of FAS is approximately 0.5–2 per 1000 births with FASDs occurring approximately three times as often.[29]

In the United States, alcohol is the most common potentially teratogenic substance to which pregnant women are exposed. In a 1991–2005 study of alcohol consumption among women in the United States, the average annual percentage of any alcohol among nonpregnant women was 53.7% and among pregnant women was 12.2%.[29] There is no threshold amount of alcohol consumption in pregnancy that has been proven safe. Women considering conception or who are not using adequate birth control should be counseled to avoid alcohol consumption.

Substance Abuse

Data from the National Center for Health Statistics estimates that in 2008 approximately 8% of individuals over the age of 12 had used illicit drugs in the last month. Substance abuse in pregnancy has increased over the past three decades in the United States, resulting in approximately 225,000 infants yearly with prenatal exposure to illicit substances.[30] Cocaine causes vasoconstriction that can lead to decreases in uterine blood flow. Use of cocaine in pregnancy can lead to premature rupture of membranes, preterm labor, placental abruption, small-for-gestational-age infants, and low-birth-weight newborns. In addition, neonatal issues include poor feeding, lethargy, and seizures.[30,31] The use of heroin and other opiates has been associated with an increase in the rate of poor obstetric outcomes by six times and neonates can undergo a severe withdrawal syndrome. Lastly, marijuana use has not been definitely linked to congenital anomalies, but has been linked to fetal growth restriction.[30] In addition to these risks, use of illicit drugs in pregnancy does not occur in a vacuum. It is associated with other comorbid conditions known to contribute to adverse maternal and fetal outcomes including other psychiatric disorders, and environmental factors such as poor nutrition, inadequate medical care, and domestic violence.[31] Routine screening for drug use in women of reproductive age, education, and referral for treatment are the most important ways that substance use in pregnancy can be decreased.

Domestic Violence

Maternal exposure to domestic violence is associated with a significantly increased risk of low birth weight and preterm birth.[32] Routine screening for domestic violence is important for women of all ages, but women who are of reproductive age are at particular risk. Women who are being abused before pregnancy are even more likely to be abused when they become pregnant. Screening for domestic violence in women should be part of every preventive health care visit. Every clinician should have a system set up for referrals to local resources and social services for patients.

Environmental Exposures

The Occupational Safety and Health Administration sets and enforces standards that require employers to maintain a workplace free of known hazards likely to cause physical harm. Patients who are at apparent risk should be encouraged to investigate this information in their workplace. High levels of exposure to organic solvents, such as those levels of exposure typically found in industrial workers, are thought to be harmful to the embryo and have been linked to an increase in spontaneous abortions.[33] Lead exposure, even moderate to low levels found in the U.S. population in the 1970s, has also been shown to increase the risk of spontaneous abortion, preterm birth, low birth weight, and developmental delays in the infant.[34] Lastly, exposure to waste anesthetic gases in the fields of human and veterinary

medicine has also been linked to an increased risk of spontaneous abortion. Studies indicating this relationship were primarily prior to the implementation of systems that scavenge waste anesthetic gases, so the actual risk at this time is not known.[35] Patients should be screened for environmental and occupational exposures.

Women contemplating pregnancy may be concerned about the safety of insect repellants. There is currently no reliable evidence that exposure to pest-control products at levels commonly used at home poses a risk either in the preconception period or during pregnancy. There is also no evidence that household cleaning products pose any additional risk in the preconception period or during pregnancy. Like all individuals, women of reproductive age should take precautions such as opening windows and doors and wearing rubber gloves when using cleaning products that contain ammonia or chlorine.

PHYSICAL EXAMINATION

The physical exam in the setting of a preconception evaluation is the same as for a routine periodic health evaluation. Aspects that should be concentrated on include the examination of the thyroid, breasts, heart, skin, and pelvis. Blood pressure and weight should also be checked. In addition, patients should be encouraged to see a dentist, as periodontal disease has been associated with pregnancy complications. If any underlying medical conditions are uncovered, they are best managed prior to pregnancy.

Laboratory testing is dependent on the woman's past medical, obstetric, and gynecologic history and in general should be individualized, and patients should be fully counseled on the implications of the testing. Laboratory testing may include those tests found in Table 66.5.

TABLE 66.5
Preconception Laboratory Testing

Test	Indication
Rubella titer	All women planning pregnancy
Hepatitis B surface antigen	All women planning pregnancy
Complete blood count with indices	Screening for hemoglobinopathy and anemia
HIV counseling and testing	All women planning pregnancy
Plasma glucose	Women at increased risk for diabetes
Mantoux test	Populations at high risk for TB
Hepatitis C antibody	Populations at high risk
Toxoplasmosis titer	Women with occupational exposure, pet cats, or high-risk food intake
Cytomegalovirus titer	Hospital workers, workers in childcare facilities
Gonorrhea and chlamydia testing	Women at high risk or under age 25
RPR	Women at high risk or under age 25
Cystic fibrosis mutation analysis	Offered to all women
Genetic carrier testing	Based on family history or ethnic origin

COUNSELING

Diet and Nutrition

A woman's nutritional status should be assessed at preconception with the goal of optimizing fetal, maternal, and infant health. The preconception period is an ideal time to reinforce that all women should eat a healthy, well-balanced diet and achieve a healthy weight. Fish and shellfish are a part of a healthy diet and are high in protein and omega-3 fatty acids. Mercury is known to be harmful in high doses to the developing fetal nervous system. Fish absorb methylmercury from the water they swim in and the food they eat. Nearly all fish contain some methylmercury. Large predatory fish accumulate the highest levels of methylmercury. Women should be advised to follow the FDA guidelines for consumption of fish and shellfish (Table 66.6) prior to pregnancy as mercury can remain in the body for several weeks after ingestion and levels can build up over time.[36]

Folic acid supplementation prior to pregnancy can significantly reduce the risk of NTDs both in women with a prior history of pregnancy complicated by NTDs and in women with no prior history. The U.S. Preventive Services Task Force currently recommends that all women planning or capable of pregnancy take a daily supplement containing 0.4–0.8 mg of folic acid.[8] For women with a prior history of a pregnancy with an NTD, those with a positive family history, or who are taking antiepileptic drugs, a dose of 4 mg/day is recommended. Folic acid is a water-soluble vitamin, easily metabolized and excreted, and no toxicity has ever been reported.

Because the neural tube closes at approximately 26 days after conception, 6 weeks after a missed period, and typically 2 weeks prior to a first prenatal visit, all women of reproductive age who are capable of becoming pregnant should be counseled to take folic acid supplements to reduce the risk of NTD. In 1998, the U.S. Food and Drug Administration mandated folic acid fortification of enriched grain products.

TABLE 66.6
2004 EPA and FDA Guidelines for Fish Consumption in Pregnancy

1. Do not eat shark, swordfish, or tilefish, tuna steak, mackerel, marlin, or grouper
2. Eat up to 12 oz of a week of a variety of fish and shellfish that are lower in mercury. Albacore "white" tuna has more mercury than canned "light" tuna so limit consumption of albacore tuna to 6 oz per week
3. Check local advisories about the safety of fish caught locally. If no advisories are available limit consumption to 6 oz per week

Source: EPA/FDA, What you need to know about mercury in fish and shellfish, EPA-823-R-04-005, March, 2004, http://www.fda.gov/food/foodsafety/product-specificinformation/seafood/foodbornepathogenscontaminants/methylmercury/ucm115662.htm

Despite this, many women consume less than 400 μg daily from their diet, and thus supplementation with folic acid in the preconception period is still recommended.

Exercise and Body Weight

Obese women are at increased risk for several pregnancy complications, and therefore preconception assessment and counseling are strongly encouraged. Providers should educate obese patients about potential complications in pregnancy and should encourage them to undertake a weight reduction program, including diet, exercise, and behavior modification before attempting pregnancy. Specific medical clearance may be indicated for some patients. Obese women are more likely to develop preeclampsia, gestational diabetes, gestational hypertension, and fetal macrosomia.[37]

In addition to pregnancy complications, obese women are more likely to have difficulty with conception. An increased body mass index is associated with ovulatory subfertility and anovulatory infertility. Overweight and obese women have poorer outcomes following fertility treatment.[38]

Regular exercise provides benefits for pregnant and nonpregnant women alike. Preconception counseling should encourage a regular exercise program prior to pregnancy. Many exercises are safe in pregnancy and prepregnancy exercise regimens may be continued. Activities to be avoided in pregnancy, but not in the preconception period, include exercises that put women at risk for abdominal trauma.

Vaccinations

The preconception or interconception period is the optimal time to make sure that women are up to date on their immunizations (Table 66.7). There is no evidence of risk from vaccinating pregnant women with an inactivated virus or bacterial vaccines or toxoids, and these should be administered if indicated during pregnancy. However, live vaccines do pose a theoretic risk to the fetus and generally should be avoided during pregnancy. The preconception period is the ideal time for vaccination with live virus vaccines, and women should be advised to wait to conceive for 1 month after vaccination with such live virus vaccines as rubella and varicella.

In 2008, looking to prevent infantile pertussis, the CDC's Advisory Committee on Immunization Practices came out with a new recommendation to vaccinate adults for pertussis who will have contact with children less than 12 years and for women during the immediate postpartum period. They specifically recommend that pregnant women who were not vaccinated previously with Tdap may (1) receive Tdap in the immediate postpartum period before discharge from hospital or birthing center, (2) receive Tdap at an interval as short as 2 years since the most recent Td vaccine, (3) receive Td during pregnancy for tetanus and diphtheria protection when indicated, or (4) defer the Td vaccine indicated during pregnancy to substitute Tdap vaccine in the immediate postpartum period if the woman is likely to have sufficient protection against tetanus and diphtheria. Although pregnancy is not a contraindication for receiving Tdap vaccine, there is currently not sufficient evidence to address its safety in pregnancy.[39]

TABLE 66.7
Immunizations

Immunization	Frequency	Patients	Safe in Pregnancy?
Diphtheria/ tetanus	Every 10 years	All	Yes
Pertussis (in TDaP)	Once	Postpartum and adults who will have contact with children <12	Unknown
Influenza	Annually	All	Yes
H1N1	Annually	All	Yes
Pneumococcal	Once	Susceptible individuals	Yes
Hepatitis B	Once (three-shot series)	All	Yes
MMR	Once	All	No
Varicella	Once	Susceptible individuals	No

CONCLUSION

Preconception care is an important part of preventive health care in women of reproductive age. As the field of preventive care has developed, the importance and demand for preconception care, counseling, and education have grown too. Primary care providers plan a key role in determining the health of the mother and the child even before pregnancy occurs. Preconception evaluation and counseling should be a standard element of the primary care of any woman of childbearing age.

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67 Nutrition and Lifestyle for a Healthy Pregnancy

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CONTENTS

A Changing Population 831
Maternal Weight Targets 832
Historical View of Weight Gain in Pregnancy 832
Counseling about Weight Gain 833
Weight Retention after Pregnancy 833
Fetal Origins of Adult Disease 833
Low-Glycemic-Index Diet 833
Vitamins and Supplements 834
Maternal Supplementation with Omega-3 Fatty Acids 834
Vegetarians 835
Food Safety 835
Caffeine 836
Alcohol 836
Smoking 837
Conclusion 837
References 838

Diet and lifestyle practices during pregnancy can provide maternal and fetal benefits as well as an investment in future health for both the mother and her baby. Pregnancy is a normal physiological state, not a disease, and healthy women can engage in work, leisure, and exercise armed with knowledge to utilize pregnancy as a launching point for a healthy diet and lifestyle that lays a solid foundation for both themselves and their children, now and in the future. Health care providers play an important role in giving evidence-based diet and lifestyle counseling that can help women make good choices in pregnancy, since myths, media, and culture can confuse even the most motivated woman.

A CHANGING POPULATION

In recent years, the characteristics of women in the United States having babies have changed dramatically. Today, women entering pregnancy are older and many are overweight or obese. Studies estimate that over 60% of adults in the United States are overweight (body mass index [BMI] of 25 or higher) and up to 32% are obese (BMI of 30 or higher). For the prime childbearing ages 20–39, 57% are either overweight or obese.[1] Since 1970, the prevalence of multiple births has been increasing. A combination of factors are associated with this change, including the widespread use of assisted reproductive techniques and advancing maternal age at conception.[2] These changing demographics and characteristics are linked with an increased risk of maternal issues that can put both the mother's and her baby's health at risk. Recommendations for diet in pregnancy must be tailored to meet these changing needs.

The diet that a fetus is exposed to in utero may set the stage for future health. Both fetal under- and overnutrition in utero have been linked with health risks later in life. The joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases identified the period of fetal development as a critical life stage to initiate prevention of chronic diseases, including obesity, diabetes, and cardiovascular disease.[3] A growing body of knowledge about fetal origins of adult diseases suggests that through the diet and environment that a fetus is exposed to in utero, there may be an opportunity to prevent or mitigate many chronic diseases that arise in adulthood.[4,5]

Helping mothers to have babies within a healthy birth weight range is an area of focus, since babies that are born either too big or too small appear to have increased health risks. On one end of the spectrum, babies who are born with low birth weight have health risks. Intrauterine growth restriction has been recognized as a long-term health risk. Later in life, babies who were born small for gestational age at birth, especially those born to undernourished mothers, have increased risks of coronary heart disease, type 2 diabetes, and hyperlipidemia.[3–5] At the other extreme, concerns

over the consequences of fetal overnutrition resulting in high birth weight have grown, especially in light of the epidemic of overweight, obesity, and diabetes among women of childbearing age. In babies exposed to overnutrition and high glucose in utero, resulting problems can include congenital birth defects, macrosomia, birth trauma, and childhood obesity.[4–6] Pregnancy is a balancing act, in which women need to take in enough, but not too many, calories and nutrients in order to optimize health for themselves and their babies.

MATERNAL WEIGHT TARGETS

Many women are gaining more weight in pregnancy than is currently recommended. The goals of nutrition during pregnancy are to provide adequate maternal and fetal nutrition and energy intake that result in the appropriate maternal weight gain. Gaining excessive weight during pregnancy is a strong predictor of high postpartum maternal weight retention and the development of overweight and obesity later in life.[7] Excessive weight gain during pregnancy, along with preexisting maternal overweight and obesity, increases the risk of maternal complications during pregnancy and delivery in mothers. Maternal weight gain influences infant birth weight, which in turn influences future health for children. Neonatal birth weights that are too high or too low have both been associated with increased risks of future diseases.

The Institute of Medicine (IOM) recommended weight gain guidelines for pregnancy were published in 1990 and revised in 2009.[8] A woman's weight at the start of pregnancy is one of the most important modifiers of pregnancy weight gain and its impact on a mother's and her baby's health. The revised weight gain guidelines take into account both the welfare of the infant and the health of the mother based upon the weight that the mother begins her pregnancy, so that nutritional needs can be balanced in order for both mother and baby to thrive. They help to clarify weight gain for expectant mothers based upon pre-pregnancy BMI, with a new category for obese women added, and more specific recommendations for women having multiple pregnancies. The guidelines help ensure that the baby will gain the appropriate amount of weight, while balancing the maternal needs so that women will not be left with a large amount of weight to lose postpartum. The guidelines and recommendations are intended to be used in concert with good clinical judgment and should include a discussion between the woman and her care provider about both diet and exercise.

The recommended weight gain during pregnancy for normal-weight women is 25–35 lb, which translates into approximately a 200–300-cal increase daily in a pregnant woman's dietary needs. Daily energy needs during pregnancy vary due to such factors as physical activity and age and range from 2500 to 2700 kcal.[8] Overweight women can limit weight gain to 15 lb, and obese women can limit it to 11 lb. Underweight women should gain a minimum of 28 lb. After the first trimester, this translates into approximately 1 lb of weight gain per week for underweight and normal-weight women, and 0.5–0.6 lb of weight gain for overweight and obese women. For many women, this means gaining less weight than in the past, which may be particularly challenging for those starting pregnancy overweight or obese. Ideally, women should be within a normal BMI range when they conceive and then should gain within the ranges recommended in the new guidelines once pregnant (Table 67.1).

TABLE 67.1
Institute of Medicine Recommended Weight Gain in Pregnancy

Weight Status	BMI	Total Weight Gain	Rates of Weight Gain
Underweight	<20	28–40	1 lb/week
Normal	20–25	25–35	1 lb/week
Overweight	25–29	15–25	6 lb/week
Obese	>30	11–20	5 lb/week

Source: Institute of Medicine, *Weight Gain During Pregnancy: Reexamining the Guidelines*, National Academy Press, Washington, DC, May 2009.

Calculations assume a 1.1–4.4 lb weight gain in the first trimester.

HISTORICAL VIEW OF WEIGHT GAIN IN PREGNANCY

The weight recommendations for pregnancy have evolved over the last 50 years. In the past, obstetricians in the United States recommended that women restrict weight gain to as little as 25 lb (12.5 kg) in hopes that it would reduce the risk of preeclampsia. When scientific evidence did not support this risk reduction through caloric limitation, the restriction on weight gain was lifted.[9] In 1990, the IOM recommended increased weight gain ranges with the primary goal of improving infant birth weight, with weight gain recommendations individualized based upon pre-pregnancy BMI.[10] These recommendations were endorsed by the American College of Obstetricians and Gynecologists in 1993.[11] However, concerns grew that the 1990 IOM guidelines resulted in overgrown newborns with increased health risks later in life.[12] Critics argued that many of the prior recommendations for weight gain in pregnancy rested on observational studies that may have had confounding factors that accounted for the adverse birth outcomes associated with low birth weight. For example, hypertension, smoking, low family income, and poor antenatal care are linked with low birth weight. Another observational study linked too much weight gain in pregnancy with future risk of obesity in the mother.[13] Women weigh more today than they did in 1990, and many experts thought the 1990 guidelines emphasized fetal health over maternal health, resulting in women gaining too much weight in pregnancy and retaining weight from one pregnancy to the next, adding to the growing problem of overweight and obesity.

COUNSELING ABOUT WEIGHT GAIN

Studies suggest that women are not getting adequate counseling about proper weight gain targets for pregnancy.[14] Women who start pregnancy at the extremes of BMI, either underweight or overweight, are prone to targeting weight gains that are outside the IOM guidelines. Women who are overweight strive to gain too much weight, and underweight women strive to gain too little. Women with low BMI have the highest risk for inadequate target weight gains, while women with high BMI have the highest risk for excessive weight gain. Patients with poor health literacy and lower education status tend to target incorrect weight gain goals. In addition, African American and Latina patients are more likely than white women to report target weight gains below the guidelines, even when controlling for education status, pointing toward cultural factors that may influence target weight gain.[14,15] It is not known if these target behaviors are due to providers giving incorrect advice, cultural factors, or lack of patient knowledge about appropriate target weights. It may be a combination of all of these factors.

Studies of the U.S. women show that 30%–40% of women gain either above or below the guidelines. Overweight women are much more likely to gain above the guidelines, and underweight women are more likely to gain below the guidelines.[16] This points toward the need for health care providers to reinforce and encourage underweight women to gain relatively more weight, and overweight women to aim to gain relatively less, as recommended by the IOM guidelines. There is currently little information about evidence-based recommendations for clinicians to follow in order to help stem excessive maternal weight gain. One trial actually demonstrated that including weight gain counseling in prenatal care resulted in increased maternal weight gain (although nonsignificant) in overweight women, suggesting that the dietary advice may not have been effective.[17]

WEIGHT RETENTION AFTER PREGNANCY

Weight retention after pregnancy is one factor contributing to the problem of overweight and obesity in adult women. The average weight retention after pregnancy ranges from 0.4 kg (0.88 lb) to 3.8 kg (8.38 lb) at 6 weeks to 1 year after pregnancy.[18,19] Studies indicate that pregnancy is associated with future weight gain beyond that expected with age alone. The weight retention appears to be largely associated with a first pregnancy. Primiparas gain 2–3 kg more weight during a 5-year period after pregnancy than do women who do not carry a pregnancy. Primiparas also have greater increases in waist-to-hip ratio that are independent of weight gain, suggesting changes in adiposity patterns that result from pregnancy. Multiparas do not show further adiposity changes, so it appears that these changes are not made worse in subsequent pregnancies. Black women demonstrate greater adverse changes in adiposity than white women. Interestingly, most studies suggest that the effect of breast-feeding on maternal postpartum weight loss is negligible.[18,19]

Studies show that women are much more likely to be able to return to their pre-pregnancy weight if they gain within the IOM weight guidelines. If the upper limit of the weight gain guidelines is exceeded, the amount of weight retained goes up exponentially. In a study of postpartum weight retention, women starting pregnancy with high BMIs who gained more than 25 lb (11.4 kg) had a high risk of significant postpartum weight retention, with 34% retaining more than 14 lb (6.4 kg) several months after delivery.[20]

FETAL ORIGINS OF ADULT DISEASE

There is a growing body of scientific evidence that suggests the environment in utero may affect future adult health and risk of disease for the fetus. There are several epidemiologic studies that support this idea. Low birth weight has been linked to an increased risk of cardiovascular disease and type 2 diabetes. It is theorized that this risk is due to an adaptation by the fetus in the in utero environment in which the fetus becomes "thrifty" by being small and insulin resistant.[21] This "thrifty phenotype" hypothesis suggests that the metabolic adjustments, which are adaptive in the face of an in utero environment in which nutrient supplies are limited, are maladaptive and unhealthy in an adult in a nutritionally rich environment.

Both under- and overnutrition, as well as the timing of the in utero exposure, appear to make a difference for disease risk as an adult. For example, survivors of the Dutch famine of 1945 had an increased risk of impaired glucose tolerance as adults if their intrauterine environment was calorie restricted in late pregnancy.[22] However, if the calorie restriction occurred early in gestation, adults had an increased risk of coronary heart disease and dyslipidemia.[23] Less information is available with regard to the specifics of macro- and micronutrient imbalances, but again, data from the Dutch famine suggest that fetal exposure in the third trimester to a low protein-to-carbohydrate ratio in the maternal diet is associated with hypertension as an adult.[24] A study of adults whose mothers had been advised to eat a high-protein diet during pregnancy showed higher blood pressure and elevated basal cortisol levels in those whose mothers had higher meat (protein) and lower vegetable intake during pregnancy.[25]

LOW-GLYCEMIC-INDEX DIET

Pregnancy is a state of maternal insulin resistance, with glucose serving as the main fuel for the fetus. As our knowledge of the potential health benefits of a low-glycemic-index diet in the nonpregnant state has increased,[26,27] interest has grown in examining the health effects of a low-glycemic-index diet in pregnancy. Poor glucose control in pregnancies complicated by gestational diabetes has known adverse effects, including fetal macrosomia, neonatal hypoglycemia, birth trauma, and other pregnancy complications.[28] There are currently some data on the potential beneficial effects of a low-glycemic-index diet in pregnancy. One study comparing a low-glycemic-index diet compared to a usual diet in pregnancy

found that women who consumed a low-glycemic-index diet had infants that were in the normal size range for gestational age, but were smaller and had less body fat than those from women who consumed a high-glycemic-index diet.[29] The infants of mothers in the low-glycemic-index group were normal size for gestational age, but the infants of mothers who consumed a high-glycemic-index diet group were more likely to be large for gestational age, with 33.3% of the infants in the >90%. Another study using a low-glycemic-index diet for women with gestational diabetes found that the number of women needing to use insulin was halved, with no compromise of obstetric or fetal outcomes.[30] One small pilot study that randomized 46 overweight or obese pregnant women to either a low-fat or low-glycemic-load diet found no differences in birth weight or infant adiposity, but in the low-glycemic-load group, gestational duration was longer (mean 39.3 compared with 37.9 weeks; P = 0.05) and fewer deliveries occurred at <38.0 weeks of gestation. Maternal benefits in women in the low-glycemic-load group showed smaller increases in triglycerides and total cholesterol and a greater decrease in C-reactive protein.[31] Studies on glycemic index in pregnancy are ongoing.

VITAMINS AND SUPPLEMENTS

Many women inquire about vitamin and supplement use during pregnancy. The evidence regarding their use is reviewed here.

Several trials of maternal calcium supplementation during pregnancy have suggested a potential role of in utero exposure to calcium and later blood pressure in offspring. A prospective cohort study found a protective effect of maternal calcium intake from supplements and infant blood pressure at 6 months of age.[32] There is evidence in the literature to support an association between maternal calcium intake during pregnancy and offspring blood pressure.[33] However, more research is needed, especially in populations with calcium deficits, to confirm these findings, given the small sample sizes and the methodological problems in many of the studies conducted to date. If confirmed, these findings could have important public health implications since calcium supplementation during pregnancy is simple and inexpensive and may be a way to reduce the risk of hypertension and its sequelae in the next generation.

The American Dietetic Association states that pregnant women should eat a diet that enables appropriate weight gain, and adequate nutrition may be obtained through consumption of a variety of foods, with vitamin and mineral supplementation appropriate for some nutrients.[9] The need for vitamin supplements in order to obtain adequate micronutrients in pregnancy has been examined in a recent Cochrane review.[34] The review identified nine trials undertaken in low- or middle-income countries. There was a reduction in low birth weight and small-for-gestational-age babies and anemia in mothers who received supplementation. Further research is ongoing to look at the maternal and fetal benefits of micronutrient supplementation, while also examining the risks of excess supplementation and adverse interactions among micronutrients.

Probably the best-known example of nutrient supplementation in pregnancy is folic acid supplementation and the subsequent reduced risk of neural tube defects (NTDs). NTDs, the most common of which are spina bifida and anencephaly, are related to homocysteine metabolism, and the risk of having a fetus with an NTD is significantly reduced with dietary folic acid supplementation.[35] Much evidence indicates that 0.4 mg (400 µg) per day of folic acid, one of the B vitamins, will reduce the number of cases of NTDs. The U.S. Public Health Service recommends that "all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs."[36] In 1998, the U.S. Food and Drug Administration mandated folic acid fortification of enriched grain products.[37] Since that time, studies suggest that fewer than 1000 NTD-affected pregnancies occur in the United States each year.[38]

MATERNAL SUPPLEMENTATION WITH OMEGA-3 FATTY ACIDS

Interest in maternal supplementation with omega-3 fatty acids during pregnancy and lactation has grown since several epidemiologic studies have shown benefits in infant neurocognitive scores as well as improved maternal depressive symptoms and maternal lipid benefits. There is a growth spurt in the human brain during the last trimester of pregnancy and the early neonatal months and a large increase in the content of docosahexaenoic acid (DHA) in the brain during this time. DHA (omega-3) is important for the development of the central nervous system, and the fetus and the breast-feeding newborn depend upon maternal consumption to supply these fatty acids. The concentrations of these fatty acids in breast milk are variable and depend on maternal consumption.[39]

One study examining the long-term effects of maternal supplementation with omega-3 fatty acid supplements during pregnancy and lactation found that 4-year-old children have higher mental processing scores when the mothers are supplemented with omega-3 fatty acids from cod-liver oil compared to omega-6 fatty acids from corn oil.[40] Another study showed that there were potential maternal lipid benefits to supplementation with cod-liver oil in pregnancy.[41] The maternal plasma triacylglycerol increase during pregnancy was less pronounced in women supplemented with cod-liver oil as compared to corn oil. The concentration of high-density lipoprotein (HDL)-cholesterol was unchanged during pregnancy in the cod-liver oil group, whereas it decreased in the corn oil group, promoting a greater increase in the ratio of total cholesterol/HDL-cholesterol in the corn oil group. Finally, one study of cod-liver supplementation in pregnancy revealed that higher levels of omega-3 fatty acids in the bloodstream of neonates correlated with longer gestational length and better cerebral maturation of the newborn, and improved neurodevelopmental outcomes in children.[42,43] Higher intakes of these *n*-3 long-chain polyunsaturated fatty

acids from fish and seafood during pregnancy are also associated with a reduced risk of maternal depressive symptoms in the postnatal period.[44] However, one randomized controlled trial, the DHA to Optimize Mother Infant Outcome (DOMInO trial), did not find improved cognitive and language development in early childhood of the offspring of mothers who used DHA-rich fish oil capsules during pregnancy compared with vegetable oil capsules, and there were not lower levels of postpartum depression in mothers who took DHA.[45] The supplement used in the DOMInO trial contained 800 mg/day of DHA and 100 mg/day of eicosapentaenoic acid (EPA). The authors did demonstrate that supplementation with predominantly DHA in pregnancy caused a small to modest increase in the duration of gestation. The effect of DHA treatment on gestational length was most notable at the extremes. In the DHA group, significantly fewer infants were born less than 34 weeks' gestation but significantly more women were induced or had cesarean sections because they were postterm. The clinical significance of these findings is difficult to balance, although the reduction in preterm birth at less than 34 weeks' gestation was also associated with fewer low-birth-weight infants and fewer admissions to neonatal intensive care in the DHA group. Other studies on omega-3 supplements and pregnancy are ongoing.

VEGETARIANS

Approximately 2.5% of adults in the United States describe themselves as vegetarian. The American Dietetic Association and Dieticians of Canada have stated that well-planned lacto-ovo vegetarian and vegan diets are appropriate for all stages of the life cycle, including during pregnancy and lactation.[46] Studies of birth weight show that neonates born to vegetarians are similar to nonvegetarians and well within birth weight norms for gestational age.[47] Pregnant vegans need to be vigilant about obtaining adequate protein, as well as reliable sources of B_{12} and zinc from their diet. Vegans can meet vitamin B_{12} needs with the use of foods fortified with vitamin B_{12}, such as yeast extracts, vegetable stock, veggie burgers, textured vegetable protein, soymilk, vegetable and sunflower margarines, and breakfast cereals. Unreliable and therefore inappropriate sources of vitamin B_{12} are tempeh, sea vegetables, and algae, since these foods may contain vitamin B_{12} analogues, substances that mimic vitamin B_{12} but actually block vitamin B_{12} absorption. Thus, there are no natural B_{12} sources available for a vegan diet, but fortified foods can be utilized.

Some studies have found that cord blood levels of the omega-3 fatty acid DHA are lower in infants of vegetarian mothers.[48] This fatty acid is most often found in fish oil and thus would be limited in the diets of vegetarians. Although DHA plays a role in the development of the brain and nervous system, the clinical significance of this observation is not known.

FOOD SAFETY

Several food-borne illnesses are of particular concern in pregnancy. *Listeria monocytogenes* is a gram-positive rod-shaped bacterium found in soil, water, and manure used as fertilizer. Uncooked meats and processed foods can become contaminated with listeria after preparation, such as soft cheeses, cold cuts from the deli counter, and ready-to-eat foods such as hot dogs, since contamination may occur after cooking but before packaging. Foods or dairy products that contain unpasteurized (raw) milk may contain the bacterium. Listeria is killed by pasteurization and cooking.

Listeria infection is a food-borne disease that, in immunocompetent individuals, is often a self-limited and mild febrile gastrointestinal process. Pregnant women are approximately 20 times more likely than other healthy adults to get listeriosis, and about one-third of all listeriosis cases happen during pregnancy. Infected pregnant women may experience only a mild, flu-like illness. However, listeria has a predilection for the placenta and can infect the fetus and neonate. In some cases, infections during pregnancy can lead to miscarriage, stillbirth, premature delivery, or neonatal infection.

Simple precautions during pregnancy can prevent listeria infection. The Center for Disease Control recommends that pregnant women avoid eating lunchmeats, hot dogs, or prepared foods from the deli counter unless they are reheated until they are hot and steamy throughout. Pregnant women should also avoid soft cheeses such as feta, Brie, and Camembert, blue-veined cheeses, or Mexican-style cheeses such as queso blanco, queso fresco, and Panela, unless they have labels that clearly state they are made from pasteurized milk.[49] Most pregnant women have limited knowledge of listeriosis prevention. A recent study suggests that most women were aware of avoiding eating unpasteurized dairy products, but were unaware of the risk associated with ready-to-eat foods.[50]

Toxoplasma gondii infection is caused by a parasite and, in immunocompetent individuals, is usually either an asymptomatic or self-limited flu-like syndrome consisting of fever, malaise, and lymphadenopathy. Toxoplasmosis can cause a mild flu-like illness in the mother during pregnancy, but can be then transmitted to the fetus and cause severe issues, especially if transmitted in the first trimester. In utero infection can result in mental retardation, blindness, and seizures.

Toxoplasma is transmitted to humans in three major ways: ingestion of raw or inadequately cooked infected meat; ingestion of oocysts, an environmentally resistant form of the organism that cats pass in their feces; and a newly infected pregnant woman passing the infection to her unborn fetus. Approximately half of toxoplasmosis infections are caused by eating contaminated meat. Immunity to toxoplasmosis is long lasting, but most U.S. adults have not been exposed to the pathogen. It is estimated that 23% of U.S. adults and approximately 14% of women of childbearing age are immune.[51] Thus, prevention is a key issue for women of childbearing age.

Pregnant women should be instructed on lifestyle and dietary precautions to prevent toxoplasma infection. These include cooking meat well, and peeling or washing fruits

and vegetables before eating. Cross contamination in the kitchen can be avoided by cleaning cooking surfaces and utensils after they have come in contact with uncooked food. Pregnant women should be counseled to avoid changing cat litter.

Fetal exposure to mercury is a health concern, because mercury is a neurotoxin. Humans are primarily exposed to mercury by consuming fish. Mercury exists in three forms: metallic, inorganic, and organic. Metallic mercury (elemental or pure form of mercury) is a metal that is liquid at room temperature and is the form used in thermometers and dental amalgam. Inorganic mercury occurs when mercury combines with chlorine, sulfur, or oxygen. Mercury enters the environment as a pollutant, most commonly from coal-fired power plants. Inorganic mercury is released into the environment in the form of air pollution, pesticides, and medical waste and accumulates in streams and oceans. Humans do not readily absorb inorganic mercury, but microorganisms in the environment can convert inorganic mercury to organic mercury. When mercury combines with carbon, the compounds are called organic mercury, the most common of which is methylmercury.[52] This form is absorbable by animals and humans, and when consumed by animals low on the food chain, it later becomes more concentrated in larger longer-lived predatory fish at the top of the food chain. Nearly all fish contain trace amounts of mercury, but these trace amounts are not harmful. However, the large predator fish accumulate the highest levels of mercury. Mercury is accumulated in humans primarily by eating fish.

Fish and shellfish are an important part of a healthy diet. However, because nearly all contain trace amounts of mercury, pregnant women, breast-feeding women, and young children should avoid seafood known to be high in mercury and limit total seafood consumption. The Environment Protection Agency recommends that the following fish be avoided in pregnancy: swordfish, shark, king mackerel, and tilefish. In addition, it is recommended that local fish advisories be followed regarding the safety of fish caught in lakes, rivers, and coastal areas. Since all fish contain some mercury, pregnant women should limit total intake of seafood to an average of 12 oz, or about two average servings, per week. Albacore ("white") tuna should be limited to 6 oz (one average meal) per week. Most women rarely exceed these amounts. The more variety in the types of fish eaten, the less likely any one will have excessive levels of mercury.[52–55]

Consumption of seafood has many benefits for both mother and fetus, and it is important that pregnant women not be overly restrictive in their seafood intake. Seafood is the major natural food source of the omega-3 fatty acids DHA and EPA, which are necessary for optimum fetal neural development. Indeed, a recent study found that consumption of fish during pregnancy outweighs any risks associated with trace contamination, since risks from the loss of nutrients were greater than the risks of harm from exposure to trace contaminants.[43] In this study, low maternal seafood intake was associated with an increased risk of children being in the lowest quartile for verbal intelligence quotient (IQ). Thus, worries about contamination need to be balanced with the need to ensure adequate maternal intake of these essential fatty acids, especially through fish consumption that are low in mercury.

CAFFEINE

Data are conflicting with regard to the effect of caffeine on pregnancy. Most authors agree that the primary concern with caffeine exposure in pregnancy is an increased risk of miscarriage; however, the magnitude of that risk varies in different studies. Caffeine passes through the placenta to the fetus. Epidemiologic evidence suggests that caffeine may be associated with an increased risk of spontaneous abortion in the first trimester. One of the most widely quoted studies on caffeine consumption and miscarriage found that there are more spontaneous abortions in women who ingest at least 100 mg of caffeine per day, and the risk increases with larger amounts of caffeine (100–299 mg per day: odds ratio, 1.3; 95% confidence interval, 0.9–1.8; 300–499 mg per day: odds ratio, 1.4; 95% confidence interval, 0.9–2.0; and 500 mg or more per day: odds ratio, 2.2; 95% confidence interval, 1.3–3.8).[56] There is wide individual variability in caffeine metabolism and clearance, and other studies have found differences in susceptibility to the effects of caffeine based upon enzyme activity differences from one individual to another.[57] It is generally recommended that pregnant women keep consumption of caffeine at or below 150 mg of caffeine per day. There have been some associations between caffeine intake and difficulties conceiving for women. This has not, however, been a consistent finding in all studies. There are approximately 100 mg of caffeine in a cup of coffee, 50 mg in tea, though this varies widely with brews and brands.

ALCOHOL

Alcohol consumption during pregnancy can lead to adverse physical and neurodevelopmental outcomes in offspring. Alcohol consumption can result in teratogenesis, including fetal facial dysmorphology and damage to the central nervous system.[58] There is no known safe level of alcohol consumption in pregnancy, and several studies have suggested that even low levels of alcohol intake, such as less than one drink per week, might be associated with. Several studies have found that even low levels of alcohol intake, <1 drink per week during pregnancy, may be associated with mental health problems and adverse child behaviors at 6–7 years of age.[59,60] However, there is controversy about the issue of low-level exposure, as a study from Australia suggested that mild gestational drinking is not associated with adverse fetal effects and may even be associated with favorable outcomes as compared to "no drinking."[61] Methodological limitations in this and other studies of alcohol use in pregnancy make drawing clear conclusions difficult, but there does appear to be a dose–response curve with respect to alcohol exposure *in utero* and adverse pediatric outcomes.

SMOKING

Smoking is known to increase a host of pregnancy-related complications, including miscarriage, premature delivery, intrauterine growth restriction, placental abruption, and sudden infant death syndrome. Smoking is the one of the most important modifiable causes of poor pregnancy outcomes in the United States, and health care providers should be certain to identify pregnant women who smoke and offer support and treatment to increase quit rates. Pregnancy appears to motivate women to stop smoking, as 46% of women quit smoking just before or during pregnancy.[62] Smoking cessation or a reduction in the number of cigarettes per day during pregnancy reduces these risks.[63] The risks of smoking during pregnancy also extend beyond pregnancy, since children born to mothers who smoke during pregnancy are at an increased risk of asthma, infantile colic, and childhood obesity.[64–66] Although quitting smoking before 15 weeks of pregnancy results in the greatest benefits for the pregnant woman and fetus, quitting at any point is beneficial. For example, smoking cessation before the third trimester can eliminate much of the reduction in birth weight caused by maternal smoking.[67]

The five As is an office-based intervention that can help health care providers work with pregnant women to quit smoking.

FIVE AS OF SMOKING CESSATION

1. *ASK* the patient about smoking status at the first prenatal visit and follow-up with her at subsequent visits. The patient should choose the statement that best describes her smoking status:
   a. I have NEVER smoked or have smoked LESS THAN 100 cigarettes in my lifetime.
   b. I stopped smoking BEFORE I found out I was pregnant, and I am not smoking now.
   c. I stopped smoking AFTER I found out I was pregnant, and I am not smoking now.
   d. I smoke some now, but I have cut down on the number of cigarettes I smoke SINCE I found out I was pregnant.
   e. I smoke regularly now, about the same as BEFORE I found out I was pregnant.

   If the patient stopped smoking before or after she found out she was pregnant (b or c), reinforce her decision to quit, congratulate her on success in quitting, and encourage her to stay smoke-free throughout pregnancy and postpartum. If the patient is still smoking (d or e), document smoking status in her medical record, and proceed to Advise, Assess, Assist, and Arrange.
2. *ADVISE* the patient who smokes to stop by providing advice to quit with information about the risks of continued smoking to the woman, fetus, and newborn.
3. *ASSESS* the patient's willingness to attempt to quit smoking at the time. Quitting advice, assessment, and motivational assistance should be offered at subsequent prenatal care visits.
4. *ASSIST* the patient who is interested in quitting by providing pregnancy-specific, self-help smoking cessation materials. Support the importance of having smoke-free space at home and seeking out a "quitting buddy," such as a former smoker or nonsmoker. Encourage the patient to talk about the process of quitting. Offer a direct referral to the smoker's quit line (1-800-QUIT NOW) to provide ongoing counseling and support.
5. *ARRANGE* follow-up visits to track the progress of the patient's attempt to quit smoking. For current and former smokers, smoking status should be monitored and recorded throughout pregnancy, providing opportunities to congratulate and support success, reinforce steps taken toward quitting, and advise those still considering a cessation attempt.

Source: Modified from Fiore MC, Jaen CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, et al. Treating tobacco use and dependence: 2008 update-clinical practice guidelines. Rockville (MD): US Department of Health and Human Services, Public Health Service, Agency for Health care Research and Quality, 2008.

The use of nicotine replacement therapy to aid in quitting smoking in pregnancy should be undertaken with close supervision and after careful consideration and discussion with the patient of the known risks of continued smoking and the possible risks of nicotine replacement therapy. If nicotine replacement is used, it should be done with the clear resolve of the patient to quit smoking. Many small studies using nicotine replacement do not show increased risks to the pregnancy, but it is not yet clear if this therapy results in improved pregnancy outcomes.[63]

CONCLUSION

Our knowledge about nutrition and lifestyle issues in pregnancy has grown tremendously in the last decade. Pregnancy is a time when many women are motivated to make lifestyle changes such as diet and exercise that can make a difference in the future health of their babies, as well as to their own health. While some foods may cause harm to the fetus, it is also clear that certain nutrients that are consumed during pregnancy may be one way to prevent or mitigate disease in her future child. Thus, eating for two is doubly important. Pregnancy is not a state of confinement; it is a state of health, and evidence-based guidance and counseling about diet and lifestyle can promote healthy mothers and babies.

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68 Exercise in Pregnancy

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CONTENTS

Benefits of Exercise in Pregnancy 841
Weight Management 841
Glycemic Control 842
Reduction of Risk of Hypertensive Disorders in Pregnancy 843
Psychological Benefits 844
Improvement in Musculoskeletal Pain 844
Lowered Rates of Intervention during the Time of Labor and Delivery 844
Other Benefits 844
Risks of Exercise in Pregnancy 845
Spontaneous Abortion 845
Fetal Distress 845
Low Birth Weight 846
Preterm Delivery 846
Maternal Injury 847
Contraindications to Exercise in Pregnancy 847
Recommendations for Exercise in Pregnancy 847
Exercise Prescription 848
Intensity of Training 848
Duration/Frequency 848
Types of Exercise 848
Know When to Stop 849
References 849

The recommendations regarding exercise in pregnancy have been in flux over the years. In 1985, the American College of Obstetricians and Gynecologists provided the first guidelines for exercise during pregnancy based on the limited evidence available [1]. Prior to this time, women were often told to avoid strenuous physical activity, stretching, or bending for fear of pregnancy complications that might result. Since that time, a great deal of research has been done focusing on the safety, risks, and benefits of physical activity in pregnancy. Currently, both the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists encourage regular physical activity during pregnancy as the benefits are thought to far outweigh the risks [2]. This chapter will review the benefits and potential risks of exercise in pregnancy, the contraindications to exercise in pregnancy, and the current recommendations for type, intensity, frequency, and duration of activity in pregnancy.

BENEFITS OF EXERCISE IN PREGNANCY

Weight Management

The population as a whole is heavier today than in previous times. A greater percentage of women are entering pregnancy overweight or obese, and many are gaining significantly more weight during pregnancy than is recommended [3]. Excessive weight gain is emerging as an important predictor of adverse pregnancy outcomes. Independent of prepregnancy weight, women who gain excessively during the course of the pregnancy are more likely to deliver by cesarean section, have an unsuccessful trial of labor after cesarean section, develop hypertension or preeclampsia, deliver preterm, have a macrosomic or small-for-gestational-age infant, retain excessive weight after delivery, and become overweight or obese later in life [4–7]. The Institute of Medicine recently reexamined the guidelines for weight gain during pregnancy and

TABLE 68.1
Recommendations for Weight Gain during Singleton Pregnancy Based on the Current IOM Guidelines

Prepregnancy BMI (kg/m^2)	Recommended Weight Gain (lb)	Rate of Weight Gain Suggested in Second and Third Trimesters (lb/week)
<18 (underweight)	28–40	1
18.5–24.9 (normal weight)	25–35	1
25.0–29.9 (overweight)	15–25	0.6
>30 (obese)	11–20	0.5

Source: Institute of Medicine, Brief report: Weight gain during pregnancy: Reexamining the guidelines, May 2009.

provided new recommendations for weight gain based on prepregnancy body mass index (BMI; Table 68.1) [3].

Exercising during pregnancy has been shown to reduce excess weight gain and decrease weight retention postpartum. In one study of women who continued their preconception exercise regimen compared to women who stopped or significantly reduced their level of physical activity during pregnancy, women who continued to exercise had a reduced rate of weight gain (though within the normal range) and decreased subcutaneous fat deposition later in pregnancy [8]. Stuebe et al. assessed the association of physical activity with excessive weight gain among women enrolled in the Project Viva cohort study [4]. The cohort included women receiving prenatal care in one of eight urban and suburban obstetrical offices in a multispecialty group practice in eastern Massachusetts. This study of 1388 women included information about prepregnancy weight, gestational weight gain, and dietary and exercise habits. Within this cohort of women, 379 (27%) were overweight entering the pregnancy and 703 (51%) experienced excessive weight gain based on the 1998 Institute of Medicine guidelines for weight gain in pregnancy. The study concluded that walking (30 min daily), vigorous physical activity in the second trimester, and increased total activity were inversely associated with excessive weight gain, while a sedentary lifestyle was associated with a nonsignificant increase in the risk of excessive weight gain [4]. These are just two studies among many that demonstrate the positive role of exercise in weight management during pregnancy.

Postpartum weight retention is strongly related to weight gain during the pregnancy [9,10]. Average estimates of weight retention postpartum range from −0.27 kg (0.6 lb) to 3.0 kg (6.6 lb) though this varies significantly between different studies [9]. Scholl et al. categorized the rate of gestational weight gain per trimester as more, less, or appropriate compared to the recommended amount of weight gain as per the Institute of Medicine guidelines at the time of the study. They found that at 6 months postpartum, women with an excessive rate of weight gain during the pregnancy weighed 12% (7.9 kg or 17.4 lb) more than they did prepregnancy and retained about 40% of the gestational weight gain. This was in contrast to women who gained weight at or below the recommended guidelines, who were only 5%–7% (3.2 kg or 7.1 lb) heavier at 6 months postpartum [11]. Rooney and Schauberger found that women who gained excessive weight during pregnancy and failed to lose the weight by 6 months postpartum were as much as 15 lb heavier at 10-year follow-up [12]. Women who exercise during pregnancy may be less likely to gain more than the recommended amount of weight and be at less risk of postpartum weight retention and lasting weight retention or obesity.

Glycemic Control

Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications affecting approximately 7% of pregnancies in the United States. It is highest among obese and overweight women [13]. GDM is associated with adverse perinatal outcomes including an increased risk for macrosomia, maternal and neonatal birth injury, neonatal hypoglycemia and hyperbilirubinemia, as well as an increased risk of impaired glucose intolerance and type 2 diabetes mellitus in the years following pregnancy (Table 68.2) [14].

Insulin resistance in normal pregnancy is estimated to increase by 40%–70% and is related to the increase in cortisol, growth hormone, human placental lactogen, estrogen, progesterone, and prolactin associated with the growth of the fetal–placental unit [14]. An increase in insulin resistance decreases maternal blood glucose uptake by the muscles, ensuring an adequate glucose supply for fetal growth and development. This balance can tip, however, leading to abnormally high maternal blood glucose and insulin concentrations yielding the diagnosis of GDM [15]. Physical activity has long been known to improve glucose homeostasis by increasing insulin sensitivity in maternal skeletal muscle and increasing lean body mass [16]. A sedentary lifestyle is one of the modifiable risk factors associated with GDM [15]. Physical activity decreases the risk of developing GDM and can serve as an adjunctive therapy in the treatment of GDM. This is of particular importance since a significant number of women with GDM go on to develop type 2 diabetes later in life.

TABLE 68.2
Risks Associated with Gestational Diabetes

Mother	Birth trauma, cesarean delivery, preeclampsia, gestational hypertension, Type 2 diabetes
Fetus	Hyperinsulinemia, cardiomyopathy, stillbirth, macrosomia, birth injury
Newborn	Respiratory distress syndrome, hypoglycemia, hyperbilirubinemia, cardiomyopathy
Child/adult	Obesity, type 2 diabetes, metabolic syndrome

Source: Adapted from Pridjian, G. and Benjamin, T.D., *Obstet. Gynecol. Clin. North Am.*, 37, 255, 2010.

Many studies have examined the impact of exercise before and during pregnancy on the development of gestational diabetes. Though there are no randomized controlled studies demonstrating exercise as a means for prevention of GDM, current evidence suggests a benefit. The influence of recreational activity on GDM risk was evaluated in a case–control study of 155 women with GDM and 386 normotensive nondiabetic pregnant controls. After adjustment for age, race, parity, prepregnancy BMI, and smoking, physical activity both prepregnancy and during pregnancy were associated with a significant reduction in GDM by 51% and 48%, respectively [17]. Similar results were confirmed in a prospective cohort study of more than 900 normotensive nondiabetic women [18]. These data are supported by a recent meta-analysis published by Tobias et al. [19]. Prepregnancy physical activity was assessed in 34,929 total participants, yielding a pooled odds ratio of 0.45 (95% CI 0.28–0.75) for developing GDM when comparing women in the highest category of prepregnancy physical activity with those in the lowest. Exercise during early pregnancy was also found to be protective, yielding an odds ratio of 0.76 (95% CI 0.7–0.83).

Exercise serves not only to prevent gestational diabetes but also as an adjunctive treatment in women who have been previously diagnosed. The American Diabetes Association suggests that women without medical or obstetrical contraindications to exercise should be encouraged to start or continue a program of moderate exercise as part of treatment for GDM [13]. Jovanovic-Peterson et al. randomized a small group of women diagnosed with GDM (N = 19) to diet alone versus diet plus exercise with an arm ergometer [20]. They found lower glycosylated hemoglobin, fasting, and 1 h postprandial plasma glucose concentrations in the diet-plus-exercise group as compared to diet alone [20]. Garcia-Patterson et al. found that women with GDM who performed light postprandial walking also showed improvement in postprandial glucose concentrations [21]. Bung et al. randomized women diagnosed with GDM who failed to attain adequate glucose control with diet alone to insulin plus diet versus exercise plus diet. There were no significant differences between the two groups in terms of glycemic control, maternal outcomes, or fetal outcomes and thus concluded exercise to be a valuable tool in the treatment of GDM [22].

Reduction of Risk of Hypertensive Disorders in Pregnancy

Hypertensive disorders occur in approximately 12%–22% of pregnancies and are among the leading causes of maternal mortality in the United States, accounting for 15%–20% of maternal deaths [23]. There is a spectrum of hypertensive disorders that affect pregnancy including chronic hypertension, gestational hypertension, preeclampsia, and HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Maternal complications resulting from hypertensive disorders in pregnancy can be catastrophic and include abruptio placentae, disseminated intravascular coagulation, cerebral hemorrhage, seizure, hepatic failure, and acute renal failure [24]. There are also significant risks to the fetus including intrauterine growth restriction, oligohydramnios, preterm delivery, and intrauterine fetal demise [24].

Metabolic disturbances associated with preeclampsia include but are not limited to hypertriglyceridemia, excessive lipid peroxidation, antioxidant deficiency, insulin resistance, plasma elevations of proinflammatory cytokines and C-reactive protein, and a thromboxane–prostacyclin imbalance favoring vasoconstriction [15]. There is considerable overlap between the epidemiology of preeclampsia with that of essential hypertension and atherosclerotic vascular disease [15]. Nonpregnant women with hypertension or vascular disease are encouraged to exercise in order to improve their blood pressures and/or halt disease progression [25]. It is likely then that increased physical activity would be associated with a decreased risk of hypertensive disorders in pregnancy.

To date, there are few studies looking at the relationship between the hypertensive disorders of pregnancy and maternal exercise. Yeo et al. suggest that exercise lowers blood pressure during pregnancy (as it does in nonpregnant women) based on the results from a randomized controlled trial conducted on a small group of pregnant women recruited before 14 weeks of gestation [26]. All women had a history significant for mild hypertension, gestational hypertensive disorders, or a family history of hypertensive disorders and were therefore thought to be at significant risk for developing hypertension in their current pregnancy. Among women randomized to the exercise arm, there was a strong trend toward lowered diastolic blood pressures though their results were not statistically significant. Other mechanisms by which exercise may reduce the risk of hypertensive disorders in pregnancy, and specifically the risk of preeclampsia, include improving pregnancy-induced dyslipidemia, decreasing concentrations of proinflammatory cytokines, and decreasing insulin resistance [15].

Sorensen et al. conducted a case–control study between 1998 and 2001 in order to characterize the relation between recreational physical activity and the risk of preeclampsia [27]. They identified 201 women with preeclampsia and 383 normotensive controls. All patients were given a structured questionnaire during their postpartum stay. Women who participated in recreational physical activity (e.g., brisk walking, stair climbing) during the first 20 weeks of pregnancy experienced a 35% reduction in the risk of preeclampsia after controlling for maternal age, race, parity, tobacco use, and prepregnancy BMI. Increased energy expenditure was inversely associated with the risk of preeclampsia. These results were similar to those published by Marcoux et al. in 1989 [28]. In this case–control study, women participating in recreational physical activity in the first 20 weeks of pregnancy were significantly less likely to develop gestational hypertension or preeclampsia.

More prospective research is needed to further characterize the relationship between exercise and maternal hypertensive disorders, but current data suggest that exercise before pregnancy and during the first 20 weeks plays a protective role.

Psychological Benefits

Maternal mental health has been reported to have a significant impact on physical health and pregnancy outcome. Mood fluctuations are common during and after pregnancy with the prevalence of prenatal depression nearly 11% [29] and postpartum depression up to 16% [30]. Several factors may increase the risk for mood disturbances during pregnancy including reproductive hormones, psychosocial stressors, isolation, personal or family history of depression, and chronic medical conditions [15]. Consequences of untreated perinatal mood disorders can be significant and are associated substance use, lack of compliance with medical care, disruption of relationships, preterm delivery, low birth weight, impaired mother–child bonding, and childhood behavioral issues [15,31,32].

Physical activity is linked with improvement of mental health in nonpregnant woman and likely confers the same benefits during pregnancy. The advantageous effects of physical activity on mental health likely result from a combination of psychological and physiological components. Proposed hypotheses regarding the psychological impact of exercise on mood include distraction, self-efficacy, social interaction [33], and improved body image [34]. Physiological mechanisms by which exercise may improve mood include the release of monoamines and endorphins [33]. Improvements noted in women who engage in physical activity include increased vigor, decreased fatigue, less stress and anxiety, decreased symptoms of negative mood and depression, and improved self-image [35].

Wallace et al. [36] found that pregnant women participating in an aerobic exercise program during pregnancy had higher self-esteem and lower fatigue than sedentary women. Goodwin et al. [37] found that women who exercised during pregnancy reported better feelings of overall well-being and had fewer symptoms of somatic discomfort, anxiety, and insomnia. These results were echoed by Marquez-Sterling et al. who demonstrated improvement in energy levels and body satisfaction in a small group of previously sedentary pregnant women randomized to an exercise program as compared to controls that remained sedentary [38]. Similarly, pregnant adolescents participating in a 6 week aerobic exercise program reported significantly less depressive symptoms and an increase in self-esteem compared to controls [39]. Given the prevalence of symptoms associated with depression and anxiety in pregnancy and the negative impact that these symptoms may have on pregnancy outcome, an exercise regimen may be a helpful tool in the maintenance of emotional well-being. Exercise during pregnancy has also been associated with improved mood postpartum and therefore may plan an important role in preventing postpartum depression [15,40].

Improvement in Musculoskeletal Pain

Studies indicate that 50%–90% of women experience some degree of musculoskeletal discomfort during pregnancy, most commonly low back and pelvic girdle pain [15,41]. Proposed mechanisms for pregnancy-associated musculoskeletal pain include a change in weight distribution and posture as well as hormonal influence on joint laxity [42]. Musculoskeletal discomfort tends to worsen over the course of the pregnancy and has been linked to disability, functional impairment, and missed work [31].

A regular exercise program before pregnancy and during early pregnancy likely reduces the risk of back pain during pregnancy [43,44]. Sternfeld et al. found that women who exercised more during early pregnancy had statistically fewer discomforts later in pregnancy and those symptoms were inversely proportional with the level of exercise women performed [44]. In women who already have low back pain associated with pregnancy, exercises to strengthen core abdominal and back muscles are likely of benefit. Sitting pelvic tilt exercises and aquatic exercises have both been shown to decrease the incidence and severity of low back pain experienced in pregnancy [45,46]. Yoga is also thought to play a role in improving back pain as well [47], possibly secondary to improvement in core strength. Beddoe et al. [31] analyzed the effect of a 7 week mindfulness-based yoga intervention on several variables, one of which was pain. They found women in the second trimester experienced fewer hours of pain and less pain interference with activity from baseline to post-intervention.

Lowered Rates of Intervention during the Time of Labor and Delivery

Though the evidence is of limited quality, some studies suggest that less medical intervention is required during labor in women who exercised routinely during pregnancy. These interventions may include analgesia, labor augmentation, operative vaginal delivery, and cesarean delivery. A case–control study by Hall and Kaufman demonstrated a lower incidence of cesarean delivery and a shorter peripartum hospitalization course in women who participated in a conditioning program over the course of their pregnancy [48]. Clapp compared the onset, course, and outcome of labor among women who continued their prepregnancy exercise regimen throughout gestation with those who discontinued their exercise routine before the end of the first trimester. Results indicated a lower incidence of operative vaginal delivery and cesarean delivery as well as a shorter active phase of labor among the women who delivered vaginally [49]. A randomized controlled trial looking at the effect of water aerobic in pregnancy did not find a difference in the duration of labor or type of delivery; however, they found that women who participated in the exercise group were significantly less likely to request analgesia [50]. This was true after controlling for parity and level of education as well.

Other Benefits

Women who are active during pregnancy may report less nausea, heartburn, leg cramps, varicose veins, constipation, and insomnia [43,50].

RISKS OF EXERCISE IN PREGNANCY

With regard to the risks of exercise in pregnancy, there are many conflicting studies and most are limited in design and quality. Concerns regarding exercise in pregnancy are generally related to the risk of spontaneous abortion (SAB), fetal distress, low birth weight, preterm delivery, and maternal injury. Physiological mechanisms hypothesized to mediate a potentially detrimental effect of maternal exercise on embryonic and fetal health include the following:

1. Reduction of placental blood flow secondary to redirection toward working skeletal muscles [51,52]
2. Rise in core body temperature/hyperthermia [53,54]
3. Release of hormones (adrenaline, noradrenaline) stimulating uterine contractility [55,56]
4. Hypoglycemia [57]

Spontaneous Abortion

The current literature yields mixed results when evaluating the risk of SAB in relation to a woman's physical activity level. Hjollund et al. [58] followed a cohort of women planning their first pregnancy in order to assess the relationship between physical strain and SAB. Women were recruited between 1992 and 1994 and followed from the time of termination of contraception until pregnancy was achieved for a maximum of six menstrual cycles. Women recorded their level of daily physical strain in a structured diary, and pregnancy outcomes were analyzed with an SAB being defined as pregnancy loss prior to 28 weeks of gestation in this study. They found an increased risk of SAB among women who reported high physical strain during the time of implantation of the embryo as calculated based on menstrual cycle length. No clear effect was seen at any other time point. Madsen et al. [59] found similar results from a study within the Danish National Birth Cohort in that women who exercised, high-impact exercisers in particular, had an increased risk of SAB prior to 18 weeks of gestation as compared to sedentary controls. Caution must be made when interpreting these results, given the potential bias that results from largely retrospective data collection and confounders such as chronic medical conditions that were not accounted for in the results.

Other studies have found substantially different results. For example, Clapp [60] followed exercise performance before and during pregnancy in 47 recreational runners, 40 aerobic dancers, and 28 controls. In this group of women, SAB occurred in 19% of pregnancies and was not statistically different among the groups and he therefore concluded that exercise in the preconceptional period and early pregnancy does not appreciably alter early pregnancy outcomes. In one large prospective study with 158 active women and 83 matched sedentary controls, there was no association between exercise and the risk of infertility, SAB, or other adverse pregnancy outcome [61]. Also, Latka et al. [62] reported a lower risk of chromosomally normal SAB among women who participated in leisure-time exercise.

In summary, the data are quite limited in both the number and the quality of studies examining the relationship between physical activity and risk of SAB. At this point, the benefits of exercise in pregnancy as mentioned earlier likely far outweigh the risk of early pregnancy loss, if there is any risk at all.

Fetal Distress

Studies of animal models have demonstrated that maternal exercise may reduce uterine blood flow secondary to redistribution toward maternal skeletal muscle and thus may result in relative fetal hypoxia [52]. Fetal heart rate (FHR) monitoring is a noninvasive method for determining fetal well-being with specific patterns recognized to be associated with fetal hypoxia [63]. For this reason, it is frequently used in studies attempting to evaluate the risk of fetal distress associated with maternal exercise. The most common response to maternal exercise is a rise in FHR, which returns to baseline after cessation of exercise [53,64] and is likely a response to a slight drop in oxygenation secondary to increased maternal consumption [63], release of maternal catecholamines, and an increase in maternal core body temperature [64]. Less common and more concerning are the few reports of transient bradycardia occurring with or following exercise [65]. Another technique used to assess fetal status is ultrasonography with attention to fetal movements and breathing as these are thought to be markers of fetal well-being [66].

Webb et al. [67] sought to evaluate the effects of acute and chronic maternal exercise on FHR. In this study, a group of women took part in a conditioning program during the second and third trimesters and were matched with sedentary controls. At three different time points, both the study group and the controls were asked to perform on a cycle ergometer. Maternal heart rate, blood pressure, and temperature were monitored as was the FHR. While the most common response was a rise in FHR baseline by approximately 10–20 bpm during exercise, there were three incidences of fetal bradycardia (one after 10 min of exercise and two following cessation of exercise). All FHRs normalized and none were associated with adverse pregnancy outcomes. Of note, there were no differences in the FHR response between conditioned and sedentary women [67]. Manders et al. described similar FHR findings and added that fetal body movements were decreased immediately following cessation of exercise whereas fetal breathing movements were increased during this time frame [68]. Winn et al., on the other hand, found a decrease in the total duration and frequency of fetal breathing and fetal body movement following acute maternal exercise [69]. Neither Manders nor Winn reported adverse pregnancy outcomes associated with these findings.

With regard to pregnancy outcomes, Clapp found that women who continued to exercise regularly throughout pregnancy were actually less likely to have clinical evidence of fetal distress as indicated by the presence of meconium,

abnormal FHR tracing, or low APGAR score at the time of labor and delivery [49]. Rose et al. showed no difference in the rate of fetal or neonatal death among women who reported moderate or vigorous activity levels during the second trimesters compared to women who reported light activity [70]. It is important to recognize that neither FHR monitoring nor ultrasound is a perfect measure of fetal oxygenation or acid base status. While transient abnormalities in fetal testing have been associated with maternal exercise, there are no differences in fetal morbidity or mortality [49,67,71,72] in pregnancy outcomes.

Low Birth Weight

Exercise leads to a redistribution of blood flow toward skeletal muscle, and splanchnic blood flow (which includes uterine blood flow) may decrease substantially. With high-intensity exercise, oxygen and glucose are shunted to skeletal muscles and away from the placenta and developing fetus [65]. There has been concern that this redistribution may lead to a decrease in birth weight or intrauterine growth restriction, but studies are inconsistent. Recent literature suggests that the timing, volume, and intensity of exercise likely impact placental and fetal growth [73,74].

Though the majority of the data regarding the effects of exercise on birth weight stem from retrospective cohort studies, two recent prospective randomized studies have been conducted to evaluate the relationship between exercise and fetoplacental growth. In the first, women who did not exercise regularly were randomly assigned at 8 weeks of gestation either to no exercise or to weight-bearing exercise—three to five times per week for the remainder of the pregnancy [73]. The midtrimester placental growth rate was faster and the birth weights were increased significantly (3.75 vs. 3.49 kg) in the exercise group.

A follow-up study aimed to further determine the effect of the timing and the volume of exercise on placental and fetal growth during pregnancy. Clapp et al. randomly assigned women at 8 weeks of gestation who exercised regularly to one of three exercise regimens for the remainder of the pregnancy [74]. The first group increased their volume of exercise in the third trimester, the second maintained a moderate exercise regimen throughout the pregnancy, and the third decreased their exercise volume in the third trimester. Women who maintained a moderate exercise regimen or increased their exercise volume in the third trimester had significantly slower fetoplacental growth than women who decreased their exercise volume in the third trimester. While these infants were significantly lighter (3.39 vs. 3.81 kg), there was no increased risk of intrauterine growth restriction or birth weight classified as small for gestational age [74].

In summary, exercise in early pregnancy seems to promote placental growth and development [73,74], which may account for the finding that many women who start or maintain exercise regimens during pregnancy actually have increased mean birth weights when compared to less active or sedentary controls [75–77]. Vigorous and high-volume activity later in pregnancy does appear to be associated with a small decrease in mean birth weight [8,49,74,78], which some believe to be the result of a loss of fat mass in the fetuses of endurance exercisers, while others feel this may be related to gestational age at delivery (addressed in the following text) or maternal weight gain [78]. In either case, there does not appear to be an increase in intrauterine growth restriction or small-for-gestational-age infants among women who exercise during pregnancy [79,80].

Preterm Delivery

Preterm birth is defined as delivery prior to 37 weeks of gestation and is associated with significant neonatal morbidity and mortality, especially for infants born prior to 32 weeks of gestation [81]. Approximately 12.5% of deliveries in the United States are preterm, and this number has been rising over the last two decades [81]. Lifestyle-related risk factors for preterm birth include maternal stress, smoking, and intensity and duration of work [81]. An association between physically demanding occupations and the risk of preterm birth has been described in the literature. The relationship between exercise and the risk of preterm delivery is questionable [82].

During exercise, catecholamine output increases substantially, which could in turn stimulate uterine activity [83]. However, studies are conflicting whether physical exercise actually increases uterine contractility [56]. The most recent literature suggests that exercise or leisure-time physical activity does not increase the risk for preterm delivery and may instead actually be protective. In a study published in 1990, Clapp compared birth weights and labor courses among women who maintained exercise at greater than or equal to 50% of preconception levels with those who stopped exercising in the first trimester [49]. The incidence of preterm labor was equivalent in the two groups at 9%. Labor did begin an average of 5 days earlier in the exercise group, which was statistically significant [49], but may be clinically irrelevant, as this did not result in preterm delivery or adverse outcomes.

Juhl et al. [56], in contrast, reported a reduced risk of preterm birth among women who engaged in some form of exercise during pregnancy as compared to sedentary women. The association was not affected by the type of exercise, and no dose–response relationship was found [56]. Important things to consider in the interpretation of these results include the reliance on patient self-report and the possibility that the women who were exercising may have been at a lower baseline risk of preterm birth, resulting in a healthy exerciser effect [56]. Randomization helps to eliminate these biases, and recently two randomized controlled trials designed to evaluate the association between exercise and gestational age at the time of delivery were published.

Barakat et al. [82] randomized previously sedentary women with singleton pregnancies to a control group or an exercise group. The exercise program consisted of light

resistance and toning exercises 3 days a week for 35 min between 12 and 39 weeks. The mean gestational age at delivery did not differ between the two groups, and there was no significant difference in the percentage of women with preterm delivery [82]. Cavalcante et al. [79] similarly randomized low-risk sedentary pregnant women to a water aerobics group or a sedentary control group, and they reported no difference in the rate of preterm delivery between the two groups.

Based on the limited available data, there is not an increased risk of preterm delivery associated with exercise during pregnancy. These studies do not address the effects of exercise on preterm birth in women who have an increased underlying risk for preterm labor. Thus, caution should be used when counseling these women with regard to exercise during the course of their gestation.

Maternal Injury

Profound physical changes occur over the course of a pregnancy. Postural changes include a significant increase in lumbar lordosis and a forward tilt of the pelvis. Combined with pregnancy-associated weight gain and a shift in the center of gravity forward, balance coordination and exercise tolerance can be greatly altered [65]. Joint laxity and mobilization are also increased secondary to the hormonal changes of pregnancy [84]. Thus, pregnant women engaging in exercise should take caution when performing high-velocity or jerking movements as they may be more prone to joint injury.

TABLE 68.3
Absolute and Relative Contraindications to Exercise in Pregnancy

Absolute Contraindications	Relative Contraindications
Preterm labor in current pregnancy	Unevaluated maternal arrhythmia
Ruptured membranes	Uncontrolled preexisting maternal medical conditions (seizure disorder, hyperthyroidism, hypertension)
Persistent second/third trimester bleeding	Orthopedic limitations
Known placenta previa	History of preterm delivery or preterm premature rupture of membranes in prior pregnancy
Incompetent cervix (± cerclage)	Eating disorders, extreme underweight/malnutrition
Multiple gestations identified at increased risk of preterm labor	
Intrauterine growth restriction or suspected placental insufficiency	
Preeclampsia	
Hemodynamically significant heart disease (valvular or ischemic)	
Restrictive lung disease	

Sources: ACOG Committee Obstetric Practice, *Int. J. Gynecol. Obstet*., 77, 79, 2002; Hammer, R.L. et al., *J. Perinat. Educ*., 9, 1, 2000; Stevenson, L., *Can. Fam. Physician*, 43, 107, 1997.

CONTRAINDICATIONS TO EXERCISE IN PREGNANCY

Understanding the absolute and relative contraindications to exercise in pregnancy is essential when counseling a patient (see Table 68.3). Any factor that may compromise maternal physiological reserve could put her health and the health of her fetus at risk. In these situations, the risks will far outweigh the exercise-related benefits. Of note, a history of sedentary lifestyle was previously described as a relative or even absolute contraindication to exercise in pregnancy as there was thought to be the potential for harm. There are now studies to show that this is unlikely and when done appropriately, beginning an exercise regimen in pregnancy is safe even for previously inactive women [79].

RECOMMENDATIONS FOR EXERCISE IN PREGNANCY

The most recent ACOG committee opinion on exercise during pregnancy and the postpartum period was published in 2002. At that time, it was recommended that in the absence of contraindications, pregnant women should engage in regular, moderate-intensity physical activity for 30 min on most, if not all, days of the week [2]. More recently, the 2008 physical activity guidelines for Americans were published by the Centers for Disease Control and Prevention, which recommends the following [85]:

1. Healthy women should get at least 150 min/week of moderate-intensity aerobic activity during and after their pregnancy. This may be broken down to 30 min/day, 5 days/week and furthermore can be done in 10 min segments of exercise.
2. For previously inactive women without medical contraindication to exercise, it is reasonable to begin a moderate-intensity exercise regimen.
3. For healthy women who regularly perform vigorous intensity aerobic activity, they may continue to do so during pregnancy so long as they stay healthy and are followed closely by a health care provider.
4. While pregnant, women should not partake in activities that involve lying directly on ones back or increase the risk of falling or abdominal trauma.

In the United States, only 16% of pregnant women comply with the physical activity recommendations compared with 26% of nonpregnant women [86]. Even healthy, otherwise active women tend to decrease physical activity in pregnancy [87]. Given the proven benefits of exercise in pregnancy, it is important to educate and encourage women to participate in moderate physical activity during the course of their gestation.

Exercise Prescription

When counseling a patient regarding an appropriate exercise regimen, there are several factors to consider: the women's age, weight, prepregnancy or current fitness level, medical history, and obstetric history. Contraindications should be ruled out or at least weighed against the potential benefits in pregnancy that exercise may confer (i.e., weight management, glucose control, reduction in the risk of hypertensive disorders, psychological benefits, and improvement in musculoskeletal pain). An exercise prescription should include recommendations for intensity, duration, frequency, and type of exercise and should be tailored to patients on an individual basis.

Intensity of Training

No safe upper limit of exercise in pregnancy has been established though many studies demonstrate that physically fit women may participate in vigorous activity without compromising the pregnancy [64]. Methods to monitor exercise intensity, including heart rate monitoring, Borg's rate of perceived exertion, and the "talk" test [88], may all be helpful in achieving a safe level of exercise. The goal is for healthy women to achieve regular moderate-intensity exercise.

Cardiovascular adaptations in pregnancy include an increased resting heart rate and a decreased maximal heart rate, which results in reduced heart rate reserve and a lowered slope of heart rate response to increasing work [89]. Thus, heart rate alone may be an inaccurate reflection of the intensity of aerobic exercise. It has been proposed that during pregnancy, the target heart rate range represents about 60%–80% of aerobic capacity [89]. Davies et al. propose that the target heart rate range for pregnant women under 20 years old is 140–155 bpm, 20–29 years old is 135–150 bpm, 30–39 years old is 130–145, and over 40 years old is 125–140 bpm [90]. Literature suggests that the target heart rate should also be adjusted according to BMI because overweight and obese pregnant women may be exercising at a higher intensity (%VO_2) than intended for a given heart rate [91]. Borg's rate of perceived exertion is a 15-point scale from 6 to 20 (see Table 68.4). A target range of 12–14, which corresponds with moderate to somewhat hard intensity, is suggested to be appropriate during pregnancy [88]. The "talk test" simply refers to exercising mothers being able to carry on a conversation while exercising [53,88]. One should be able to hold a conversation during moderate-intensity exercise. It is likely a combination of the earlier methods that allows for determination of the appropriate intensity of exercise.

Duration/Frequency

The current recommendation for exercise in pregnancy is for 150 min of exercise per week [85], and it is generally suggested that this be spread over the course of the week on most, if not all, days (rather than performed in long but infrequent sessions). During exercise, glucose levels decrease and temperature increases with time [57]. Blood glucose decreases at a faster rate and to a significantly lower level postexercise in pregnant women as compared to nonpregnant women. After 45 min of continuous exercise at 50%–60% of maximal oxygen consumption, the blood glucose in pregnant women may fall substantially, which could adversely impact the fetus [57]. It is therefore important to balance caloric intake with output, and perhaps limiting exercise sessions to 45 min or less may be advisable [89]. Core body temperature also rises but when exercise is self-paced, body temperature tends to stay within safe limits [57]. In order to avoid complications such as hyperthermia, women should exercise in a thermo-neutral environment or in controlled environmental conditions and pay careful attention to hydration and subjective feelings of heat stress [89].

TABLE 68.4
Borg's Rate of Perceived Exertion Scale

	Effort (%)	Correlates with
6	20	
7	30	Very, very light (near rest)
8	40	
9	50	Very light (gentle walking)
10	55	
11	60	Fairly light
12	65	
13	70	Somewhat hard (moderate)
14	75	
15	80	Hard
16	85	
17	90	Very hard
18	95	
19	100	Extremely hard
20	Exhaustion	

Source: Melzer, K. et al., *Am. J. Obstet. Gynecol.*, 202, 266e1, 2010.

Types of Exercise

Most forms of exercise are safe during pregnancy, though there are some that involve risks and should be avoided. Women should avoid exercises that require them to lie flat on their backs (especially after 16 weeks of gestation) or stand still for prolonged periods of time, as well as those activities that place women at risk for injury or abdominal trauma [89,92]. Reasonable activities to suggest for pregnant women include walking, jogging, cycling, aerobics, swimming, and yoga [2,89,92]. Contact sports such as soccer, basketball, hockey, or football put one at risk for abdominal trauma, and it generally thought best to avoid such activities [2]. Participation in skiing, snowboarding, gymnastics, and horseback riding comes with a significant risk for falls and thus should be discouraged [2]. Scuba diving is considered to

be particularly dangerous during pregnancy secondary to the risk of fetal decompression sickness because the fetal pulmonary circulation is unable to filter bubble formation and therefore should be avoided during pregnancy [93].

Know When to Stop

There are a few basic principles that pregnant women should adhere to: stay cool, stay hydrated, stay nourished, and know when to stop. It is important for women exercising during pregnancy to have a clear understanding of the signs and symptoms that should prompt them to stop exercising and contact a physician. Any symptoms of excessive fatigue, chest pain, shortness of breath, palpitations, dizziness, lightheadedness, difficulty walking, vaginal bleeding, uterine contractions, or decreased fetal movement should prompt immediate cessation of exercise and medical assessment as soon as possible [2,88].

For most women, the benefits of exercise far outweigh any potential risks, and clinicians should educate themselves so that they can provide evidence-based advice to pregnant women.

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69 Breast-Feeding

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CONTENTS

Introduction 853
Anatomy and Physiology of the Breast 854
Anatomy 854
Hormonal Influences 854
Milk Content 855
Benefits of Breast-Feeding 855
Maternal Benefits 855
Infant Benefits 856
Gastrointestinal Effects 856
Infectious Processes 857
Atopic Disease and Asthma 857
Other Diseases 857
Neurodevelopment 858
Practical Management of Breast-Feeding 858
Assessment of Intake Adequacy 859
Contraindications to Breast-Feeding 860
Problems Related to Breast-Feeding 860
Engorgement 860
Mastitis 861
Prior Breast Surgery 861
Medications and Lactation 861
Breast-Feeding Support 861
Pumping Breast Milk (Working and Nursing) 862
Weaning 862
Conclusion 863
References 863
Further Readings 866

INTRODUCTION

Breast-feeding is a lifestyle that promotes health for both mother and baby. Physicians and other health care providers play a major role in encouraging, teaching, and helping to manage breast-feeding. From practices as simple as ensuring educational messages through posters and brochures in the offices to communication styles that encourage breast-feeding, today's health care provider is a vital part of the team that encourages this behavior in our society.

Human breast milk is the physiological form of nutrition for infants and young children. Although formula feeding is widespread worldwide, a significant body of literature and research strongly supports infant as well as maternal benefits of breast-feeding. It is the responsibility of providers to counsel and encourage patients to breast-feed. Education on and evaluation of the mother regarding breast-feeding should begin at the initial prenatal appointment and extend through the postpartum period. The impact that providers may have on breast-feeding initiation and maintenance should not be underestimated.[1,2] There are few circumstances where breast-feeding should be discouraged.

The American Academy of Pediatrics (AAP) states that breast-feeding ensures the best possible health outcome for the child and recommends exclusive breast-feeding for at least the first 6 months of life.[3] The World Health Organization endorses breast-feeding for the first 2 years of life.[4] Based upon these recommendations, the goals of Healthy People 2010 were established: an initiation rate of 75% and a continuation rate of 50% at 6 months and 25% at 12 months after delivery.[5] However, the current U.S. rates for breast-feeding miss this target. Of infants born in 2007 to U.S. mothers, 75% were initially breast-fed, but only 43% breast-fed at 6 months, and 23% at 12 months.[6] The Healthy People 2020 guidelines are more ambitious, with a goal of 82% of babies to have ever been breast-fed, and continuation rates of 61% at 6 months, and 34% at 1 year.[7]

To help improve breast-feeding rates, the WHO proposed guidelines for "Baby Friendly Hospitals" in 1991. These include 10 steps that hospitals should follow in the immediate peripartum period to increase breast-feeding initiation rates. Throughout the world, many hospitals have adopted these recommendations and are certified as "Baby Friendly." In these hospitals, breast-feeding rates have gone up.[8] However, in the United States, the designation applies to only 105 hospitals.[9] In addition, not only do current U.S. surveys estimate breast-feed rates well below public health guidelines among African American babies; the rates are significantly lower than the general rates: 58% start out breast-feeding, and 28% breast-feed at 6 months, with 8% exclusively breast-fed at 6 months.[7]

National breast-feeding rates have been further scrutinized to evaluate potential regional, ethnic, and socioeconomic differences. One study identified significant variation among geographic regions, with the highest rates of breast-feeding noted in the Pacific, Northwest, and New England region. The lowest rates of breast-feeding were identified in the East South Central region, which includes Alabama, Kentucky, Mississippi, and Tennessee. There also appeared to be an association between breast-feeding rates and socioeconomic status and ethnicity. Mothers of non-Hispanic black children were less likely to initiate and continue breast-feeding as compared to mothers of non-Hispanic white children (51.5% vs. 72.1%). Finally, mothers of a higher socioeconomic status consistently had higher breast-feeding rates compared to their counterparts. These data demonstrate several instances of significant disparity and identify potential populations where it is possible to conduct outreach and initiate change to improve infant and maternal health.

Breast-feeding is most often viewed and presented as a "choice" by providers. Given the ample availability of formula as a substitute, many people do treat breast-feeding as a lifestyle choice. Formula is viewed by many as equivalent, rather than inferior to, breast milk. Women should be educated that breast-feeding and formula feeding are not equal and that breast-feeding is indeed the best "choice" they can make for themselves and their infants. It has long-lasting influence on the health of both. One breast-feeding expert has carried this a step further and has written about the risks of not breast-feeding and the harms of formula feeding.[10] We propose that this concept be considered by medical professionals in their approach to counseling patients regarding breast-feeding.

ANATOMY AND PHYSIOLOGY OF THE BREAST

Anatomy

The breast undergoes a series of developmental changes throughout a woman's lifetime, most notably during puberty, pregnancy, and lactation and then at menopause. The breast tissue is composed of two main components, the stroma, which contains fat and connective tissue, as well as a network of tubules and glands that are responsible for the formation and excretion of breast milk.

Each breast is composed of approximately 15–25 lobes and each lobe is composed of a series of lobules with a single lactiferous duct draining each lobe at the nipple. Each lobule is composed of a number of alveoli and ductules.[11] The alveoli are surrounded by myoepithelial cells. Secretory cells of the alveoli are responsible for milk production; milk is secreted into the lumen of the ductule and excreted by contraction of the myoepithelial cells. Natural hormonal cycles influence further development of these structures as well as milk production and excretion.

At puberty, estrogen production stimulates duct formation and lobule development within the breast.[12] The ductal tree extends and forms new branches and lateral buds alongside ducts. Alveolar buds begin within the first 2 years following the onset of menses. In the follicular phase of the menstrual cycle, the stroma becomes less dense and lumina expansion occurs in the ducts.[13] In the luteal phase, the stroma becomes more dense, and the ducts now have a lumen and may begin secretion. Without establishment of a pregnancy, apoptosis of epithelial cells occurs. The majority of breast development occurs by age 20, although the most significant changes take place in pregnancy and lactation.

The first 3–4 weeks of pregnancy are marked by estrogen-stimulated sprouting of ducts. External changes to the breast are evident by 8 weeks, with increased breast heaviness and increased nipple and areolar pigmentation. As pregnancy progresses, ductal tissue infiltrates and replaces the adipose and connective tissues of the breast. The cells of the alveoli proliferate and develop secretory abilities, most rapidly in the third trimester of pregnancy. Involution of the milk production apparatus occurs as breast-feeding ceases, and in between pregnancies the breast returns to the quiescent state.[12]

Hormonal Influences

There are two major stages of lactation initiation: secretory differentiation and secretory activation.[14] As described, secretory differentiation begins when epithelial cells in the breast become secretory cells with the capacity to produce milk constituents and can happen only with the occurrence of pregnancy. This is called stage I of lactogenesis. As the breast gains the capacity for milk production, high levels of progesterone—released by the placenta—inhibit the production of milk itself (secretory activation). The rapid decline of progesterone following delivery of the placenta releases this negative feedback, resulting in milk production and excretion—this constitutes stage II of lactogenesis. Other hormones required for this process include estrogen, prolactin, placental lactogen, human chorionic gonadotropin, insulin, and growth hormones.

The alveolar cells initially produce colostrum, which can be manually expressed in small amounts by most women in the late stage of pregnancy. Colostrum is the only product of the breast for the first 30–40 h after birth. Colostrum is a yellowish-clear, thick, fluid containing high amounts of secretory IgA and lactoferrin. Mature milk contains lactose, lipids, and proteins and is a more dilute substance than colostrum.

Approximately 30 mL are produced in the first 24 h after birth.[15] The volume and concentration of colostrum is thought to allow for the most effective coating of the infant's gastrointestinal (GI) tract with these protective substances.

While milk synthesis occurs continuously, milk ejection is the result of a neurohumoral reflex. The areola is the most sensitive part of the breast and plays the largest role in stimulating the milk ejection reflex. With adequate infant latching and subsequent suckling, oxytocin from the posterior pituitary is released and enters the blood stream where it causes the myoepithelial cells to contract and eject milk from the alveoli into the ducts. Prolactin is also released and stimulates milk synthesis and secretion.

Once the milk supply has been established, it is imperative that the mother continue to empty the breasts on a regular basis. Failure to empty the breasts regularly leads to alveolar distension and increased intramammary pressure. It has been shown that increased intramammary pressure leads to feedback inhibition that downregulates receptors for prolactin.[16] It is important to emphasize, especially with the growing number of women who are pumping, that frequent breast emptying is required to establish and maintain milk supply.

The physiology explained earlier clarifies the reason for some important aspects of initiating breast-feeding addressed later, such as the importance of frequent and regular feedings as well as breast emptying.

Milk Content

Milk is a complex fluid composed of a variety of components, including proteins, fats, and carbohydrates. It is species specific. The major nutrient in human breast milk is lactose, a disaccharide that is a primary determinant of milk volume due to its osmotic effects.[17]

Protein content of human milk is highest in the immediate postpartum period and decreases over the next 2 weeks.[18] Protein accounts for 8% of caloric requirement of full-term infants.[19] Milk proteins are divided into two fractions based on their solubility in acid: the whey fraction (soluble) and the casein fraction (insoluble). Human milk whey:casein ratios change during lactation, with a higher proportion in early milk, 90:10, compared to late milk, 50:50.[20] In comparison, bovine milk is 18% whey and 82% casein.[21] Whey is more easily digested and contains lactalbumin, lactoferrin, secretory IgA, and lysozyme, which promote host defense.[22] The amino acid content of human milk is also very specialized, containing a relatively large amount of cysteine, methionine, and taurine compared to bovine milk.[12] Nucleotides and carnitine are also present.

Fat represents 50% of the caloric content of human milk, and the fat content increases throughout lactation.[23] Human milk fat is organized into globules that are easily digested. Human milk contains a high proportion of long-chain polyunsaturated fatty acids, such as arachidonic acid and docosahexaenoic acid (DHA); these are both important for brain development. The final drops of milk, called "hindmilk" have the highest fat and calorie content.[24] Breast massage at the end of feeding can increase the expression of hindmilk, as well as assisting in complete emptying of the breasts, reducing the potential for blocked ducts and mastitis.

Carbohydrate content in human milk is primarily due to lactose, a disaccharide composed of galactose and glucose. A multitude of oligosaccharides have been identified in human milk as well and are the third largest component of milk after lactose and fats. More than 130 oligosaccharides have been identified.[25] The composition of oligosaccharides may be genetically determined.[26]

Vitamin content in human milk reflects maternal nutritional status. For instance, there is a direct relationship between maternal and infant levels of 25-hydroxy vitamin D and maternal diet.[27] It is the recommendation of the AAP that all infants receive 200 IU of oral vitamin D drops daily for the first 2 months of life[3] because of the high incidence of vitamin D deficiency in women. Minerals may be bound to proteins or available in complex or ionized states. Although iron content of human milk is less than the recommended dose for infants, exclusively breast-fed infants do not need iron supplementation for the first 6 months of life[28] as iron content in human milk is easily absorbed and sufficient to support optimal growth and development.

Milk also has cellular components such as macrophages and lymphocytes, and these are present at approximately the same concentration as found in maternal peripheral blood.[29] The total number of cells appears to decrease during the first 3 months of lactation.[30] These cells in human milk are thought to play a protective role in the infant GI tract.

BENEFITS OF BREAST-FEEDING

The literature on breast-feeding has exploded in the last 20 years. The benefits of breast milk for infants and the benefits of breast-feeding for mothers are both much better understood, although many questions are unanswered and new research in this field continues.

Maternal Benefits

A lactating mother may spend nearly 500 kcal/day more to produce breast milk.[31] Likely related to this increased energy expenditure, a breast-feeding mother may lose more weight postpartum.[32] and also keep this weight off longer than women who do not breast-feed although not all women who breast-feed lose weight.

Metabolic changes induced by lactation may persist into later life.[33] Data from the Nurses' Health Study showed that parous women who had breast-fed had a reduced risk of developing type II diabetes.[34] Data from the Women's Health Initiative (WHI) demonstrated that women who had breast-fed for 1–6 months had an odds ratio of developing type II diabetes of 0.91, and women who had breast-fed for 13–23 months had an odds ratio of 0.75.[35] The risk of developing the metabolic syndrome also appears to be decreased in women who had ever breast-fed, with an increased benefit seen for longer duration of lactation.[36]

Data from both the WHI and the Nurses' Health Study have been used to examine the relationship between future risk of cardiovascular disease and breast-feeding. The WHI data demonstrated that for postmenopausal women, an increased duration of lactation (>12 months total) was associated with a lower prevalence of hypertension, diabetes, and cardiovascular disease.[35] These authors estimated that for every 29 women who breast-fed for more than 1 year, 1 case of postmenopausal hypertension could be prevented. They also estimated that for every 40 women who breast-fed for over 1 year, one case of hyperlipidemia could be prevented. Parous women who had never breast-fed were 28% more likely to develop cardiovascular disease than women who had breast-fed for 7–12 months. In the Nurses' Health Study, women who had breast-fed for 2 years had a 37% decreased risk of coronary heart disease compared to parous women who had never breast-fed.[37]

Some studies demonstrate that breast-feeding can impact a woman's future chance of breast cancer. In 2002, a meta-analysis in the Lancet[38] analyzed data from 47 studies comprising 50,302 women with breast cancer and 96,973 women without. They showed a decrease in relative risk of breast cancer of 4.3% for every 12 months of breast-feeding, with an additional relative risk reduction of 7% for each birth. Other evidence has been mixed, however, and many studies may be limited by recall bias.

The Nurses' Health Study looked at the risk of epithelial ovarian cancer in women who breast-fed for over 18 months compared with parous women who had never breast-fed[39] and found a significant difference. It has been postulated that this may be related to the presence of antibodies to epithelial mucin (MUC1 antibodies); these antibodies have been associated with a more favorable prognosis in women with ovarian cancer.[40] Formation of these antibodies may be precipitated by episodes of mastitis in women who have ever breast-fed.[41]

Breast-feeding promotes child spacing. The lactational amenorrhea method is up to 98% effective when used properly; women attempting to use this method should be exclusively breast-feeding infants who are under 6 months of age.[42] Women who frequently supplement with formula should be advised to use other contraceptive methods.

Hormonal changes induced by breast-feeding may be beneficial to the mother. Oxytocin secretion during the milk ejection reflex assists in uterine involution. Oxytocin secretion is also felt to play a role in maternal–infant bonding.[43] Breast-feeding appears to reduce the maternal response to stress,[44] perhaps due to modulation of the sympathetic nervous system.

The long-term effect of lactation on osteoporosis is unclear. A study on women aged 20–25 who had breast-fed their infants during pregnancies as adolescents demonstrated increased DEXA scores compared to women who had infants during their adolescent years but who had not breast-fed.[45] Whether this difference persists and has any measurable effect on the development of osteoporosis or decrease in hip fracture rates is still uncertain, with some studies proving an effect,[46] and others not.[47]

Infant Benefits

Human breast milk is specifically made for human infants. Similar to other mammals, the composition of milk has the appropriate nutrients to supply a growing infant's needs. Many of the beneficial effects of breast-feeding are presumed to be due to the unique factors inherent to human breast milk; formula is an expensive albeit improving imitation.

Significant short- and long-term infant benefits to breast-feeding have been identified through extensive epidemiological research. These infant benefits include decreasing rates of chronic diseases and infectious diseases, improving neurodevelopment, and decreasing the rate of childhood autoimmune diseases. The breadth and depth of the literature in this topic continue to expand; while areas of controversy certainly remain, the benefits of breast-feeding are numerous.

The particular effects of breast-feeding in developing countries should not be overlooked. Morbidity and mortality are lower in breast-fed compared with formula-fed infants. They have a lower incidence of gastroenteritis and respiratory infections.[48,49] In developed countries, breast-fed infants are hospitalized less and require fewer outpatient visits for acute illness than formula-fed infants.[50]

While data extolling the benefits of breast-feeding are vast, breast-feeding research is still incomplete. Some studies are limited by recall bias, as mothers may over- or underreport the time they actually breast-fed their infants. Older studies may be limited by presenting breast-feeding as "ever-breast-fed" versus "never-breast-fed" without taking into account the length of time or role of supplementation. Few are prospective and even fewer are randomized—indeed, it would be unethical to randomize to breast-feeding versus not-breast-feeding. In the review that follows, we have attempted to discuss only points that have stood up to multiple investigations. As in most contentious areas of research, further investigation into the benefits of breast-feeding is crucial, in particular regarding the long-term effects of breast-feeding.

Gastrointestinal Effects

The fetus has a sterile GI tract; upon delivery and exposure to the outside world, a newborn's gut is colonized. The colonization of the infant gut begins with delivery. This can take up to 1 week to become stable.[51] Differences in infant gut flora are seen at 1 month of age based on mode of delivery as well as based on breast or formula feeding.[52] Breast-fed infants have a preponderance of *Lactobacillus bifidus* and *Bifidobacterium*, up to 95% of organisms in culture. Infants fed formula have a predominantly gram-negative-based flora, including *Enterobacter*, *Bacteroides*, *Clostridium*, and *Escherichia coli*.[53] Infants born through cesarean section may also have a lower number of bifidobacteria and lactobacillus. Breast milk and colostrum appear to facilitate the preponderance of bifidobacteria; oligosaccharides found in human milk appear to specifically facilitate their growth.[54] The actions of lactoferrin and lysozyme in human milk also seem to control growth of pathogenic bacteria.[55] Free amino

acids such as taurine and glutamine may assist in intestinal growth.[56] Compared to formula, human milk increases the rate of gastric emptying,[57] increases the lactase activity in premature infants,[58] and decreases the intestinal permeability in early life in premature infants.[59]

There is a great deal of literature from premature infants demonstrating a reduced risk of necrotizing enterocolitis in infants fed breast milk.[60] This may be related to a number of anti-inflammatory agents (interleukin 10) and mediators (polyunsaturated fatty acids, PUFAs) present in breast milk.[61,62] This may also be due to the large differences in flora seen in these infants compared with infants who are fed only formula.

Infectious Processes

The immunological factors present in breast milk protect breast-fed babies and infants against infections in the first year of life. The concept of the enteromammary and bronchomammary immune systems may play a role.[29,63] Plasma cells from both of these locations migrate to the mammary epithelium, where they then produce IgA antibodies and provide specific protection against local pathogens. Formula-fed infants are more likely to develop a GI infection within the first year of life than breast-fed babies.[64,65]

Oligosaccharides also prevent attachment of respiratory pathogens such as *Haemophilus influenzae* and *Streptococcus pneumoniae to* respiratory epithelium.[66] Breast milk may also transfer an innate immunity against respiratory syncytial virus (RSV). Compared to infants breast-fed for over 4 months, non-breast-fed infants were shown to be 3.6 times more likely to be hospitalized in their first year of life with lower respiratory tract infections.[67] Most hospitalizations for respiratory issues are related to RSV infections. RSV-specific IgA has been shown to be expressed in breast milk,[63] and milk lipids have antiviral activity as well.

Episodes of acute and recurrent otitis media are also decreased in breast-fed infants. Infants breast-fed for at least 4 months had half the number of episodes of acute OM compared to infants who were not breast-fed.[68] In this same study, infants breast-fed for over 6 months had a 10% rate of recurrent OM compared to infants breast-fed for less than 4 months.

Atopic Disease and Asthma

In families with a history of allergic disease, breast-feeding may confer a protective effect on high-risk infants. Infants are at high risk for developing allergic disease when they have one or more affected first-degree relatives. In a meta-analysis of 18 studies, a protective effect against atopic disease (i.e., eczema) was shown with breast-feeding for over 3 months in infants with an affected first-degree relative.[69] The prospective PROBIT trial (Promotion of Breast-feeding Intervention Trial), where breast-feeding was promoted at specific "intervention" hospitals, demonstrated a decreased risk in the first year of developing eczema among infants born at these intervention hospitals.[70]

Development of asthma also appears to be decreased in infants who have been breast-fed. A meta-analysis of 12 studies demonstrated that less than 3 months of exclusive breast-feeding increased the risk of developing asthma 1.9 times that of infants who were breast-fed for over 3 months.[71] However, further research is needed, as not all studies support this conclusion. In particular, a large population-based cohort from Tasmania found no protective effect of breast-feeding on the development of asthma after age 7; in fact, breast-feeding was instead a risk factor for current asthma at age 14 and older.[72]

Development of food allergies in relationship to breast-feeding is also another issue under scrutiny. Breast-feeding for 4 months or longer may be protective in the development of cow's milk allergy.[73] Once a food allergy has developed, intact allergens may be passed directly into breast milk.[74] Regarding peanut allergy, an association between increased consumption by the mother during pregnancy and lactation has been shown to be associated with increased risk of peanut allergy in infants.[75,76]

Other Diseases

Available studies point to an increased risk of developing type I diabetes mellitus later in life in infants exposed early to cow's milk protein or breast-fed for shorter intervals. A meta-analysis from 1994 of available case–control studies showed that patients who had type I DM were less likely to have been breast-fed for >3 months and were more likely to have been exposed to cow's milk protein under 4 months old.[77] This is theorized to be due to a higher prevalence of islet cell autoantibodies in infants exposed to cow's milk.[78]

The risk of developing type 2 DM in breast-fed infants has been studied in several observational trials, but the data are mixed and do not clearly indicate a protective effect. In theory, adipokines, such as ghrelin and leptin, that are present in breast milk[79,80] may influence energy intake as well as the risk of future obesity and the metabolic syndrome.

The data on childhood obesity and breast-feeding are also mixed. An American study of over 15,000 children showed a decreased risk of obesity from ages 9 to 14 in children who were breast-fed for 7 months or longer after adjusting for a number of variables such as energy intake, physical activity, or maternal BMI.[81] However, at the 6.5 year follow-up point for the PROBIT trial, children who had been part of the intervention group (increased breast-feeding promotion in the postpartum period, with a 3-month continuation rate of 43.3% at 3 months) did not have any differences in adiposity or blood pressure than children who were part of the control group.[82] Clearly, further investigation of this subject is necessary.

Breast-feeding may be protective against future development of childhood leukemia, perhaps related to increased immunity to viral infections that may predispose children to the development of leukemia. Breast-feeding over 6 months is protective against acute lymphoblastic leukemia as well as acute myeloblastic leukemia.[83]

Neurodevelopment

Establishing a clear benefit of breast-feeding on infant cognitive development is challenging. There are numerous variables that may confound studies, including maternal social class, maternal cognitive ability, or intrauterine events. Additionally, breast-feeding may have effects that are limited to the time of active breast-feeding or it may induce a "programming" effect on infants, with effects that carry over onto later periods of development.

We do know that the human brain nearly triples in size in the first year of life.[12] Fifty to sixty percent of this growth is lipid. Fatty acid composition appears to be dependent on dietary intake, and breast-fed infants have been shown to have a higher cortical DHA content than formula-fed infants when necropsy specimens were examined after sudden death.[84] Brain growth is also associated with increased uptake of PUFAs into cerebral cortex phospholipids.

The PROBIT study was able to demonstrate a long-term effect of their breast-feeding intervention on verbal IQ scores—children in the intervention group had scores that were 7.5 points higher at 6.5 years compared to the control group. A study in Honduras randomized children to early introduction of complementary foods at 4 months versus exclusive breast-feeding for 6 months. Infants who were in the complementary food group crawled later and were less likely to be walking at 12 months.[85]

It is postulated that these effects may be related to intake of PUFAs found normally in breast milk. Increased dietary intake of these compounds has been linked to protection against heart disease and inflammatory diseases.[86] Visual acuity has been studied in very-low-birth-weight infants who had diets supplemented with omega-3 fatty acids versus linoleic acid ± linolenic acid and demonstrated improved parameters in the omega-3 supplemented infants.[87] Arachidonic and docosahexaenoic acids have been associated with improved cognition, growth, and vision.[88] There is evidence that these two PUFAs regulate a gene called FADS2, which encodes an enzyme involved in their metabolism; in a study investigating this gene, breast-feeding, and IQ, a certain variant was found in over 90% of the study cohort.[89] Infants with this variant who were also breast-fed were found to have significantly higher IQs (6.4–7.0 points higher) than infants without this variant; breast-fed infants with other variants did not have the same IQ advantage.

PRACTICAL MANAGEMENT OF BREAST-FEEDING

To establish an optimal cycle of milk production and release, mothers who plan to breast-feed their infants should begin to do so immediately after birth. The WHO and UNICEF published the guideline "Ten Steps to Successful Breastfeeding" in their Baby-Friendly Hospital Initiative.[90] These provisions are listed in Table 69.1. The 10 steps include initiation of breast-feeding within the first hour after delivery. Direct skin-to-skin contact between mother and infant immediately after delivery may assist with latching and future breast-feeding success. Most infants can latch on to the breast within an hour after birth. All infant care may be provided with the infant on the mother during the immediate postpartum recovery period. But most importantly, the memory of her baby successfully nursing immediately postpartum can sometimes help sustain a mother's confidence that her baby can and will latch through the next ≥24 h when many newborns are reluctant and uncoordinated feeders.

TABLE 69.1
Ten Steps to Successful Breast-Feeding

1. Have a written breast-feeding policy that is routinely communicated to all health care staff.
2. Train all health care staff in skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breast-feeding.
4. Help mothers initiate breast-feeding within 1 h of birth.
5. Show mothers how to breast-feed and how to maintain lactation, even if they are separated from their infants.
6. Give newborn infants no food or drink other than breast milk, unless medically indicated. (A hospital must pay fair market price for all formula and infant feeding supplies that it uses and cannot accept free or heavily discounted formula and supplies.)
7. Practice rooming-in—allow mothers and infants to remain together—24 h a day.
8. Encourage breast-feeding on demand.
9. Give no artificial teats or pacifiers to breast-feeding infants.
10. Foster the establishment of breast-feeding support groups and refer mothers to them on discharge from the hospital or clinic.

Source: Adapted from the World Health Organization, Division of Child Health and Development, *Evidence for the Ten Steps to Successful Breastfeeding (Revised)*, World Health Organization, Geneva, Switzerland, 1998.

The breast-feeding mother should be supported and educated during her postpartum care in the hospital. Rooming-in allows parents to learn the infant's feeding cues in order to feed on demand. Nurses caring for multiple babies in a nursery are not likely to be in tune with these sometimes-subtle activities.

Direct assistance with and feedback regarding positioning and latching should be provided by nursing and medical staff. Proper positioning is crucial to establishing a proper latch-on. The three common positions are the cradle, football (also referred to as the "clutch"), and side-by-side positions. The infant's head should be opposite the nipple, with the neck slightly extended. The infant's head, shoulders, and hips should then be in alignment. Latching involves forming a tight seal between the infant's lips around the nipple, drawing the nipple into the back of the mouth. The breast may be supported by the mother or her support person's hand in the shape of a "C," with four fingers below the breast and the thumb above the areola, pointing toward the midline. The infant's head and neck are supported with the mother's other hand, and the infant's lips can then be rubbed with the nipple to elicit a rooting reflex. As the infant opens his or her mouth wide (which sometimes requires waiting 30–60 s), the infant's head is quickly brought to the breast with the mouth over the nipple. A proper latch

includes the whole nipple and as much of the areola as possible. The pressure of the infant's hard palate during suckling compresses lactiferous sinuses beyond the base of the nipple to increase the amount of milk transferred.

Specific features of an adequate latch can be assessed. Audible sucking can be heard. The infant's cheeks should be full. Both the chin and nose are close to the breast, and the lower lip should be turned out toward the breast. The tongue may extend over the lower dental ridge and should be in contact with the breast when the lower lip is moved away. An audible swallow provides some assurance the baby is accomplishing nutritive sucking.

Length of feeding on each breast varies with infant age. In the immediate postpartum period, this ranges from 10 to 15 min, while after 1 month, the range is 8–10 min. In a typical feeding session, the infant should first be offered one breast. Feeding from this breast should continue until the infant demonstrates a loss of interest. The infant should then be offered the second breast and may need to be awakened by undressing, changing the diaper, or repeatedly changing the infant's position in order to encourage latching.

The infant signals satiety by voluntary release of the nipple and relaxation of the facial muscles and hands, and young infants may fall asleep. Breast-feeding for some infants may be soporific, leading to sleep almost immediately after latching on to the breast. In these cases, stimulation of the infant to maintain an awake state in order for milk transfer to occur requires careful attention by the parents. Normal satiety signals may not apply to these infants, and their nutritional adequacy may have to be monitored by weight gain and assessment of hydration.

The initial frequency of breast-feeding in the first 1–2 weeks postpartum may be as often as every hour, with an average of 8–12 times/day. Breast-feeding mothers should be encouraged to wake their infants at least every 4 h for feeding during the first 2 weeks postpartum. This will promote the infant receiving adequate nutrition. The overall frequency of breast-feeding diminishes by 4 weeks, with an average of seven to nine feedings per day. This is a result of improved nursing skills and increased milk volume. Cluster feeding, or periods where the infant feeds with greater frequency during growth spurts, is also common intermittently.

Sore nipples are a frequent challenge for the new nursing mother. The sensation of suckling should be perceived by the mother as a painless undulation. Nipples are increasingly sensitive in the immediate postpartum period, peaking around 4 days postpartum. Nipple soreness or pain should be differentiated from sensitivity when assessing a woman with this complaint. Normal sensitivity typically goes away after the first minute of suckling and should overall disappear after 1 week. Nipple pain is typically persistent throughout the cycle of breast-feeding and may be a result of trauma to the nipple. This is frequently the result of poor latch or positioning. Skin breakdown is manifest by blistered, cracking skin with bruising of the nipples and areola.

Infant thrush and candidiasis of the breast are a common cause of nipple pain, and both the mother and infant should be treated if this is suspected. In women with sore nipples, the infant should also be assessed for ankyloglossia, or "tongue tie," which is caused by a tight frenulum limiting tongue extension and possibly impairing latch. Sometimes this requires that the frenulum be clipped—a simple procedure for those familiar with the technique. Additionally, the mother's choice of breast cleansing agents may play a role in skin breakdown, and the use of harsh agents or abrasive cleansing should be discouraged.

Relief of soreness can be provided in several ways. Nipples should be air-dried after nursing to promote healing; in addition, breast milk or colostrum can be expressed and spread on the affected surface and to assist with healing. The use of soap to clean the breast should be avoided as it removes the natural lubrication produced by the glands of Montgomery. Lanolin cream application can also provide moisture to promote healing. "All Purpose Nipple Ointment," a combination of mupirocin, steroid cream such as betamethasone, and an antifungal powder, can be prescribed for women with refractory breakdown and pain. Although no formal evaluations of its efficacy have been performed, it is widely used as an apparent helpful adjunct for women in this situation. The formulation is mupirocin 2% ointment (15 g), betamethasone 0.1% ointment (15 g), and miconazole powder mixed to a final concentration of 2%; the ointment is available only through compounding pharmacies. This may be applied sparingly after each feeding and does not need to be washed off in between feedings. Most importantly, the mother should be supported and encouraged to continue breast-feeding during the time of nipple soreness.

Flat or inverted nipples can be another challenge encountered by the breast-feeding mother. It has been estimated that 10% of women have inverted or non-protractile nipples, which may contribute to breast-feeding problems.[91] To diagnose a truly inverted nipple, one may press the areola between the thumb and index finger; an inverted nipple will retract while a normal or flat nipple will protrude. Multiple treatments have been suggested for inverted nipples, such as Hoffman exercises, which involve stretching or pulling on the nipple, or wearing breast shells, which are plastic disks with holes in the center. However, evidence suggests that these do not improve breast-feeding rates in these women.[91] When flat or inverted nipples are identified prenatally, mothers should be instructed to seek consultation from a lactation consultant in the postpartum period to address any problems with latching. The use of a pulsatile electric pump may facilitate latch-on in these patients. Sometimes a nipple shield will be required (a nipple-shaped flexible device placed over the areola to help the baby latch), but these should be used only with instruction.

Assessment of Intake Adequacy

Infants typically lose 5%–7% of body weight in the first 5 days of life. This weight is usually regained by 1–2 weeks. Infants receiving appropriate nutrition should gain between 15 and 40 g/day. The AAP recommends a post-discharge hospital visit within 3–5 days of age for all breast-feeding infants.[92] At this time, the infant should be weighed,

TABLE 69.2
Breastfeeding Checklist for New Mothers

Day	Feedings/Day	Wet Diapers/Day	Bowel Movements/Day
1 (in the hospital)	6	2	1 (black, tarry soiled diaper)
2	8–12	3	2 (brown, tarry soiled diapers)
3	8–12	3 or 4	2 or 3 (green soiled diapers)
4	8–12	4	3 or more (yellow soiled diapers)
5	8–12	4 or 5	3 or more (yellow soiled diapers)
6	8–12	6–8	3 or more (yellow soiled diapers)
7	8–12	8 or more	3 or more (yellow soiled diapers)

After day 7, your baby should continue to have at least eight wet diapers a day. The number of bowel movements varies. If you are still concerned about how much milk your baby is getting, talk to your pediatric clinician. She or he may want to weigh the baby.

breast-feeding practices can be assessed, and the mother can be instructed and encouraged.

In our hospital, we give new mothers a checklist to help them track the number of feeds, voids, and bowel movements their infant has on a daily basis (Table 69.2). A well-hydrated infant should have three-to-five voids and three-to-four stools daily by days 3–5, then four-to-eight voids and three or more stools daily by days 5–7 of age.[3] Weight loss greater than 7% from birth weight indicates possible feeding problems and should initiate investigation into practices and improvement of milk transfer.

Clinicians caring for the nursing dyad are often faced with the dilemma of when to supplement.

Health care workers sometimes offer formula to support tired mothers while not taking into account the adverse effect this may have on the initiation and maintenance of milk supply.

The American Academy of Breastfeeding Medicine recommends hospitals have a policy that supplementation of a breast-fed baby requires a physician's order. Their thorough protocol is available at http://www.bfmed.org/Resources/Protocols.aspx.[93]

Contraindications to Breast-Feeding

In the United States, there are a few contraindications to exclusive breast-feeding. These are as follows[3]:

- Infant with classic galactosemia
- Maternal active untreated tuberculosis
- Maternal positivity for human T-cell lymphotropic virus type I or II
- Mothers receiving diagnostic or therapeutic radioactive isotopes or with exposure to radioactive materials (at least until the materials are no longer present in the milk)
- Maternal antimetabolite or chemotherapeutic agent use
- Maternal drug abuse
- Active herpes simplex outbreak on the breast

Maternal HIV infection is also considered a contraindication to breast-feeding in the United States,[94] while in developing countries many experts think that the risks to infants of infectious diseases and nutritional deficiencies outweigh the risks of HIV transmission in breast milk.

Maternal infection with hepatitis B or C is not a contraindication to breast-feeding, as the risk of transmission of either of these viruses via breast milk is low.[12] Infants born to hepatitis B-positive mothers should receive the hepatitis B immunoglobulin at birth and the full vaccine series; if a breast-feeding mother has acute peripartum hepatitis, it is reasonable to abstain from breast-feeding until its etiology can be determined.

Maternal cytomegalovirus (CMV) seropositivity does not seem to be related to significant clinical illness in healthy full-term infants; however, premature infants should not be given milk that is known to be CMV-positive.[95] Freeze–thaw cycles may reduce CMV transmission, but further prospective studies are needed.

Recent alcohol use is a relative contraindication to breast-feeding, and mothers should be encouraged to abstain from feeding for 2 h after a single alcoholic beverage in general.[96,97]

PROBLEMS RELATED TO BREAST-FEEDING

Engorgement

Engorgement is a problem best managed with prevention. It involves three elements[12]: (1) congestion and increased vascularity of the breast, a physiological response following delivery of the placenta, (2) milk accumulation, and (3) edema from swelling and obstruction of lymphatic system drainage by alveolar fullness. When skin edema is noted on the breast, intervention is needed.

Areolar engorgement may be solved by manual expression or warm soaks of the nipple prior to feeding. Peripheral engorgement may be a physiological response as milk production increases in the immediate postpartum period; for these women, pumping early does not help relieve this engorgement. Women may feel throbbing or aching pain. Proper support of the breasts is crucial with a well-fitting brassiere. Standing in a warm shower and massaging the breasts to express milk may provide some relief and facilitate the baby's latch to further empty the breast. Cold packs may reduce edema and pain. Medications for pain relief may also be used safely. The application of cooled cabbage leaves to the breast has been used for generations, but in a small study comparing cold gel packs and cabbage leaves, no differences

in relief were found.[98] If an infant is less interested in breast-feeding in the early postpartum period, women may need to manually express breast milk. However, the most important step is to ensure continued drainage of the breasts however possible to prevent increased intraductal pressure, which may ultimately decrease milk supply.[16]

Mastitis

Mastitis is a bacterial infection within breast tissue that may be seen at any time during lactation. The incidence is up to 20%, and it is most common within the first 6 weeks postpartum. The symptoms include redness, tenderness, and warmth of the overlying skin, with systemic symptoms of fever of 101°F or higher, myalgias, and malaise. The most common organisms are staphylococcus species and *E. coli*; streptococci are less commonly implicated. Risk factors include incomplete emptying of the breasts or missed feedings, plugged ducts, broken skin on the nipples, or breast constriction.

Treatment includes oral antibiotic therapy for 10–14 days. Dicloxacillin is first-line in women who are not allergic to penicillins. Sulfa drugs should be avoided for women with infants less than 1 month. In addition to antibiotics, it is equally important that women with mastitis use local measures to promote recovery. They can continue feeding on both sides and should use heat and massage prior to feedings to increase emptying of the breasts.

Many centers are noticing an increase in mastitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[99] Trimethoprim-sulfamethoxazole, clindamycin, and linezolid are all appropriate outpatient therapies for women suspected of having MRSA mastitis. If a patient is unresponsive to first-line treatment, milk cultures and sensitivities should be obtained.

Breast abscess formation is an infrequent complication of mastitis, with a reported incidence of 0.1%, and may be related to delayed or inadequate treatment. It may be more common when MRSA is the offending organism. The primary treatment is drainage, and fluid collected should be sent for culture and sensitivities. Drainage may be accomplished with needle aspiration, with or without ultrasound guidance, for women without overlying skin changes and should be repeated every 2–3 days until the fluid collection resolves.[100,101] For women with more advanced cases, incision and drainage should be considered. Both of these approaches require adjunct use of antibiotics with anti-staphylococcal coverage or coverage based on culture results. Breast-feeding should be continued if the site of drainage does not interfere with latching. If that is the case, pumping or hand expression should continue until feeding can be resumed.

Prior Breast Surgery

Breast augmentation surgery has become a more accepted and common procedure. According to the American Society of Plastic Surgeons, 289,328 women underwent augmentation mammoplasty in 2009.[102] Many young women who undergo this surgery do so prior to childbearing and lactation. Most implants used are inserted between the chest wall and breast and do not interfere with breast tissue. The incision used to place the implant may be on the axilla or near the areola; for women who desire future breast-feeding, an axillary incision is preferable. Saline implants have replaced silicone implants, and women with intact silicone implants do not have any contraindications for breast-feeding. Women who undergo augmentation for underdeveloped breasts may not have adequate functional breast tissue, which may lead to underproduction during lactation, but this is rare.

Because of its destructive nature, breast reduction surgery may pose a different picture for the woman who desires to breast-feed. In 2009, 78,427 women had breast reduction surgery.[102] This surgery often interferes with ductal anatomy and the innervation of remaining tissue. Breast-feeding may be successful in up to 65% of women after reduction,[103,104] depending somewhat on the location of tissue removed. Importantly, breast-feeding should not be discouraged in these patients. Rather they should be offered anticipatory guidance and support, and the baby's weight should be carefully monitored. Women who have undergone breast surgery may find the website www.BFAR.org[105] a helpful resource—this site compiles information and supports resources for women who have undergone breast or nipple surgery.

Medications and Lactation

The risks and benefits of medications in lactating women must be considered by all prescribers. Many factors influence the passage of a medication into the milk supply as well as its effect on infants. These include consideration of each drug's route of administration, absorption, size, solubility, and protein binding. Passive diffusion is the main way most drugs enter into milk. The effects of drugs on the infant itself is often less well-studied but is important to consider as nearly any drug a breast-feeding mother consumes will be found in her milk. Length of time of administration may also be a factor. In certain cases, a woman may need to pump and discard milk until she has completed her course of therapy.

As women breast-feed for longer periods of time, physicians from all medical specialties will care for them and will need to be familiar with principles of medication use. Many resources exist both online and in print form. LactMed[106] is a searchable online reference developed by an expert panel through the National Library of Medicine. The web address is http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT

BREAST-FEEDING SUPPORT

Support for breast-feeding is best begun with the provider in routine medical encounters, but does not end there. Physicians and other providers should educate themselves about the resources in their own community to better serve their breast-feeding mothers.

International Board Certified Lactation Consultants (IBCLCs) are specialists in the clinical management of breast-feeding. They may work in a variety of settings, including in hospitals, pediatric practices, private clinics, and public health settings. They provide support and management of many common breast-feeding concerns. In the United States, the International Lactation Consultant Association is the professional association for IBCLCs, and their website, www.ilca.org, provides information about practitioners throughout the country. As of December, 2010, the United States had over 11,000 IBCLCs, with practitioners in every state and territory.[107]

Many community resources also exist. La Leche League, International (LLLI), is an international organization initially formed in the 1950s to combat low breast-feeding rates. Today, they have a global mission to help women breast-feed. Their Internet resources are available to practitioners and patients at www.llli.org, and there are LLL chapters in every U.S. state.[108]

Many states also offer breast-feeding resources and support. The U.S. Breastfeeding Committee is an independent nonprofit coalition with organizations in all 50 states. Their website, http://www.usbreastfeeding.org/, provides links to the coalition sites for each state, which in turn provides resources for patients and practitioners in their areas.[109] Often hospitals or sometimes organizations that do childbirth education have breast-feeding support programs. Identifying such local options is important for those who work in clinical settings that frequently deal with the breast-feeding dyad.

Pumping Breast Milk (Working and Nursing)

With so many women in the workforce, it is impossible to meet national breast-feeding goals without the expression of breast milk, often referred to as "pumping." Data from the Infant Feeding Practices Study II revealed that from 2005 to 2007, 85% of mothers with infants under 4.5 months had expressed milk at some time since delivery.[110] The commercial market for breast pumps has expanded greatly from the initial manual pumping devices. These devices are all FDA-regulated and are available to mothers for purchase or rent.

Many insurance companies cover these for various indications, in particular for mothers who must be separated from their infant. In most states, women, infants, and children (WIC) also provides breast pumps at no cost. Pumping supplies are now considered a deductible medical expense by the IRS.[111] For women who plan to pump only occasionally, manual pumps or battery-operated pumps may be adequate. For women who intend to return to work, need to pump large volumes of milk for their infant for any reason, or need to stimulate their milk supply, an electric pump is ideal. These pumps both allow a greater volume of milk to be obtained including milk with a higher cream content and employ a certain number of pressure cycles per minute, which more naturally simulate the sucking reflex of an infant.

The federal Fair Labor Standards Act states that employers are required to provide "reasonable break time for an employee to express breast milk for her nursing child for 1 year after the child's birth each time such employee has need to express the milk."[112] Employers are also required to provide "a place, other than a bathroom, that is shielded from view and free from intrusion from coworkers and the public, which may be used by an employee to express breast milk." While there are exceptions to these rules, an increasing number of workplaces are making breast-feeding facilities available to their workers. Legislation protecting a woman's right to breast-feed in public and at work is an important component to reaching national breast-feeding goals.

Ideally, women should empty their breasts at the same frequency they would as if they were doing in-person feeding. This helps maintain the supply necessary for adequate nutrition. Mothers who pump should also be encouraged to breast-feed while at home, not only for the purpose of feeding but also to promote bonding and maintain supply. Massage of the breast while pumping increases delivery of hindmilk as well.

The Human Milk Banking Association of North America recommends storage of breast milk at room temperature (<79°F) within 4 h.[113] Breast milk can also be immediately refrigerated, where it may be used for 48 h after collection. Bactericidal capacity of breast milk declines after 48 h of refrigeration. If breast milk is to be frozen, this should be performed immediately. Guidelines for limits on the use frozen milk vary from 3 to 6 months in storage. Milk stored in a conventional refrigerator-freezer should be stored near the back and should be used within 1 month, as the freeze–thaw cycles decrease the energy content of the milk and increase the likelihood of separation of the fat layer.[12] Fat in frozen milk may be broken down by lipase, leading to altered smell and taste. While this breakdown is not harmful, some infants may refuse to drink it. Many of the beneficial compounds present in milk such as immunoglobulins, lactoferrin, lysozyme, and other enzymes and proteins are generally preserved in frozen milk.[114]

Weaning

Timing of weaning can be a complex process related to the interplay of multiple factors. Women may stop because they think their infant is "old enough to wean," a phrase that is interpreted differently based on perspective.[115] In practice, mothers are the primary determinants to weaning time. The return to work, demands of breast-feeding, or multiple other social factors may play a part in their decisions. Additionally, lack of knowledge regarding the benefits of prolonging breast-feeding and psychological difficulties in the postpartum period may also decrease the length of breast-feeding.[116]

While there is still considerable controversy regarding the timing of introduction of solid foods, the AAP recommends exclusive breast-feeding for 6 months, with gradual introduction of complementary iron-rich foods at 6 months. They say "Breastfeeding should be continued for at least the first year of life and beyond as long as desired by the mother-infant dyad."[117] As discussed, increased breast-feeding duration does confer health benefits on both the infant and the mother, and there is no upper limit to breast-feeding.

For infants who are fully breast-fed, solids can be given during the day and breast-feeding should continue on demand. With a diet increasing in solid content, women may expect fewer or shorter feedings. Weaning can also be accomplished by eliminating one breast-feeding session every several days and replacing it with a solid meal. Gradually, only the morning and night feedings remain in this schedule, and they can be maintained for months to years. Abrupt weaning is sometimes demanded due to maternal medical problems or necessary separation of the mother and the infant. Interestingly, studies of women who had to abruptly stop breast-feeding demonstrated that involuting mammary tissue remained partially functional for up to 42 days,[118] although the milk content changed over time to become saltier and more protein rich.

It is normal for mothers to experience sadness at the thought of the last feeding.[119] This may be both an emotional process and a physiological one. In particular, the decrease in prolactin, which has been associated with a general feeling of well-being, may lead to a relative depression. Medical professionals can help normalize these feelings and provide professional support to women during this period.

CONCLUSION

A single chapter is inadequate to address the many issues and challenges that breast-feeding can to present both the nursing dyad and those who care for them. That said, there are many resources available to support both women and their providers in this immensely valuable effort. A list of places to seek more information is provided in the following, and thankfully many of these organizations are involved in furthering our understanding of this awe-inspiring physiological phenomenon whereby a mother nourishes her newborn with a highly evolved, species-specific, perfectly balanced food.

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70 Contraception

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CONTENTS

Introduction 867
Oral Contraception 868
Mechanism of Action 868
Initiation and Administration 869
Clinical Considerations 869
Myocardial Infarction 869
Stroke 869
Venous Thromboembolism 869
Transdermal Contraceptive Patch 870
Mechanism of Action 870
Clinical Considerations 870
Contraceptive Vaginal Ring 871
Progestin-Only Methods 871
Depot-Medroxyprogesterone Acetate 871
Mechanism of Action 872
Clinical Considerations 872
Contraceptive Implant 875
Efficacy 875
Mechanism of Action 875
Clinical Considerations 875
Intrauterine Contraception 875
Mechanism of Action 876
Clinical Considerations 876
Emergency Contraception 877
Mechanism of Action 877
Efficacy 877
Options 877
References 877

INTRODUCTION

The ability to plan and control reproduction is an essential part of a healthy lifestyle. Contraceptive success requires an understanding of the efficacy of each method, the risks and benefits associated with each method, and matching the method to the individual needs of each woman. Despite an apparent myriad of choices, unintended pregnancy remains a public health challenge in the United States. The goal of this chapter is to assist clinicians in informing women about their contraceptive options, reviewing the risks, benefits, and efficacy of these methods while helping women choose a method that will be highly efficacious for them and their unique lifestyle thus.

Approximately one-half of the 6.3 million pregnancies in the United States annually are unintended and one-half of these unintended pregnancies end in elective abortion.[1] What is most striking about the unintended pregnancies in the United States is that almost one-half of these pregnancies occur among women who report using some form of reversible contraception at the time of conception and the other half are among women who did not use any contraception even though they did not desire a pregnancy.[2] Analysis of reasons for contraceptive failure include failure to adhere to a method, inappropriate use, lack of continuation of the method, inability to access the method regularly, as well as failure of the method itself.

American women have fewer contraceptive options than women in most other industrialized nations because of lack of awareness and misconceptions about methods and because contraception is more expensive for most women in the United States. More than half of women, including those who are highly educated, are not accurately aware of the efficacy or the benefits and side effects associated with many methods of contraception.[3–5]

For clinicians, the approach to contraceptive counseling should include discussion of the efficacy of a method, which should be discussed in terms of both the theoretical (perfect use) efficacy and the actual (typical use) efficacy of a method. Theoretical (perfect use) is based on pregnancy rates among women who use the chosen method correctly on every occasion, while actual (typical use) efficacy of a method is the pregnancy rate that occurs among women who use the method inconsistently or incorrectly. The actual use efficacy rates are important to emphasize during comprehensive contraceptive counseling because they reflect real-life experiences of women. Though no method of contraception is without failure, there are methods in which the actual efficacy is the same as the perfect use or lowest expected failure rate.

Reversible methods of contraception include intrauterine contraception, contraceptive implants, injectables, oral, transdermal, and vaginal ring contraceptives. These methods can be categorized by actual efficacy rates or the usual expected failure rate. Intrauterine contraception and implants are considered long-acting reversible contraception (LARC) and are associated with the lowest pregnancy rates (less than 1 pregnancy per 100 women in 1 year) and are considered most effective because they are minimally influenced by adherence to the method and can be left in place for extended periods of time. With LARC, the actual efficacy approaches perfect use.

Injectable contraceptives are considered effective methods with very low pregnancy rates and high actual efficacy, but do require adherence with periodic follow-up for reinjection. Other methods in this category include user-controlled methods that rely on more frequent adherence with a method, including oral contraceptives, the transdermal contraceptive system, and the vaginal ring. These methods are also associated with a very low pregnancy rate if utilized consistently in an optimal fashion, but actual pregnancy rates are significantly higher because of frequent misuse by women in the general population.

Other methods of contraception such as condoms, diaphragms, cervical caps, spermicides, and natural family planning methods, including withdrawal and abstinence, are considered least effective and are associated with actual pregnancy rates that are significantly higher than perfect use rates. The overall actual efficacy rates of these methods have varied among studies but generally have a rate of about 30 pregnancies per 100 women in 1 year.

Along with a discussion of method effectiveness, clinicians should individualize care for each woman with a discussion of method safety in relation to each woman's medical history. In general, contraceptives pose few serious health risks to most women and the risks of pregnancy, delivery, and abortion outweigh the risks of using contraception for most women. However, particular attention needs to be given to women with certain characteristics and medical conditions, as use of a method that is unsafe within a certain context could result in harmful medical consequences.

The use of evidence-based guidelines in counseling women about their options will ensure that women are not exposed to inappropriate risks, while also assuring that women are not denied access to methods that are medically appropriate. The World Health Organization (WHO) has created a set of consensus guidelines—*The Medical Eligibility Criteria for Contraception*—which addresses contraceptive guidelines for women based on personal characteristics and medical conditions based on the best available evidence. This information is easily accessible in comprehensive online tables of medical conditions and personal characteristics that may affect contraceptive choice. In 2010, these guidelines were adapted for the U.S. clinical context by the Centers for Disease Control and Prevention and can be found at U.S. Medical Eligibility Criteria for Contraceptive Use, 2010: http://www.cdc.gov/mmwr/pdf.

The use of these guidelines in counseling women has ensured that unnecessary restrictions are not placed on women's choices for contraception, resulting in improved access to family planning services.

ORAL CONTRACEPTION

In 2002, the most frequently used method of contraception was the oral contraceptive pill.[6] Oral contraceptive methods continue to be the most commonly used method among American women and are a reliable method of contraception if used correctly and consistently. Studies have shown that oral contraceptives result in 3 pregnancies in 1000 women or 0.3% failure within the first year of use when used perfectly. However, an 8% failure rate has been reported with typical use. The average woman misses at least one pill per cycle,[7] and greater than 50% of users miss more than two pills by their third cycle of use.[8] It is for these reasons that oral contraception is considered a second-tier method in terms of efficacy as compared with more effective methods such as intrauterine contraception, injectables, and implants. Non-contraceptive benefits of combined oral contraceptives (COCs) include a decreased risk of endometrial cancer, pelvic inflammatory disease, endometriosis, and uterine fibroids.[9]

Mechanism of Action

COCs all contain an estrogen and a progestin component. Most current COCs in the United States contain ethinyl estradiol (EE) as the estrogen component in a 20–35 mcg dosage, which is decreased from the earlier high-dose 50 µcg EE pills, while the progestin component is one of eight different progestins. Depending on the dosage of the EE and the type of progestin, COCs are categorized as first- through fourth-generation COCs. The oldest or first-generation COCs were those with 50 µcg of EE and first-generation progestins (norethindrone, norethindrone acetate, and ethynodiol diacetate). While the first-generation progestins are tolerated well and have excellent potency, unscheduled bleeding occurs more commonly with these progestins as the dosage is lowered. Second-generation progestins (norgestrel and levonorgestrel) were developed with higher potency and longer half-lives as compared with the first-generation progestins, thus resulting in lower rates of unscheduled bleeding. Second- through fourth-generation COCs are those with a lower dosage of EE (20, 30, or 35 µcg). The second-generation progestins, however, are more androgenic than

the first-generation progestins. As a result, the third-generation progestins (desogestrel, norgestimate, and gestodene) were developed, which have increased progestational activity similar to the second-generation progestins, but with lower androgenic activity allowing for greater impact of estrogen on sex hormone-binding globulin. With higher levels of sex hormone-binding globulin, the overall levels of testosterone are reduced with the third-generation COCs, thus having a greater impact on acne and hirsutism. The newest group of progestins, the fourth generation, is drospirenone, which is a derivative of spironolactone and also has significant anti-androgenic activity and is beneficial for androgenic states such as acne, hirsutism, and polycystic ovary syndrome.[10]

Pregnancy prevention on COCs occurs by prevention of fertilization. The primary mechanism of action is due to the progestin component, which results in ovulation suppression through negative feedback on the hypothalamic–pituitary system. The levels of progestin in the chosen pill suppress GnRH pulsatility resulting in suppression of LH and FSH production and inhibition of the mid-cycle LH surge. It is critical that therapeutic serum levels of the progestin component be maintained for at least 24 h and the potency of the progestin in the pill is dependent on its potency and dosage.[9] Additionally, the progestin component results in thickening of cervical mucus, which prevents sperm from entering the cervical canal.

Initiation and Administration

Hormonal contraception can be safely initiated after careful medical history has been taken and the only required examination is a blood pressure measurement. All other routine screening tests including pap smears, breast exams, and sexually transmitted disease screening, while important, are not required at the time of initiation of contraception.[11] Traditionally, COCs are started on the Sunday after the next menses or the first day of the next menses. However, COCs can be started at any time during the cycle as long as pregnancy has been excluded. The Quick Start or Same-Day Start method allows women to begin taking their COC on the day they receive the prescription and is the preferred approach recommended by the WHO.[12] This is because Quick Start avoids a delay between method prescription and method initiation associated with the other traditional start methods. Up to 25% of women given prescriptions to start a method with their next menses or the Sunday after their menses fail to initiate their pill as instructed due to multiple factors including failure to fill the prescription, fear of side effects, or becoming pregnant in the interim.[13,14] In addition, Quick Start not only has resulted in greater initiation of a method but has also been found to have great continuation of the method by the third month as compared with the conventional methods for starting contraception.[15]

Clinical Considerations

Myocardial Infarction

Previous studies established that higher-dose estrogen pills were associated with an increased risk of arterial thrombosis and thus increased risk of MI. This increased risk of MI on COCs is attributed to the estrogen component of the pill in a dose-related response.[16] The advent of pills with less than 50 mcg of EE has decreased this risk. A comparison of women on low-dose COCs with women who have never used the pill found current users to have a relative risk of 1.3 for MI compared with nonusers. However, the increased risk was seen among women with known risk factors for MI, indicating that low-dose COCs do not significantly increase the risk of MI or stroke in healthy, nonsmoking women.[17] The overall risk for MI increases with age and is further amplified by other risk factors such as smoking and hypertension.[18,19] In addition, it has been established that the duration of use of COCs or previous use of the method does not increase the risk of MI.[20]

Stroke

Cerebrovascular disease or stroke is rare among younger women, but more common among women in their age of 40 and beyond. Women with risk factors such as smoking, hypertension, diabetes, obesity, and lower socioeconomic status have a higher risk of ischemic stroke at baseline, and healthy women who used low-dose COCs in one study did not have an increased risk of stroke.[21] Women with hypertension on COCs have 3 times the risk of ischemic stroke as compared with those women without hypertension on COCs and 15–20 times the risk of ischemic stroke in smokers on COCs as compared with nonsmokers.[22,23] Past use of COCs or duration of use does not increase the risk of either type of stroke.[24] Similarly, hemorrhagic stroke is associated with risk factors including age, hypertension, smoking, and obesity. The risk of hemorrhagic stroke is 10 times higher in COC users with hypertension as compared with COC users without hypertension and triple the risk in COC users who smoke compared with nonsmokers.[25]

Venous Thromboembolism

Venous thromboembolism (VTE) includes deep vein thromboses and pulmonary embolism and can be life-threatening. Risk factors for VTE include increasing age, obesity, previous venous compromise, immobilization, and estrogen-rich states such as pregnancy and COC use. Estrogen promotes a hypercoagulable state by increasing the clotting factors VII, VIII, and X while also increasing resistance to anticoagulant effects of activated protein C.[26] The reduction in estrogen dosage in the newer formulation of COCs has greatly decreased the risk of VTE risk associated with the COCs. Among healthy young women, the incidence of VTE is—4–5 per 100,000 women years. Pregnancy confers a significant risk of VTE because of its associated hypercoagulable state with an RR = 12 when compared with the general population (incidence of VTE = 48–60 events per 100,000). Previously prescribed higher-dose COCs containing 50 µcg or higher of EE have an RR = 6–10 when compared with the general population and an incidence of 24–60 events per 100,000. Studies have shown that with lower doses of estrogen (35 µcg or less of EE), the risk of VTE is reduced to an RR = 3–4 and an incidence of 12–20 events per 100,000 as compared with

the general population while the contraceptive efficacy is not reduced when compared with the higher-dose pills.[27–29] The absolute risk of VTE in the setting of COCs is low despite the increased relative risk when compared with nonusers because VTE is rare. The greatest risk of thrombosis in the setting of COCs is within the first year of use, a slight increase in risk persists subsequent to the first year, and the risk diminishes 30 days after discontinuation of COCs.[30] The impact of obesity and increasing age on VTE risk in the setting of COC use is significant. A large study looking at the incidence of thrombosis among women undergoing venography reported an incidence of 0.5 per 10,000 for women under 20, 1.1 for women aged 20–29, 2.6 for women aged 30–39, and 9.7 for women aged 40–49.[31] Another study compared the risk of VTE in women with body mass index (BMI) less than 25 on COCs to those with BMI greater than 25 and found that the relative risk was 1.78 for COC users with BMIs between 25 and 30, and the relative risk is 3.47 for COC users with BMI greater than 30.[32] It is for these reasons that the American College of Obstetrics and Gynecology (ACOG) cautions the use of methods with estrogen in obese women (BMI > 30) who are over 35.

The progestin component of hormonal contraception does not have any impact on the clotting system alone but, in combination with estrogen, can modify the risk of VTE. Older studies in the 1990s reported that COCs with desogestrel and gestodene (third-generation progestins) are possibly associated with an increase in venous thrombosis risk compared with formulations containing levonorgestrel and norgestrel (second-generation progestins).[33–35] These studies have been critiqued for confounding factors that may have influenced these findings. A recent large Danish prospective cohort study assessed the risk of VTE by the type of progestin and the dosage of estrogen and found that compared with oral contraceptives with the same dose of estrogen-containing levonorgestrel (second generation) and with the same dose of estrogen and length of use, the rate ratio for oral contraceptives with norethisterone was 0.98 (0.71–1.37), with norgestimate 1.19 (0.96–1.47), with desogestrel 1.82 (1.49–2.22), with gestodene 1.86 (1.59–2.18), with drospirenone 1.64 (1.27–2.10), and with cyproterone 1.88 (1.47–2.42).[36]

Genetic thrombogenic mutations such as factor V Leiden mutation, the most common inherited coagulation disorder, as well as other inherited disorders including deficiencies in prothrombin, protein C, and protein S are associated with increased risk of VTE in the setting of COC use. A WHO literature review reported an increased risk of VTE by 6.4–99.0 times the risk in COC users with factor V Leiden mutations as compared with nonusers without a mutation.[37] The use of COCs by a prothrombin gene mutation carrier increases VTE risk by 100-fold than nonusers without the mutation.[38] Despite this increased risk of VTE in the setting of inherited thrombophilias, routine screening in healthy women prior to initiation of hormonal contraception is not warranted because of the low incidence of VTE in the general population (4–5 per 100,000 women year).[39,40] The prevalence of all mutations is also rare occurring in only 0.5% of the asymptomatic population. Thus, it would require screening of a large number of women to detect and prevent one death from VTE. Screening prior to initiation of COCs is recommended only in women with a history of previous VTE or a positive family history of VTE in a first-degree relative (parent or sibling).[41]

TRANSDERMAL CONTRACEPTIVE PATCH

A transdermal contraceptive patch (Ortho Evra™) is a newer method of combined estrogen-and-progestin-based contraception. It was approved for use in the United States in 2002. The patch is a 20 cm^2 three-layer system with an outer protective water-resistant layer, a middle medicated adhesive layer, and a clear release liner inner layer, which is removed at the time of patch application. Each patch contains a total of 0.75 mg of EE and 6 mg of norelgestromin, the primary metabolite of norgestimate (third-generation progestin), and provides 20 mcg of EE and 150 mcg of norelgestromin daily.[42] This results in a sustained release of hormonal contraception over several days, thereby avoiding peak and trough hormone levels and need for daily administration. The patch is applied once a week for 3 weeks in a different discrete location each week followed by a patch-free week during which menses occurs. Application of the patch should be rotated between the lower abdomen, upper outer arm, the buttock, or the upper torso excluding the breasts.

Transdermal contraception is highly effective with efficacy rates equal to oral contraceptives with pregnancy rates equal to less than 1 pregnancy per 100 women years with perfect use.[43–45] Although typical use efficacy has not been established for the patch, studies suggest higher compliance with the patch as compared with oral contraception with patch users achieving perfect compliance more often than oral contraceptive users (88% vs. 78% of cycles).[46]

Mechanism of Action

The patch, like other combined hormonal contraception, works primarily through ovulation inhibition by hormonal suppression of gonadotropins.[47] Because transdermal contraception has the same mechanism of action and hormonal levels as the combined pill, it should be given the same considerations for contraindications and non-contraceptive benefits.

Clinical Considerations

Overweight and obese women require additional counseling regarding patch failure, as increasing weight is associated with lower serum levels of EE and norelgestromin in patch users.[48] Women weighing more than 90 kg (198 lb) may be at higher risk for failure based on findings from 3 clinical trials in which 5 of the 15 pregnancies across the 3 studies occurred in women weighing more than 90 kg.[47] Though there is a potential decrease in efficacy among heavier women, it is unclear how much lower efficacy is for these women. It is likely that a small decline in efficacy, and with appropriate counseling, may still be a reasonable choice for contraception for these women.

As is the case with combined oral contraception, transdermal contraception is also associated with an increased risk of VTE due to the estrogen component of the method. The average overall EE concentration and exposure to estrogen is 60% higher among patch users than in women using a 35 mcg EE combined pill, although the peak concentration is 25% lower.[49,50] Because of the higher overall exposure to estrogen with the patch, there is concern for increased risk of VTE as compared with COCs. Studies comparing the risk of VTE in the norgestimate-containing 35 mcg EE oral contraceptive pill with the patch have mixed results. The Boston Collaborative Drug Surveillance Program (BCDSP) has an ongoing nested case–control study that uses managed care claims data to evaluate the risk of nonfatal VTE. The primary outcome of this study is to measure the risk of nonfatal VTE in new users of either transdermal contraceptive patch or a 35 mcg EE and norgestimate COC. Their initial findings analyzing data from 2002 to 2006 reported similar risks of VTE in both the patch and the pill users with an OR of 1.0 (95% CI 0.7–1.5).[51] However, in subsequent analysis reported to the Food and Drug Administration (FDA) in 2008, BCDSP found an increased risk of VTE compared with COC users of a 30 mcg EE and levonorgestrel pill (OR = 2.0, 95% CI 0.9–4.1).[52] The same group then evaluated the risk of nonfatal risk among patch and OC users by age and found that patch-using women under 40 did not have an increased risk compared with COC users, but for women between 40 and 44 years of age, a significantly increased risk could not be excluded.[53] Another study also using insurance claims data also compared patch users with 35 mcg EE and norgestimate pill users and found a significantly higher risk of VTE among patch users compared with the pill group with an OR = 2.2 (95% CI 1.2–4.0). This study, however, compared new users of patch with continuing COC users. This introduces "new user" bias to the results, since it is well known that the highest risk of VTE in the setting of hormonal contraception occurs within the initial months of use.[54]

CONTRACEPTIVE VAGINAL RING

Many methods of vaginal contraceptive rings are available worldwide. In the United States, a combined hormonal contraceptive ring, the Nuvaring™, is the only available method currently. The ring is a flexible, soft, plastic ring made of ethylene vinyl acetate copolymer with crystals of hormone within the ring. The ring delivers 15 mcg of EE and 120 mcg of etonogestrel daily. The plastic ring is placed vaginally for 3 weeks and does not need to be fitted or placed in a specific location in the vagina, since it needs only to be in contact with the vaginal mucosa. Menses occur during the fourth ring-free week.[55]

The ring has similar risks, benefits, mechanisms of action, and clinical considerations as COCs and the patch. The ring has some specific advantages over the other methods. Monthly placement of the ring allows for ease of use and higher compliance with the method. The vaginal route of administration of hormones increases the bioavailability, as it bypasses the first-pass metabolism, resulting in lower doses of hormones required to achieve equal efficacy. A systematic review of studies comparing COCs with the ring found that overall exposure to EE was significantly lower with the ring with half of the systemic exposure to EE as compared with 30 mcg COC, less fluctuation in serum levels, but equally effective.[56] This results in lower rates of side effects related to estrogen such as breast tenderness and nausea and lower rates of breakthrough bleeding and spotting compared with these side effects on COCs.[54,57,58]

Despite the lower levels of EE in the ring, there is equivalent inhibition of gonadotropins and suppression of ovulation as a compared with a COC with 30 mcg of EE and 150 mcg of desogestrel with pregnancy rates of less than 1% in clinical trials of perfect use.[54,56,59] Like the patch, typical use efficacy has not yet been established for the ring, but perfect compliance with the ring is reported to be as high as 86%–91%, suggesting potentially higher typical use efficacy when compared with the pill.[54,60] Though the ring is conventionally placed for 3 weeks at a time, there are sufficient hormones within the ring to prevent ovulation for up to 5 weeks; therefore, the ring can be used in a continuous fashion.[58] If removed from the vagina for greater than 3 h, it is recommended that backup contraception be used until the ring has been replaced for 7 days.

PROGESTIN-ONLY METHODS

Progestins primarily act by inhibition of gonadotropin secretion inhibiting follicular development and suppressing ovulation. This results in a hypoestrogenic state less suitable for implantation. In addition, progestin causes cervical mucous thickening and decrease tubal motility resulting in difficulty for sperm to enter the cervix or travel through the tubes. As a result, fertilization is prevented even if ovulation does indeed occur. In addition, unlike estrogen-based methods, large studies have not shown an increased risk of stroke, myocardial infarction, or VTE among users of progestin-based methods.[35,61–64] Thus, progestin-only contraceptive methods are a reasonable choice for women with a history of VTE or at high risk for VTE.

Depot-Medroxyprogesterone Acetate

Injectable contraceptive methods are safe, highly efficacious, and commonly used worldwide.

Depo-Provera (depot-medroxyprogesterone acetate) is the only injectable contraceptive used in the United States. It is a convenient, discrete, and low-maintenance method and is ideal for women with contraindications to estrogen use and certain medical conditions. In addition, there are many noncontraceptive benefits to use.

According to the 2002 National Survey of Family Growth (NSFG), 5.3% of all U.S. women between the ages of 15 and 44 currently use depot-medroxyprogesterone acetate (DMPA or Depo-Provera) as their chosen method of contraception.[65] A higher proportion of women in younger age groups use DMPA with 13.9% of women aged 15–19 using DMPA compared with 10.1% between the age of 20 and 24, and 1.6%

between the ages of 40 and 44. DMPA is one of the most widely used and thoroughly studied contraceptive methods. It was approved for use as contraception in the United States in 1992. It is composed of microcrystals suspended in an aqueous solution. Studies comparing 100 mg intramuscular (IM) doses compared with 150 mg IM doses found that 150 mg IM dose (gluteal or deltoid) is required to effectively prevent pregnancy with a theoretical effectiveness of 99.7% and a lowest expected first-year pregnancy rate of 0.3%.[66] A new formulation of DMPA, 104 mg, has recently been approved for subcutaneous administration in the United States and has been dose adjusted for to be given every 12 weeks with similar efficacy rates as the IM formulation. Typical use efficacy for both options is 97% based on follow-up reinjection at 11–13 weeks.[67] Following either IM or SC DMPA injection, ovulation does not occur for at least 14 weeks (98 days).[68] However, follow-up injections are routinely scheduled at 12 weeks. Serum concentrations of DMPA are high, so efficacy of the method is not compromised by increasing body weight or medication-induced increased hepatic enzyme activity in patients with contraindications to estrogen use. DMPA, a progestin-only method, is a safe and effective alternative.

Mechanism of Action

Depo-Provera, like other progestin-only methods, alters the endometrial lining, thickens the cervical mucus, and blocks the luteinizing hormone surge to prevent ovulation. After method discontinuation, ovulation resumes at 14 weeks, but can take up to 18 months. In comparison with combined hormonal methods, DMPA does not impact follicle-stimulating hormone as consistently or as intensely. Thus, for one-third of DMPA users, estradiol levels remain unchanged from early- to mid-follicular phase levels at approximately 40–50 pg/mL. For most DMPA users, estradiol levels vary throughout the injection period and may reach postmenopausal levels of <20 pg/mL, but vasomotor symptoms such as hot flashes and vaginal atrophy are uncommon in DMPA users. Absence of these symptoms is likely due to the fact that progestins, like estrogens, also suppress these symptoms and can be used for menopausal women who need to avoid estrogen therapy.[69]

Onset of contraceptive efficacy of DMPA is within 24 h after injection and is maintained for at least 14 weeks, providing a margin of protection if reinjection typically scheduled at 12 weeks is delayed. If reinjection is delayed beyond 14 weeks, women should be questioned regarding unprotected intercourse since they were due for their injection and should be evaluated for emergency contraception.[70] Subsequent studies have suggested that a grace period as long as 4 weeks is reasonable, and the WHO has adopted the longer grace period in its updated guideline.[71]

DMPA takes 6–8 months after the last injection to disappear, and clearance is slower in heavier women. Approximately half of women who discontinue DMPA can expect normal menses to return in 6 months after the last injection, but 25% will take a year before resumption of a normal menstrual pattern. This delay should be taken into consideration when counseling patients about method choice.[72]

Clinical Considerations

DMPA as a progestin-only method can be used in patients with contraindications to estrogen, such as women over age 35 at risk because of smoking, hypertension, or diabetes. DMPA can also be used safely in women with seizure disorder, sickle-cell anemia, congenital heart disease, migraines with aura, and a previous history of VTE. Observational data from epidemiologic studies and a WHO case–control study have not shown increased risks of stroke, myocardial infarction, or VTE.[60] DMPA is a good contraceptive option for women with a history of seizure disorder and sickle-cell anemia. In patients with seizure disorder taking antiepileptic drugs, hepatic enzyme activity increases the metabolism of contraceptive steroids, and thus oral contraceptives are not recommended in these patients as per WHO guidelines. However, DMPA hormone levels are high enough that contraceptive efficacy is not compromised by increased metabolic activity of hepatic enzymes. Furthermore, DMPA can have a beneficial effect on seizure control, as it is thought that progestins increase the seizure threshold in patients with seizure disorders. In patients with sickle-cell anemia, there is evidence that DMPA results in decreased sickling of red blood cells and a reduction in the frequency and intensity of sickle-cell crisis. Non-contraceptive benefits of DMPA also include a decreased risk of endometrial cancer,[73] which is similar to that observed with oral contraceptive pills. In addition, like oral contraceptive pills, DMPA decreases the risk of pelvic inflammatory disease, endometriosis, and uterine fibroids.

Lactation

The physiologic changes required for breast-feeding are dependent on the drop in serum concentrations of progesterone after the delivery of the placenta. This mechanism causes some concern regarding the use of DMPA during breast-feeding. A prospective cohort study evaluated the effect of early administration of DMPA on initiation of breast-feeding. This study found no adverse effects on breast-feeding. However, the mean time of initiation of DMPA was 50 h postpartum.[74] This delay should be kept in mind when initiating DMPA postpartum as there is a theoretical risk of decreasing breast-feeding if progesterone is introduced too soon after delivery, not allowing for the natural physiologic drop in progesterone to occur for initiation of milk production. Studies have shown no adverse effect on breast-feeding in women who receive DMPA at postpartum follow-up visits. In particular, there was no effect on the quantity and quality of milk production while on Depo-Provera. Thus, DMPA can safely be administered at the 2 or 6 week postpartum visit. This schedule will provide full contraceptive protection for lactating mothers in whom ovulation does not occur until at least 12 weeks after delivery.

Use of DMPA does not affect the duration of breast-feeding. The concentration of DMPA in the breast milk is negligible, and no effects of the drug on infant growth and development have been observed. One group of women, obese Latina women with prior gestational diabetes, requires extra

caution when prescribing DMPA postpartum. In this group of breast-feeding women who were taking the progestin-only oral contraceptive pill, a threefold increased risk of non-insulin-dependent diabetes was observed.[75] It is unknown whether other progestin-only methods might pose a risk in obese Latinas who have a history of gestational diabetes.

Unlike most other methods of hormonal contraception, there are a few major side effects associated with Depo-Provera use. Proactive counseling about the expected side effects should be provided as women who are well informed about their method tend to have higher continuation rates. Major side effects on DMPA include irregular menstrual bleeding, breast tenderness, weight gain, depression, acne, and headache. These side effects combined resulted in over 70% discontinuation at 1 year with irregular bleeding being the most common side effect. One-quarter of women initiating DMPA use discontinue it due to irregular bleeding in the first year.[76] If bleeding occurs shortly after beginning DMPA, patients should be counseled and advised that irregular bleeding decreases with the use of DMPA for a few more cycles. Overall incidence of irregular bleeding is 70% in the first year with a decrease in irregular bleeding with each reinjection, and rates as low as 10% after the first year. Fifty percent of the patients report amenorrhea by 1 year with 10% becoming amenorrheic by the first injection interval, 40% reporting amenorrhea by the fourth injection cycle, and 80% reporting amenorrhea at 5 years.[71] Irregular bleeding that begins several months after initiation is due to decidualization of the endometrium and can be treated with exogenous estrogen such as 1.25 mg conjugated estrogens, or 2 mg estradiol, given daily for 7–14 days. In addition, nonsteroidal anti-inflammatory drugs given for a week or oral contraception pill supplementation during the first 1–3 months of DMPA injection, which is when irregular bleeding tends to be worst, can be used for treating it. These interventions will decrease bleeding in the short term, but irregular bleeding will resume after discontinuation.[77,78] Overall continuation of DMPA at year 1 is about 33%, 50% at year 2, and as low as 20% at the end of 3 years.[76]

Weight gain is a common complaint among DMPA users with approximately 2.1% of users discontinuing the method due to weight increase. As is the case with other hormonal contraceptive methods, weight gain while using DMPA may be a result of dietary changes and aging and not hormonally induced. Studies of weight gain and DMPA use have shown mixed results. Prospective randomized controlled studies evaluating weight gain in normal-weight women showed no relationship between DMPA use and food intake, energy expenditure, or body weight.[79]

However, in certain subgroups, DMPA use has been correlated with weight gain. A systematic review found that obese adolescent DMPA users gained more weight compared with normal-weight users, but this was not the case with adults.[80] Similarly, it has been show that Navajo women using DMPA have significant weight gain.[81] Potential weight change should be taken into consideration when counseling patients about using DMPA.

Cancer

Though earlier small studies were suggestive of an association between DMPA use and breast cancer,[82] recent studies have shown that there is no such increase in risk. A large international case–control study found the overall relative risk of breast cancer associated with the use of DMPA was 1.1 (95% CI = 0.97–1.4) with no increase in risk with the duration of use. However, those DMPA users who had initiated use within the past 5 years were found to have increased risk (RR = 2.0; 95% CI = 1.5–2.8).[83] As is the case with oral contraceptive pills and hormone replacement therapy, it is possible that DMPA accelerates the growth of an already present tumor or detection of the tumor occurred earlier because of study-related surveillance. More recent data have also shown no association with DMPA and breast cancer and also did not show an increase in risk in recent or current users of the method.[84,85]

Multiple studies including data from the WHO Collaborative Study of 2009 women with invasive cervical cancer and greater than 9000 controls failed to demonstrate a significantly increased risk of cervical cancer among DMPA users (RR = 1.1; 95% CI = 1.0–1.3).[86]

Strong evidence supports a reduction in the risk of endometrial cancer in DMPA users at least as great as that seen with oral contraceptive users; relative risk was 0.21 (95% CI = 0.06, 0.79) in women who had never used DMPA.[73] There is no evidence for increased risk of ovarian cancer with DMPA use, and potentially a modest decrease in overall risk.

Depression

Although DMPA labeling suggests that depression may worsen with use of the method, studies regarding the impact of DMPA use on mood are inconclusive. One study showed a slight increase in DMPA users while other studies have not shown an association.[87–89] A prospective study set in an urban clinic compared adolescents on DMPA with controls and used two standardized questionnaires, the Beck Depression Inventory and the Multiple Affect Adjective Checklist-Revised, and found no statistically significant differences in depressive symptoms when using DMPA as a contraceptive agent over a period of 12 months and no significant changes in negative or positive affect.[90] There is little evidence for increasing depression with short- or long-term DMPA use, and it is not a contraindication to DMPA use as per WHO and CDC guidelines. Thus, depression should not be a reason to withhold DMPA administration in patients for whom DMPA is an ideal contraceptive method.

Cardiovascular Disease

Studies have not shown an increase in adverse cardiovascular effects including venous thrombosis, stroke, and acute myocardial infarction in the past or current DMPA users.[60,91–93] The ACOG states that progestin-only methods of contraception including DMPA are an appropriate contraceptive option for women with a previous history of VTE or in women with other contraindications to estrogen therapy.[94]

The overall impact of Depo-Provera on lipoproteins remains uncertain. There seems to be no clinically significant

alterations in lipoprotein profiles while on Depo-Provera. It is thought that there may be no impact on lipoproteins due to the avoidance of a first-pass metabolism through the liver. However, there does seem to be a theoretical risk of increased total cholesterol and low-density lipoprotein cholesterol and a decrease in high-density lipoprotein cholesterol during the initial period after initiation of DMPA. A multicenter clinical trial by the WHO found a transient adverse impact in the first few weeks after injection when hormonal levels in the blood were high.[86] In addition, use of DMPA has been shown to reduce plasma high-density lipoprotein levels and peripheral arterial hyperemia-induced flow-mediated dilatation. However, there is no increase in coagulation factors and there is no impact on blood pressure.[95–97] The clinical significance of these findings is unclear. Depo-Provera does not affect carbohydrate metabolism or coagulation factors, and lipid changes have not been linked to adverse cardiovascular effects.[98]

Effect on Bone Density

A major concern about the safety of long-term DMPA use is its effect on bone mineral density (BMD). Due to the decrease in endogenous serum estradiol levels secondary to DMPA's suppression of gonadotropins, a relative hypoestrogenic state exists among users, which is associated with increased bone resorption.[99] Given this physiologic change in DMPA users, there has been increasing concern about the impact of DMPA on bone health. In 2004, the U.S. FDA added a black box warning to DMPA labeling, which stated that women who use DMPA might lose significant BMD. The warning also cautioned providers that bone loss increases with greater duration of DMPA use and may not be completely reversible. Furthermore, the warning states that it is unknown whether use of DMPA during adolescence or early adulthood will reduce peak bone mass or increase risk for osteoporotic fracture later in life. The FDA then concluded that DMPA should be used as birth control for longer than 2 years only if other contraceptive methods are not advisable.

The BMD effects of DMPA are equivalent to those during hypoestrogenic states of pregnancy and lactation. A hypoestrogenic state occurs in which bone resorption exceeds bone formation, resulting in a decline in bone density.[100]

Comparing DMPA users with nonusers, it appears that BMD at the hip and spine of DMPA users decreases by 0.5%–3.5% after 1 year of use and by 5.7%–7.5% after 2 years of use.[101] However, the greatest loss in BMD occurs within the first year to second year of use with little incremental BMD loss during additional years of use.[102–107]

Available data do not suggest that DMPA will reduce peak bone mass and increase the risk of osteoporotic fracture rate. A systematic review of DMPA studies revealed that longitudinal data from adult DMPA users had results that differed about the rates of BMD reduction and seemed to change over time. Most studies showed reduction in BMD of less than 1% per year of use.[108]

There are no data on postmenopausal fracture rates in women who used DMPA as adolescents or adults; thus, the clinical significance of DMPA-associated decline in BMD is unknown. Furthermore, most of the evidence currently available indicates that women regain BMD after discontinuation of DMPA use. A 7 year prospective study found that at 96 weeks (1.8 years) after DMPA was discontinued, total hip BMD had returned almost to baseline levels, only −0.20% lower than baseline, and BMD measurements at the lumbar spine showed partial recovery (−1.19%).[109] After discontinuation of DMPA in adult women users, BMD recovery differed by anatomic site and length of DMPA use. All women had returned to levels comparable with nonuser controls by 76 months and returned to baseline levels by 92 months. Two years after discontinuation of long-term (median 10 years; range: 3–17 years) DMPA use, BMD in the lumbar spine increased significantly ($P < 0.002$), with mean increases overall of 3% (0.4%–5.6%) at 1 year and 6.4% (3.4%–9.4%) at 2 years.[110] Because adolescence is a period of critical bone formation, there has been even more concern about the use of DMPA in adolescent users. Evidence regarding DMPA use in adolescents and BMD recovery is similar to that in adults and is overall reassuring. A population-based prospective cohort study of 170 adolescent girls of age 14–18 including 80 DMPA users at baseline followed BMD at various anatomic sites every 6 months for up to 24–36 months and compared measurements among girls who used DMPA, those who discontinued use during the study, and nonusers. DMPA use was associated with BMD loss during use; however, the mean BMD at all anatomic sites reached or exceeded the levels of never-users by 12 months after DMPA discontinuation, a faster rate of recovery than that seen in the adult studies.[111]

In response to the FDA black box warning and changes in Depo-Provera labeling, many professional organizations including the ACOG, the Society for Adolescent Medicine (SAM), and the WHO reviewed the existing evidence and endorsed guidelines differing from DMPA product labeling. All three of these organizations stated that though there is an association between DMPA use and decreased BMD, there is a lack of quality evidence demonstrating a significant increase in risk of fractures in DMPA users, and the advantages of DMPA use for contraception generally outweigh the theoretical concerns about skeletal health.[112] There should be no restriction on initiation or duration of Depo-Provera use in adult women who are eligible to use this method as the risk of osteoporotic fractures is only theoretical and does not warrant alteration in current practice patterns. Furthermore, adolescents should not be denied DMPA as the risk of unintended pregnancy far outweighs the theoretical concerns about fracture risk. Overall risks and benefits for continuing DMPA use and counseling for all methods of contraception should be reviewed and reconsidered at 2 years and then periodically over time with individual users.

Bone densitometry testing or antiresorptive agents should not be used in otherwise healthy adolescents or adults before, during, or after DMPA use.[113,114] All users of contraception, including DMPA users, should be encouraged to perform weight-bearing exercise, not to smoke, and have a sufficient amount of dietary calcium (1300 mg) and vitamin D (400 IU) daily in order for adolescents to attain peak bone mass and adults to decrease osteoporotic risk. Concerns about skeletal

health in adults and adolescents should not restrict initiation, continuation, or duration of DMPA use.

Effect on Future Fertility

Despite concern about the delay in becoming pregnant after cessation of DMPA use, it does not permanently suppress ovarian function, and the pregnancy rate in women with a desire to become pregnant after discontinuing DMPA is normal. By 18 months after discontinuation of the method, 90% of Depo-Provera users have become pregnant, which is the same proportion as other methods.[115] There is, however, a delay in conception after DMPA. This delay is approximately 9 months after discontinuation of the method, and there is no increase in the delay with duration of use. Need for pregnancy planning should be taken into consideration when counseling patients as those patients wanting to conceive immediately after stopping the method should not use DMPA. If menstrual function remains suppressed beyond 18 months after discontinuation, further evaluation of other etiologies unrelated to DMPA administration should be pursued.

CONTRACEPTIVE IMPLANT

A number of different contraceptive implants have been developed, with Implanon™, a single-rod progestin implant, the only one available in the United States. Implanon is a 40 mm × 2 mm semirigid plastic rod made of ethinyl acetate with 68 mg of etonogestrel crystals suspended within. It is placed within the subdermal region in the inner upper arm and is effective for up to 3 years. There is an initial release of 60–70 mcg/day with a decline to 35–45 mcg/day at the end of the second year followed by additional decline to 25–30 mcg at the end of the third year.[116]

Efficacy

Implanon is a highly effective method with less than 1 pregnancy per 100 women in 1 year. It is considered among the most effective methods of contraception with actual efficacy equivalent to sterilization and intrauterine contraception because it does not rely on patient compliance with the method.[117] An analysis of 942 women enrolled in 11 clinical trials over 2–4 years found no pregnancies to occur during this time period.[63] The efficacy of Implanon has not been evaluated in women with a BMI greater than 30 kg/m^2. Efficacy may be decreased in women taking medications that are hepatic enzyme inducers that affect the metabolism of etonogestrel, as is the case with other hormonal methods of contraception including the pill, patch, and ring.

Mechanism of Action

Implanon's primary mechanism of action is suppression of gonadotropin secretion thereby inhibition of ovulation.[118] In addition, the progestin inhibits gonadotropin secretion resulting in a hypoestrogenic state. This leads to inhibition of endometrial proliferation resulting in a less hospitable environment for implantation. The progestin effect also leads to thickening of the cervical mucous and decrease in tubal motility, impeding sperm penetration and migration.[119]

Clinical Considerations

As is the case with other progestin-only methods, Implanon causes significant bleeding changes among most users, and this is the most common reason for discontinuation. The changes with Implanon are unpredictable and can fall into a wide range of bleeding patterns including prolonged bleeding, frequent bleeding, irregular bleeding, infrequent bleeding, or amenorrhea.[120–125] After Implanon removal, etonogestrel levels become undetectable within 1 week, and most women ovulate within 6 weeks, with menses returning to normal for the majority of women by 3 months.[117,126]

Implanon is approved for contraception only, but has also been shown to treat dysmenorrhea and endometriosis. One study of 315 women reported a 48% decrease in dysmenorrhea after insertion likely due to decrease in ovulatory bleeding induced by Implanon. It has also has been shown to decrease endometriosis-related pelvic pain.[119,127] Unlike DMPA, the progestin levels in Implanon are significantly lower, and thus it does not appear to have an effect on bone density despite the hypoestrogenic state. There is also no evidence to suggest changes in lipid metabolism or liver function.[128]

Insertion and removal of Implanon requires a simple office-based procedure under local anesthesia by a trained provider who has undergone an FDA-required training session through Merck, the marketer of the device. Complications related to insertion or removal are rare. The device can be removed at any time, but must be removed by the end of 3 years. If the patient desires reinsertion at 3 years, Implanon can be removed and replaced with a new rod simultaneously through the same incision or in the other arm.

INTRAUTERINE CONTRACEPTION

Intrauterine contraceptives (IUCs) are one of the oldest methods of contraception used worldwide, with numerous types of devices available globally. Most modern IUCs contain either copper or progestin to accentuate the mechanism of action of the device itself and increase contraceptive efficacy. Progestin-containing IUCs are known as an intrauterine system (IUS). The modern IUC is a long-acting highly effective, reversible method of contraception with minimal side effect.[129]

Despite these benefits, IUCs remain underutilized in the United States with only 2% of contraceptive users choosing the method in 2002 as compared with 27% of contracepting women in Europe and 50% of contracepting women in Asia.[130–132] The limited use of modern IUCs currently in the United States stems from much of the fear that surrounded the Dalkon Shield, an IUC used in the 1970s, which was linked to increased risk of pelvic inflammatory disease, which resulted in discontinuation of the method. The risk of infection with the Dalkon Shield was due to the braided multifilament string. Modern IUCs have monofilament strings

and do not have the same infectious complications as the Dalkon Shield.[133,134] In addition, other factors such as misperceptions about the risks of ectopic pregnancy, infection, and infertility as well as lack of clinical training and fears of litigation have also led to limited use within the United States.[135]

Recent data from the NSFG show a changing trend with an increase to 5.5% of women using the method between 2006 and 2008 as compared with 2.0% in 2002 likely due to the increasing data on safety and non-contraceptive benefits as well as women's positive experiences.[136]

In the United States, women can currently use the Copper T380A (CuT380A or Paragard™) IUD or the levonorgestrel-releasing intrauterine system (LNgIUS or Mirena™). CuT380A was approved by the FDA in 1984 and first marketed in 1988 for 10 years with evidence indicating efficacy through 20 years.[137,138] The CuT380A is composed of a T-shaped polyethylene frame with 380 mm^2 of exposed surface consisting of fine copper wire and an attached polyethylene monofilament string. The device is radiopaque and latex free, and clinically significant allergy to copper is very rare.[139]

Perfect use efficacy and typical use are extremely high for all IUCs as they are long-acting reversible methods of contraception with little need for patient compliance. If women use the CuT380A perfectly, which means that they are checking strings routinely to detect expulsion, the first-year pregnancy rate is 0.6% while with typical use (no routine string checks), the first-year pregnancy rate is 0.5%–0.8%.[140,141]

The LNgIUS was approved in December 2000 and was first marketed in 2001 for 5 years of use though evidence supports efficacy through 7 years.[142] It consists of a T-shaped polyethylene frame with 52 mg of levonorgestrel, which initially releases 20 mcg of levonorgestrel daily declining to about 14 mcg/day after 5 years, which is within the therapeutic range. Limited systemic absorption of levonorgestrel does occur, and some women can experience some systemic side effects related to this. However, compared with an oral contraceptive containing 150 mcg levonorgestrel, the mean plasma concentration with the LNgIUS is only 5% of that with the pill. It is the hormonal method with the lowest possible systemic levels of hormone.[143] LNgIUS is also latex free and radiopaque and, thus, visible by x-ray. Similar to the CuT380A, the LNgIUS is highly effective with the first-year pregnancy rate equal to 0.1% with perfect use and 0.1%–0.2% with typical use.[141]

Mechanism of Action

The exact mechanism by which IUCs prevent pregnancy is not completely understood. However, it is likely that several factors are involved, including a foreign body effect secondary to the plastic frame, in addition to actions specific to the copper or levonorgestrel. The primary mechanism of action is prevention of fertilization. They do not act as an abortifacient as they do not interrupt an implanted pregnancy.[139] The foreign body effect results in a sterile inflammatory reaction within the uterine cavity that is toxic to sperm and inhibits sperm motility and survival. It is also toxic to ova and impairs implantation.[139,144–149] The CuT380A undergoes an in utero oxidation, which releases free copper and copper salts, enhancing the cytotoxic inflammatory reaction within the endometrium, which is toxic to sperm and ova.[145,146] Levonorgestrel secreted by the LNgIUS causes cervical mucous thickening, which creates a barrier for sperm, preventing penetration into the upper genital tract.[132] Additionally, like other progestin-based methods, the LNgIUS causes endometrial decidualization and glandular atrophy resulting in a suboptimal environment for fertilization.[150] Because the serum levels of levonorgestrel are very low, there is a limited effect on ovarian follicular development and ovulation, with at least 75% of women who use the LNgIUS ovulating regularly.[151]

Clinical Considerations

For most women, an IUC is an excellent option for contraception as it is a highly effective, long-acting, rapidly reversible, and cost-effective method with very few side effects. It offers a minimally invasive, but equally effective alternative to tubal sterilization. Ideal candidates for IUCs include women of reproductive age who desire highly effective reversible contraception, are not planning a pregnancy for at least a year, are at low risk of acquiring sexually transmitted infection, and want or need to avoid estrogen-based methods. In addition, nulliparous women, adolescents, and women with a history of pelvic inflammatory disease or ectopic pregnancy can all safely use the IUC.[141,152–155] IUCs can be placed safely immediately postpartum and post-abortion and in women who are breastfeeding.[156] There is a rapid return to fertility immediately after the removal of either IUC, and no increased risk of infertility. A large case–control study of nulligravid women with tubal infertility found no association with history of CuT380A use, but there was an increased risk of tubal infertility among women who had a history of prior Chlamydia infection.[157]

There are very few evidence-based absolute contraindications to intrauterine contraception. Major conditions in which an IUC is contraindicated include severe uterine distortion including bicornuate uteri, fibroids severely distorting the cavity, and other distorted uterine cavities that can result in increased risk of expulsion.[158,159] Fibroids that minimally distort the cavity are not contraindicated, and IUCs have been placed bilaterally in bicornuate uteri to ensure efficacy from placement in both horns. Active pelvic infection including pelvic inflammatory disease, endometritis, mucopurulent cervicitis, and pelvic tuberculosis are contraindications for IUC, as presence of a foreign body may worsen infection or delay resolution. Women with previous infections can have an IUC placed 3 months after treatment.

Most women can safely use either the CuT380A or LNgIUS. Counseling is focused on a discussion of a woman's menstrual history, medical history, preferred bleeding pattern, desire for lighter bleeding or spotting, and less painful menses. Women who may prefer the copper IUC include women with breast cancer within 5 years, women who want to avoid exogenous hormones, and those who want to continue to have monthly

menses. Women choosing the CuT380A should be counseled about that their menses may be heavier, longer, and more uncomfortable especially during the first 3–6 months after insertion. Several non-contraceptive health benefits with the LNgIUS may result in women choosing the method instead of the CuT380A. Women using the LNgIUS have a reduction in dysmenorrhea and menorrhagia including decreased bleeding among women with bleeding diatheses and on anticoagulation.[160,161] The LNgIUS also decreases pain from endometriosis, has a protective effect on the endometrium, can be used for treatment of nonatypical endometrial hyperplasia, and protects against pelvic inflammatory disease due to the barrier effect of progestin-induced cervical mucous thickening.[158,162–165] The LNgIUS is a good choice for women who prefer amenorrhea, which occurs over time, and are comfortable with unscheduled light bleeding. Of LNgIUS users, 50% have amenorrhea at 24 months, 25% have oligomenorrhea, and 11% have spotting while the rest have normal or heavy bleeding.[166]

EMERGENCY CONTRACEPTION

Women who have had recent unprotected intercourse or possible failure of another method of contraception are candidates for emergency contraception. In the United States, emergency contraception is available over the counter for men and women who are of age 17 and older while a prescription is required for patients who are 16 and under. There are no medical contraindications to emergency contraception.

Mechanism of Action

The mechanism of action of emergency contraception is not completely understood, but strong evidence indicates that the primary mechanism is inhibition of ovulation and prevention of fertilization. In addition, there is some impact on the endometrium preventing implantation and decrease in tubal transport of sperm and ova in the setting of emergency contraception.[167–172]

Efficacy

Although women can conceive only during specific periods of time during their cycle, emergency contraception is offered when indicated at any point in the menstrual cycle due to the uncertainty in the timing of ovulation. Use of oral emergency contraception is reported to result in pregnancy rates of 0.2%–3% and 0.0%–0.2% with use of copper intrauterine contraception.[173–176]

Options

Several methods of emergency contraception are available in the United States including combined EE (Yuzpe regimen) plus levonorgestrel, levonorgestrel alone (Plan B™), CuT380A and IUC, and the newest available method is the antiprogestin ulipristal acetate (Ella™).

Levonorgestrel alone (Plan B™) is the preferred method over the Yuzpe regimen as it has been proven to be more effective and associated with lower side effects. It can also be self-administered, thus not requiring a clinic visit as compared with the CuT380A IUC. Levonorgestrel is now available in a single 1.5 mg single dose as Plan B One-Step™. Both the Yuzpe and levonorgestrel regimens are most effective if given as soon as possible after unprotected intercourse, and efficacy is the highest within the first 72 h after unprotected intercourse.[177–180] Both regimens can be given up to 120 h from unprotected intercourse, but women should be counseled that efficacy is likely reduced as compared with administration at less than 72 h.

The advantage of placing the CuT380A for emergency contraception is that it is slightly more effective over a longer period of time (through 120 h) than the oral regimens and provides ongoing contraception after the initial event.

Ulipristal acetate is a 30 mg antiprogestin and was found to be as effective as levonorgestrel within the first 72 h after unprotected intercourse. Studies have shown that ulipristal has greater efficacy as compared with levonorgestrel between 72 and 120 h after unprotected intercourse and has been FDA approved since August 2010 for use up to 120 h from unprotected intercourse.[181]

No routine follow-up is required after administration of emergency contraception, but women should be advised that they should take a pregnancy test if they do not have menses within 3–4 weeks of taking emergency contraception. Women should be counseled to seek medical care if they have persistent vaginal bleeding or abdominal pain. Lastly, women should be counseled to start another method of contraception immediately after using emergency contraception because of the ongoing risk of unintended pregnancy with unprotected intercourse.

An essential part of providing holistic care to women includes evidence-based reproductive health care. Health care providers should arm themselves with the latest knowledge in order to help care for women as equal partners in their health care, allowing them to make informed choices in contraception.

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71 Prevention, Screening, and Treatment of Sexually Transmitted Infections

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CONTENTS

Prevention 885
Epidemiology 885
Education 886
Contraceptive Counseling 886
Vaccines 887
Viral Suppression 887
Male Circumcision 887
Screening 887
Sexual History 887
Risk Factors 887
Screening Guidelines 888
Special Populations 888
Adolescents 888
Pregnant Patients 888
Lesbians 888
Sexual Assault Victims 888
Diagnosis and Treatment 888
General Principles 888
Pelvic Inflammatory Disease 889
Chlamydia 889
Gonorrhea 890
Syphilis 890
Hepatitis B Virus 891
Hepatitis C Virus 891
Human Immunodeficiency Virus 892
Herpes Simplex Virus 892
Condylomata Acuminata 893
Trichomoniasis vaginalis 894
Molluscum Contagiosum 894
Pediculosis Pubis 894
Chancroid 895
References 895

Physicians and other health care providers play a major role in prevention, screening, and treatment of sexually transmitted infections (STIs). From practices as simple as ensuring educational messages through posters and brochures in the offices to communication styles that encourage open dialogue, to offering up-to-date prevention, screening, and treatment practices, today's health care provider is a vital part of ensuring the sexual and reproductive health of the population.

PREVENTION

Epidemiology

Every year nearly 900,000 women are diagnosed and treated for chlamydia while nearly 200,000 are diagnosed and treated for gonorrhea. These infections represent the two most common STIs; however, a myriad of other infections also result in significant morbidity. Several of the most common STIs are reported to the Centers for Disease

TABLE 71.1
Incidence of STIs in Women as Reported to the CDC in 2008

Disease	Incidence	Rate per 100,000 Women
Chlamydia	899,860	579.98
Gonorrhea	182,849	117.85
HIV (2006)	14,472	9.33
Total syphilis	13,210	8.51
Chancroid	14	0.01

Note: Most recent data available for HIV is from 2006.

Control (CDC) as seen in Table 71.1; however, these numbers probably reflect a significant underrepresentation.[1] Many STIs are undiagnosed while others are not required to be reported to the local public health department.

Of particular concern is the prevalence of STIs among America's youth. Of the approximately 19 million cases of STIs that occurred in 2000, 48% were among persons aged 15–24. Of these infections, 88% consisted of human papillomavirus (HPV), chlamydia, and trichomoniasis.[2]

Education

Education is of critical importance in the prevention of STIs. There are many opportunities for education, including in schools, in community groups, and at the health care provider's office. Sexual education in public schools has a potentially broad reach but has been subject to great controversy in recent years, particularly surrounding abstinence-only education. Under Title V, Section 510 of the Social Security Act in 1996, Community Based Abstinence Education projects, and the Adolescent Family Life Act Program, the federal government supplies approximately $175 million annually for abstinence-only education.[3] Notably, multiple organizations including the American College of Obstetricians and Gynecologists (ACOG) and Planned Parenthood, as well as the American Academy of Pediatrics, strongly recommend against abstinence-only education.[4,5] In 2007, the U.S. Congress sponsored a study of abstinence-only education's efficacy. The resulting document by Mathematica Policy Research showed no differences in the rates of abstinence or condom use among adolescents exposed to the abstinence-only education programs as measured in 2500 adolescents 4 years after the educational exposure. Additionally, these youth were less likely to acknowledge that condoms prevent STIs and human immunodeficiency virus (HIV) in particular.[6] Concerns have been raised that abstinence-only education may be inaccurate, reinforcing the role of the health care provider in giving evidence-based counseling.[5]

Contraceptive Counseling

Arguably the best contraceptive method for prevention of STIs is the male condom.[7] It is sometimes lauded as the singular method of contraception also effective at preventing transmission of infection, including HIV; however, it is not without disadvantages.[8] First, condoms do not fully protect against diseases spread by skin-to-skin contact, namely, genital herpes simplex, syphilis, chancroid, and HPV.[9] Second, the failure rate is approximately 14% with typical use, as it is dependent on consistent use and proper placement. Still, the male condom is responsible for reducing the number of infections in communities. With regard to HIV, consistent use of the male condom appears to reduce the risk of infection by 80% in heterosexual couples as compared with couples without any condom use.[10] An extensive meta-analysis showed that condoms also reduce the genital herpes simplex virus (HSV)-2, syphilis, and chlamydial infection rates in both men and women as well as reduce gonorrhea and trichomoniasis infections in women.[11]

Other barrier methods are also worth noting, including the female condom and cervical barriers such as the cervical cap and diaphragm. The female condom first became available in the United States in 1993 with an updated model (the nitrile FC2 condom) receiving FDA approval in 2009. The updated FC2 has pregnancy failure rates of 5% and 21% at 12 months for perfect and typical use respectively.[12] Limited data suggest that the female condom is impenetrable to HIV, cytomegalovirus (CMV), and presumably other sexually transmitted diseases.[13] One study investigated the rate of STIs in a group of sex workers using only the male condom or using their preference of the male or female condom. This study group had a nonsignificant reduction in STI after 24 weeks in those with access to the female condom, again suggesting that the female condom is an efficacious barrier to STIs.[14] There are limited data on cervical barriers as a means of preventing infection. A review in 2005 concluded that there was a "suggestion" that these methods did indeed provide some protection although this review cites only observational data.[15]

An exciting area of research and development is vaginal microbicides, which are topical agents that potentially would prevent HIV transmission and may function well as an adjunct to another method such as the male condom. Several classes of microbicides have been developed including surfactants, membrane disruptors, vaginal milieu protectors (altering pH), viral entry inhibitors, and reverse transcriptase inhibitors.[16] Unfortunately, to date no effective microbicide is available.[16]

Of note, intrauterine contraceptive devices are not contraindicated in patients with a prior history of sexually transmitted disease or pelvic inflammatory disease (PID). As per the World Health Organization Medical Eligibility Criteria, only current PID, current purulent cervicitis, active chlamydial, and gonorrheal infection are relatively or absolutely contraindicated (WHO category 3 or 4) in an otherwise low-risk patient.[17] Placement of an intrauterine device elevates a patient's risk of PID approximately sixfold for 20 days.[18] Beyond this window, there is no elevated risk of PID. If a patient has an active chlamydial or gonorrheal infection at the time of insertion, there is an approximately 11% risk of

developing PID.[19] There is currently no recommendation for routine screening at the time of insertion or any role for prophylactic antibiotics in a patient with a benign pelvic examination. The manufacturers of both the Tcu380A and LNg 20 devices recommend testing "as indicated" by the patient's risk factors.[20,21] This recommendation is concordant with those issued by the ACOG.[22]

Vaccines

Vaccines are now available for two STIs: hepatitis B virus (HBV) and select stains of HPV. The hepatitis B vaccine is administered in a series of three immunizations at 0, 1, and 6 months. Approximately 3%–6% of recipients do not seroconvert.[23] The CDC recommends universal immunization starting at the time of birth.[24]

Initially marketed in 2006, there are now two different vaccinations for HPV. The first vaccine, Gardasil produced by Merck, protects against HPV strains 6, 11, 16, and 18, which are responsible for both genital warts (6 and 11) and cervical dysplasia (16 and 18). A more recent vaccine, Cervarix produced by GlaxoSmithKline, protects against strains 16 and 18 only. There is some evidence that Cervarix offers protection from additional oncogenic strands of HPV in addition to 16 and 18.[25] Both of these vaccines are given in a series of three immunizations. The Advisory Counsel on Immunization Practices recommends immunization of all girls ages 11 and 12 with a catch-up schedule up to age 26.[26] Notably, protection from cervical intra-epithelial neoplasia 2 or more is greatly affected by timing of the vaccine. Efficacy among women who were HPV naive was approximately 97% while for the general population this number fell to 44%.[27] Thus, universal administration of the vaccine series prior to the initiation of sexual activity significantly increases its efficacy and reduces HPV infections.

Viral Suppression

Medical viral suppression is available for genital herpes as a method of prevention of transmission, in addition to symptomatic relief for the patient. In a study of heterosexual herpes-discordant couples, taking valacyclovir 500 mg once daily reduced transmission over the course of 8 months from 3.6% to 1.9%. Additionally, the affected partner had a decrease in outbreaks.[28]

Male Circumcision

By removing the foreskin and thus eliminating a moist environment where infection can proliferate, male circumcision significantly reduces the risk of HPV, HIV, and HSV transmission.[29] Randomized controlled trials on adult men in Kenya showed a 50%–60% reduction in the rate of HIV acquisition as well as a significantly reduced risk of high-risk HPV (14.8% decreased from 22.3%), a trend to lower rates of trichomoniasis infection, and no effect on gonorrheal infection. These data may potentially be extrapolated to neonatal circumcision as well. Although circumcision is clearly not a complete solution to the prevention of STIs, it may play a role. Furthermore, the decision to perform a male circumcision is influenced by surrounding cultural and religious practices.

SCREENING

Sexual History

The first step in screening any patient for STIs is to take a sexual history. This can allow for targeted screening of asymptomatic patients according to risk group. Of utmost importance is creating a nonjudgmental open environment in order to obtain the essential information. The CDC has developed a five-part questionnaire for this purpose (Table 71.2).[30]

Risk Factors

The sexual history allows the provider to identify a patient's risk factors and counsels the patient appropriately. Statistically significant risk factors for current infection include younger age (less than 17 years old) at the time of evaluation, younger age at first intercourse, multiple sexual patterns, history of prior STI and/or PID, low socioeconomic

TABLE 71.2
Five Ps of Sexual History Taking According to the CDC

1. Partners
   - Do you have sex with men, women, or both?
   - In the past 2 months, how many people have you had sex with?
   - In the past 12 months, how many people have you had sex with?
2. Prevention of pregnancy
   - Are you or your partner trying to get pregnant? If not, what are you doing to prevent pregnancy?
3. Protection from STIs
   - What do you do to protect yourself from STIs including HIV?
4. Practices
   - Have you had vaginal sex, meaning "penis in the vagina" sex?
     - Do you use condoms never, sometimes, or always? If never, why not? If sometimes, in what situations or with whom do you not use condoms?
   - Have you had anal sex, meaning "penis in the rectum/anus sex"?
     - Do you use condoms never, sometimes, or always? If never, why not? If sometimes, in what situations or with whom do you not use condoms?
   - Have you had oral sex, meaning "mouth on the penis/vagina"?
5. Past history of STIs
   - Have you ever had an STI?
   - Have any of your partners had an STI?

Additional questions
- Have you or any of your partners ever injected drugs?
- Have you or any of your partners exchanged money or drugs for sex?
- Is there anything else about your sexual practice that I need to know about?

status, race, tobacco use, and exposure during menses.[30–33] It is difficult to assign a precise rate of elevated risk to each of these variables as these numbers have varied widely in the literature. Thus, these risk factors must be considered in a clinical context for any given patient. Considerations such as a recent new partner or potential exposure may influence screening decisions. At any time, a patient may request screening without indicating his or her reasons.

Screening Guidelines

The U.S. Prevention Services Task Force has made a series of recommendations regarding routine screening for STIs.[34] Their most recent recommendations in 2007 call for all women under age 25 to be screened for chlamydia annually as well as all those patients above this age limit who are at a higher risk based on their risk factors. The risk factors they cite include "previous chlamydial infection or other STIs, new or multiple sexual partners, inconsistent condom use, and sex work." These guidelines apply to both pregnant and nonpregnant women. Given the lower prevalence of gonorrheal infection, they recommend screening for this infection only in high-risk populations.[35]

The ACOG recommend that patients undergo "routine HIV screening" with an opt-out policy as part of their routine gynecologic care.[36] A single negative test may be sufficient if subsequent sexual histories identify no new risk factors. However, for those identified to be at high risk, annual HIV screening should be performed.

Outside of chlamydia, gonorrhea, and HIV screening, there is little in the way of guidelines for STI screening. If a patient initiates a request for screening, a complete panel might include a cervical swab for chlamydia and gonorrhea, a serum sample for HIV, syphilis, and hepatitis B immune status, and any other testing as indicated by the patient's particular history. For example, for a patient with known IV drug use, or who had sex with those with IV drug use, consideration should also be given for testing for hepatitis C.

Special Populations

Adolescents

As noted earlier, adolescents are at increased risk for STIs. The ACOG recommends that chlamydia, gonorrhea, and HIV be tested at the patient's first gynecologic visit if the patient is sexually active.[37]

Pregnant Patients

Pregnant patients may be thought of as two separate patients: the mother and the fetus. Therefore, screening is not only directed at the mother with consideration of her pertinent risk factors but also directed toward the fetus. Given the risk of congenital infection, there are several additional screens that are considered routine during pregnancy. At the initial prenatal visit, women should be screened for hepatitis B, chlamydia, gonorrhea, syphilis, and HIV as well as clinically examined and questioned regarding genital herpes.[38]

Lesbians

Women who have sex with women represent a unique population, although there are no separate screening guidelines currently available.[39] A thorough history should ascertain if shared penetrative sex items are used, as these may act as a fomite for STIs. This might in part explain the high rate of bacterial vaginosis as well as the concordant strains of HPV that have been isolated in monogamous female partners.[40,41] Also of note, 53%–99% of women who have sex with women have had intercourse with men and may continue to do so.[42] This emphasizes the importance of a thorough sexual history in determining the need for screening for STIs in women who report female partners, but may have had heterosexual relationships in the past or will have them in the future.

Sexual Assault Victims

A post-assault examination should be conducted by a trained provider. The CDC recommends obtaining a swab for chlamydia and gonorrhea from any attempted sites of penetration, as well as a wet mount for trichomoniasis. The wet mount can also be examined for yeast or bacterial vaginosis as indicated by the physical examination. A serum sample should be collected for HIV, hepatitis B, and syphilis.[30]

DIAGNOSIS AND TREATMENT

General Principles

There are several general principles for evaluation and management of STIs. Previously, it was thought that patients should return to the clinic for a "test of cure." Current treatment regimens are, in general, quite efficacious and a "test of cure" is no longer recommended. The exception to this guideline is for pregnant women, as well as any patient in whom noncompliance is suspected, symptoms persist, or reinfection is suspected.[30] Repeat testing should be in no less than 3 weeks, as nucleic acid amplification tests (NAATs) may yield a false-positive due to the presence of dead organisms. Reinfection may be symptomatic or asymptomatic, requiring clinical judgment to assess which cases are high risk and thus merit rescreening. In 2006, of 1236 women seen at an STD clinic who had initially screened positive, 25.8% had one or more new infections.[43] Of these patients, 66.2% reported no symptoms. A similar study of women aged 15–19 showed slightly higher rates (41.1%) of reinfection within 1 year of initial diagnosis.[44] This study also showed that nearly 10% of this population was reinfected with more than one organism, an indication for complete repeat screening. Thus, for high-risk populations, including adolescents, screening for reinfection with chlamydia, gonorrhea, and trichomoniasis 3 months after initial diagnosis is indicated.

After being diagnosed and treated for an STI, it is of crucial importance that the patient's partner also be screened and treated prior to reinitiating sexual relations. The optimal method of notification and treatment of partners is not clear, and it is complicated in many locations

by legal barriers. In 2005, a group in Seattle, Washington, enrolled partners of infected patients in an expedited treatment program by giving them therapy without a clinical examination. The patients in the expedited treatment group had significantly reduced persistent and recurrent infections (relative risk 0.76) and patients were more likely to report all of their partners.[45] If using expedited therapy, the partner must receive written instructions on how to take the medication, as well as information on potential side effects, general health counseling, and indications to seek further care, including signs and symptoms of PID in female partners. Regardless of the mechanism of treatment, there should be a period of abstinence usually of 1 week's duration after both partners have been treated to allow for complete treatment of the infection.[46]

Reporting requirements for STIs vary by state; however, syphilis, gonorrhea, chlamydia, chancroid, HIV, and acquired immune deficiency syndrome (AIDS) are reportable diseases in all 50 states.[30] The local department of public health can be contacted for more information regarding guidelines in specific locations. Records of infection are kept confidentially and protected from subpoena by nearly all states.

Pelvic Inflammatory Disease

PID is an acute infection of the upper genital tract in women. PID is a potential complication of an STI, particularly chlamydia and gonorrhea. It is important to recognize this potential complication at the time of diagnosis of an STI, as PID carries the risk of future infertility.[47] Of those women with laparoscopically confirmed PID who desired conception, 16% had infertility compared with 2.7% of those with a normal laparoscopic exam. Of those in the infertility group, 67.6% were diagnosed with tubal factor infertility. As would be expected in a group with increased tubal factor infertility, there is a higher rate of ectopic pregnancy after PID. In the same cohort study, 7.8% of the study group had an ectopic pregnancy compared with 1.3% in the control group.

The diagnosis of PID is largely clinical; however, laboratory results may confirm the diagnosis. Diagnostic guidelines from the CDC can be seen in Table 71.3.[48]

STIs, including *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, are universally implicated in the pathogenesis of PID although bacterial vaginosis is present in up to two-thirds of cases. Thus, most cases are considered polymicrobial.[49,50] There are a number of different inpatient and outpatient regimens recommended for PID although all regimens are designed for broad coverage including coverage for the most commonly indicated STIs. As an outpatient, a single dose of ceftriaxone 250 mg intramuscularly as well as doxycycline 100 mg orally twice daily for 14 days with or without metronidazole 500 mg orally twice daily is recommended. As an inpatient, cefoxitin 2 g intravenous every 6 h with doxycycline 100 mg orally twice daily can be given.[30] There are a number of alternative regimens available if a patient has known allergies.

TABLE 71.3
Diagnostic Criteria for PID

Clinical PID

Cervical motion tenderness, uterine, or adnexal tenderness with lower abdominal pain, plus one or more of the following:

- Oral temperature >101°F (38.3°C)
- Abnormal cervical or vaginal mucopurulent discharge
- Presence of abundant number of white blood cells on saline microscopy of vaginal secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein

Confirmed PID

Pelvic pain or tenderness, plus one or more of the following:

- Acute or chronic (plasma cell) endometritis or acute salpingitis on histological evaluation of a biopsy
- Demonstration of *N. gonorrhoeae* or *C. trachomatis* in the genital tract
- Gross salpingitis visualized at laparoscopy or laparotomy
- Isolation of pathogenic bacteria from a clean specimen from the upper genital tract
- Inflammatory/purulent pelvic peritoneal fluid without another source

Definitive PID

Pelvic pain or tenderness, plus one or more of the following:

- Histological evidence of endometritis on an endometrial biopsy
- An imaging study revealing thickened fluid-filled tubes with or without free pelvic fluid or tuboovarian complex
- Laparoscopic abnormalities consistent with PID (e.g., tubal erythema, edema, adhesion; purulent exudate or cul-de-sac fluid; abnormal fimbriae)

Source: Centers for Disease Control and Prevention, *MMWR Recomm. Rep*. 55(RR-11), 1, 2006.

Chlamydia

Chlamydial infection is caused by the bacteria *C. trachomatis*. It is the most common STI in the United States with 579.98 infections per 100,000 women, as reported by the CDC in 2008.[1] Although it is a reportable disease in all 50 states, this number is probably an underrepresentation as not all infected women present for care. Patients may present with vaginal discharge and vague lower abdominal pain; however, nearly 50% of infected women will be asymptomatic.[51] On physical examination, a friable erythematous cervix with mucopurulent discharge may be observed.[52] Chlamydial infection may present with more disseminated infection including urethritis causing dysuria and pyuria, perihepatitis causing Fitz-Hugh–Curtis syndrome, or PID. Less commonly invasive serovars L1, L2, and L3 *C. trachomatis* can cause lymphogranuloma venereum, an inflammation of the lymphatics and inguinal lymph nodes.

There are several methods of laboratory detection for chlamydia infection. Perhaps most commonly, the provider collects a cervical swab that then undergoes NAAT; however, there are multiple other collection and detection methods. As an alternative to the office examination, the patient may collect her own vaginal swab or provide a urine specimen.

Patients and adolescents in particular may feel more comfortable with these less invasive screening methods. Once the specimen is collected, the test may be performed using one of many laboratory methods, such as NAAT, ligase chain reaction, polymerase chain reaction, or gene probe, which are all DNA based or using an enzyme immunoassay (EIA). A 2002 meta-analysis compared these methods and found DNA-based tests to be more accurate than the EIA tests regardless of specimen type.[53] For the PCR assay, the sensitivity and specificity were 83% and 99.5% for urine samples and 86% and 99.6% for cervical samples.[54]

There are two recommended treatment regimens. Azithromycin 1 g orally one time may be administered under direct observation to ensure compliance. Alternatively, doxycycline 100 mg twice daily for 7 days may be given. Both of these regimens have an excellent efficacy (97% and 98%).[55] In pregnancy, the same azithromycin regimen may be used or amoxicillin 500 mg three times daily for 7 days. For patients with allergies, there are a number of other acceptable regimens including 7 days of any of the following: erythromycin base 500 mg four times daily, erythromycin ethylsuccinate 800 mg po once daily, ofloxacin 300 mg po twice daily, or levofloxacin 500 mg po once daily. Untreated chlamydia leads to PID in approximately 30% of cases.[56]

Gonorrhea

Gonorrheal infection is caused by the bacteria *N. gonorrhoeae*. It is the second most common STI with 117.85 cases per 100,000 women as of 2008.[1] As with chlamydia, approximately 50% of women with an active gonorrheal infection are asymptomatic.[57] Of those patients with symptoms, complaints usually consist of mucopurulent discharge and/or vaginal pruritus. Abdominal pain is more indicative of PID and would not be expected in uncomplicated gonorrheal infection.

Gonorrhea can infect multiple mucosal surfaces, including the cervix, urethra, anal mucosa, and oropharyngeal mucosa. In a high-risk population, *N. gonorrhoeae* may be responsible for up to 10% of urethral infections.[58] Physical exam findings include purulent urethral discharge, which should be collected for gram stain and culture on Thayer–Martin agar. Alternatively, urine DNA testing is available but may have a lower sensitivity and specificity as compared with a traditional urethral sample.[54] Infection is also possible in the anal mucosa, although patients are generally asymptomatic as one study found in 97% of cases; rarely these patients report anal itching, rectal discharge, rectal fullness, and painful defecation.[59] One investigation examined 127 women with known exposure to gonorrhea. In this population, 50% had an active gonorrheal infection in the genital region. Of this group, 46% had gonorrhea isolated from the rectum as well as the cervix and/or urethra while 6.3% had gonorrhea isolated from the rectum without concomitant vaginal infection.[60] Rectal disease can be identified using a blind swab technique.[61] Lastly, gonorrheal infection may be present in the oropharyngeal mucosa. The prevalence of pharyngeal gonorrhea varies widely from less than 1% to as high as 22.5%, depending on the risk level of the population.[62] Those reporting orogenital sexual activity had increased rates of colonization and infection with particularly high infection rates in pregnant women. Pharyngeal culture remains the laboratory testing standard as gram stain is frequently contaminated.

The CDC recommends that laboratory evaluation for cervical disease be performed with NAAT.[30] Using this method, samples can be stored at room temperature for days prior to testing and once tested offers rapid results. As compared with the gold standard diagnosis on modified Thayer–Martin culture medium, NAAT has an excellent sensitivity and specificity, 95.2% and 99.4%, respectively.[63] This method, however, has a significantly lower sensitivity (ranging from 56% to 91% depending on the technique) for urine specimens and thus is not recommended by the CDC. Furthermore, urine specimens are not approved by the FDA for use on nongenital sites.[54]

Gonorrhea can be treated swiftly in the office with one dose of 125 mg of intramuscular ceftriaxone.[64] Over the past decade, increasing resistance to fluoroquinolones has been seen, and this is no longer recommended as an appropriate treatment regimen. Similarly, resistance has been seen for many other alternative regimens, including cefixime, which is given 400 mg orally once. In 2001, there were three cases of cefixime-resistant gonorrhea.[65] For this reason, providers should be aware of local microbiology and treat accordingly.

Syphilis

Syphilis, caused by the spherocyte *Treponema pallidum*, was once called "the great imitator" as a result of its nonspecific clinical presentation as well as its prevalence. The peak incidence in the United States was in 1946 when there were 66.6 new cases of syphilis diagnosed per 100,000 people.[66] Since then, the prevalence has fallen drastically through the widespread use of penicillin therapy and focused eradication efforts. In 2008, the incidence was 8.51 per 100,000 people.[1] Although this trend is overall reassuring, exploring the data from recent years has revealed that the number of cases of primary and secondary syphilis as well as congenital syphilis is slowly on the rise again.[67]

The clinical presentation of syphilis can be described according to its stage. Classically, primary syphilis presents as a singular painless lesion on the genitals after an incubation period of 2–3 weeks. This lesion originates as a macule and then progresses to a papule until it ulcerates and drains serous fluid. There may be associated non-painful inguinal lymphadenopathy. Generally, this will heal spontaneously in about 4–5 weeks. This lesion may occur in an inconspicuous site such as the vagina, so it may not be recognized by the patient.[68] Secondary syphilis may be seen 4–8 weeks later. Symptoms include a macular–papular rash on the palms and soles associated with general lymphadenopathy and malaise. Treatment is commonly sought at this time if not earlier; however, symptoms should spontaneously improve in 3–6 weeks if the patient remains untreated. Syphilis that remains

untreated can progress to early or late latent syphilis, which includes neurosyphilis and cardiovascular syphilis.

Diagnosis of syphilis is made by either serologic or direct testing. Serologic testing uses a series of tests: a screen and a confirmatory test. First a nontreponemal test such as Venereal Disease Research Laboratory or Rapid Plasma Reagin is performed by testing the patient's serum for reactivity against a cardiolipin–cholesterol–lecithin antigen. If this test is positive above a critical titer (generally 1:32), a specific treponemal test such as fluorescent treponemal antibody absorption (FTA-ABS) is reflexively sent. Although less commonly used, the diagnosis may be made by direct visualization of *T. pallidum* by dark-field microscopy or histopathologic staining using direct fluorescence antibody testing. These methods are limited by specific preparation requirements as well as the availability of trained technicians.[69]

Syphilis is easily treated in its early stages. Patients with primary, secondary, or early latent disease may be treated with 2.4 million units of intramuscular penicillin G once.[70] Patients with late syphilis require three doses at weekly intervals. If the duration of infection is unknown, it is presumed to be late, and the patient is treated with three doses of penicillin accordingly. Penicillin desensitization remains the optimal therapy for patients with penicillin allergies as there have been no reports of penicillin resistance. For those unable to tolerate penicillin, the suggested alternative regimen is doxycycline 100 mg orally twice daily for 14–28 days depending on the stage of disease. Previously macrolides, such as azithromycin, were commonly used; however, multiple resistant strains have emerged and thus this is no longer recommended.[71] The Jarisch–Herxheimer reaction is a known complication of therapy that occurs within the first 24 h. This acute febrile reaction associated with headache and myalgias is thought to result from lipopolysaccharides released from dying spirochetes. Patients are treated supportively.

Hepatitis B Virus

There is a relatively low prevalence of HBV in the United States with approximately 1.25 million chronic HBV infections and 200,000–300,000 new cases annually.[72] This represents approximately 0.2% of the U.S. population compared with endemic areas, such as Sub-Saharan Africa, where approximately 8%–25% of the population has an active infection.

HBV is transmitted by percutaneous, sexual, and perinatal contacts. In the United States, it is most commonly acquired in adolescence or young adulthood by percutaneous routes during IV drug use or sexual intercourse. There is an incubation period of 4 weeks to 6 months although approximately 50% of patients with HBV infection remain asymptomatic.[70] Those who do present for care note nonspecific symptoms, such as fatigue, anorexia, and jaundice. Physical examination will reveal hepatomegaly as well as splenomegaly. Of note, 5%–10% of patients may present with a serum sickness-like illness and rarely patients may present with fulminant liver failure.

Diagnosis is made by a series of serologic tests. The presence of hepatitis B surface antigen (HBsAg) is the marker for current infection. Antibody status to hepatitis B core (HBc) can differentiate acute from chronic disease. Those patients with IgM anti-HBc have an acute infection while those patients with IgG anti-HBc have a chronic infection. Hepatitis B e antigen (HBeAg) is a marker of high infectivity and is seen at the peak of viral load. This is replaced by anti-HBe within 2–3 months. Lastly, patients with anti-HBs, anti-HBe, and/or anti-HBc without a positive HBsAg have cleared the disease and are immune by prior infection. Of note, one would expect a vaccinated patient to have an isolated anti-HBs antibody.

Patients with HBV are generally referred to a hepatologist rather than managed by a primary care provider. Generally, the prognosis is encouraging. Ninety-five to ninety-nine percent of infected patients have a complete recovery. Without complete recovery, patients progress to chronic HBV with deleterious sequelae, such as hepatocellular carcinoma and cirrhosis. Risk factors for this progression include comorbid illnesses such as diabetes mellitus, congestive heart failure, immunosuppressive disease such as HIV, as well as young age.

Hepatitis C Virus

Hepatitis C virus (HCV) is most commonly an asymptomatic chronic disease. There are 2.7–3.2 million chronic HCV infections in the United States with less than 30,000 new cases annually.[72,73] These statistics highlight the near-universal incidence of chronic disease and the low clearance rate in those who are infected. In fact, HCV is the leading cause of chronic liver disease and the number one indication for liver transplant in the United States.

The spread of HCV is primarily through exposure to infected serum. The high-risk population includes IV drug users, recipients of blood transfusion or clotting factors prior to 1992, patients who have been on hemodialysis, and rarely health care workers with occupational exposures. There is a low rate (approximately 5%) of perinatal transmission. HCV appears to be transmitted sexually as well, but there is a much lower efficacy of seroconversion. For example, otherwise low-risk spouses of patients with chronic HCV infection have only a 1.5% conversion rate.[74] Screening for HCV has a place in STI screening, as 15%–20% of HCV patients report no exposure other than sexual contact.[75]

The incubation period for HCV is 2–12 weeks. As with HBV, most patients are asymptomatic but those who do present commonly complain of fatigue, fever, nausea, and vomiting. Chronic HCV will develop in 60%–85% of infected patients. Liver function tests (LFTs) will fluctuate in these patients; however, at any given time, approximately 60%–70% of chronically infected patients will have elevated LFTs.

Diagnosis is confirmed by serologic testing. Anti-HCV antibody represents prior exposure and usually develops within 8–9 weeks although may take up to 6 months. This test is performed by EIA and has 99% specificity and sensitivity,

although in immunosuppressed patients this antibody may never develop. Detection of HCV RNA confirms active infection. HCV RNA is quantified according to the World Health Organization international units (IU) per milliliter. This allows differentiation between high- and low-level diseases based on whether a patient's HCV RNA exceeds 800,000 IU/mL. The last laboratory test available, HCV genotyping, is not diagnostic but prognostic for a patient.

Patients with confirmed HCV should be evaluated and treated by a hepatologist. There are several treatment options including interferon, pegylated interferon, and ribavirin depending on a patient's genotype and comorbidities as these therapies have significant side effects. With regard to prognosis, 20% of patients will develop cirrhosis over two to three decades of infection. Once a patient develops cirrhosis, 1%–4% of cirrhotics will develop hepatocellular carcinoma annually.

Human Immunodeficiency Virus

HIV was first recognized by the CDC in 1981 with the first five cases diagnosed in Los Angeles. Since then, there has been a dramatic rise in the number of infections and a similarly impressive response from the research community allowing for effective treatment and drastically improved prognosis for these patients. Rates of HIV infection in the United States have not been directly measured, but advanced modeling estimates an incidence of 56,000 cases per year and a prevalence of 1.1 million patients as of 2006.[76,77] An estimated 21% of these cases are undiagnosed. These same models show a significantly increased risk of infection among black and Hispanic populations, as well as men who have sex with men.

HIV is transmitted by exposure to blood, vaginal secretions, semen, breast milk, as well as vertical transmission from mother to child. Approximately 31% of new infections are acquired through heterosexual contact, while 53% of new infections are acquired through male homosexual contact. Injection drug users represent 12% of new infections. Overall, women represent 27% of new infections.

Diagnosis is made by assessing HIV antibody status. Antibodies appear between 2 and 12 weeks after exposure. Initial testing is performed by EIA, which has a high sensitivity (>99.5%), and then confirmed by Western blot. There are a number of direct tests available, including the p24 antigen capture assay. This assay is used when initial testing is non-diagnostic and when infection must be detected prior to the development of antibodies such as in blood donors, as well as in a research capacity. Once infection is confirmed, a patient's disease course is followed by $CD4^+$ count and HIV RNA, indicating viral load.

HIV is a retrovirus that infects $CD4^+$ helper T cells resulting in immunodeficiency. Infection can be described in four stages: incubation, acute infection, latency, and AIDS.[78] The incubation stage, a period of 2–4 weeks, includes the time from exposure to initial symptoms. Acute infection is a manifestation of HIV viremia lasting approximately 4 weeks. Patients generally present with nonspecific viral symptoms including fever, generalized lymphadenopathy, pharyngitis, rash, and oral sores. During latency, patients are generally asymptomatic. This stage has a greatly variable duration, lasting from 2 weeks to indefinitely in a small group of patients termed "long-term nonprogressors." Generally, the median duration of latency is 10 years. HIV may then progress to its final stage, AIDS. This progression is defined by a decrease in $CD4^+$ cells to less than 200 cells/μL of blood or 14% of all lymphocytes as well as the presence of AIDS-defining illnesses (Table 71.4).[79]

TABLE 71.4
List of AIDS-Defining Illnesses

Candidiasis of bronchi, esophagus, trachea or lungs	Kaposi sarcoma
Cervical cancer that is invasive	Lymphoma that is Burkitt type, immunoblastic, or that is primary and affects the brain or central nervous system
Coccidioidomycosis that has spread	*Mycobacterium avium* complex or disease caused by *Mycobacterium kansasii*
Cryptococcosis that affecting the body outside the lungs	*Mycobacterium tuberculosis* in or outside the lungs
Cryptosporidiosis affecting the intestines and lasting more than a month	Other species of mycobacterium that has spread
CMV disease outside of the liver, spleen, or lymph nodes	*Pneumocystis jiroveci*, formerly called *carinii*, pneumonia
CMV retinitis that occurs with vision loss	Pneumonia that is recurrent
Encephalopathy that is HIV related	Progressive multifocal leukoencephalopathy
Herpes simplex including ulcers lasting more than a month or bronchitis, pneumonitis, or esophagitis	Salmonella septicemia that is recurrent
Histoplasmosis that has spread	Toxoplasmosis of the brain, also called encephalitis
Isosporiasis affecting the intestines and lasting more than a month	Wasting syndrome, caused by HIV

Treatment of HIV is directed by an infectious disease specialist. Since 1995, highly active antiretroviral therapy (HAART) has been the principal treatment. Recommendations from the U.S. Department of Health and Human Services are constantly evolving as the virus and the pharmaceutical industry progress. In general, HAART initiation may be considered in acute HIV syndrome, all pregnant women, patients with symptomatic disease, and patients with asymptomatic disease with $CD4^+$ T cell counts less than 350 cells/μL. Life expectancy is significantly increased with HAART, and recent studies have suggested that earlier initiation of this therapy may further prolong life expectancy.[80]

Herpes Simplex Virus

Infection with HSV results in genital and labial herpes. Approximately 50 million people, or one in four over the age

of 30, have genital HSV, although many infected persons are unaware.[81] Previously, HSV-1 was strongly associated with oral lesions while HSV-2 was associated with genital lesions. As a result of changing sexual practices, nearly 50% of new genital herpes is caused by HSV-1.[82] Transmission occurs by contact with the mucosal surfaces both while active lesions are present and through asymptomatic viral shredding.[83]

The incubation period is approximately 4 days. At the time of primary infection, patients present with painful genital lesions as well as tender inguinal lymphadenopathy. Classically lesions will form as macules and progress to form vesicles. Those on mucosal surfaces will ulcerate while those on keratinized skin will scab.[84] Constitutional symptoms such as fever and malaise appear in 40% of patients during a primary outbreak.[85] Rarely, significant neurological complications such as aseptic meningitis may be present at the time of primary outbreak. Of note, up to 25% of patients presenting with initial clinical infection may in fact be presenting with recurrent infection.[86] After resolution of the primary infection, the virus remains dormant in the neuronal bodies until it is reactivated. HSV is never cleared. Recurrent outbreaks may be preceded by prodromal symptoms such as pain or tingling.[87] Generally, these outbreaks are much milder with fewer lesions (6 vs. 16 lesions) and shorter duration (4 days vs. 11 days) as compared with primary infections.[85] Recurrence decreases over time, HSV-1 to a greater extent than HSV-2.[88]

Diagnosis is generally made by viral culture of an active lesion. Higher yield results from a primary vesicular lesion as compared with a recurrent or ulcerated lesion. PCR testing is available, which has a higher sensitivity and faster result than viral culture. Most institutions continue to use viral culture due to lower cost; however, when assessing for more acute conditions such as HSV meningitis, PCR is frequently used as an alternative. Serologic testing may be performed to evaluate whether disease is caused by HSV-1 or HSV-2; however, the mean time to antibody formation is 22 days and presumably these antibodies would be negative at the time of initial presentation.[89]

There is effective episodic treatment and prophylaxis available for HSV. At the time of presentation with a primary infection, patients should be treated with a 7–10 day course of oral antiviral therapy, such as acyclovir 400 mg three times daily, valacyclovir 1000 mg twice daily, or famciclovir 250 mg three times daily.[90] If neurological involvement is suspected, admission and workup by a neurologist are indicated. After the primary episode, patients should be counseled on the options for either episodic or suppressive therapy. Options for episodic therapy consist of acyclovir 400 mg three times daily, valacyclovir 500 mg twice daily, or famciclovir 125 mg twice daily all for 5 days. Another option includes suppressive therapy, which reduces outbreaks by 80% and reduces transmission by about 48%.[91] To reduce vertical transmission to the neonate, suppressive regimens are recommended by the ACOG for women with known HSV during the third trimester of pregnancy. Options for suppressive therapy include acyclovir 400 mg twice daily, valacyclovir 500 mg once daily, or famciclovir 250 mg twice daily.

Condylomata Acuminata

Condylomata acuminata, or genital warts, are caused by the HPV. Although there are over 100 strands of HPV, types 6 and 11 are responsible for 90% of anogenital lesions.[92] Exposure to this virus is extremely common. In fact, over 50% of sexually active women will be exposed to HPV over the course of their lifetime; however, not all exposed women will have clinically apparent disease.[93] The incidence of clinical disease is unclear as women do not always present for care; however, the CDC estimates that 1% of the sexually active population has active genital warts at any given time.[94] Risk factors for acquisition of HPV include new sexual partners, tobacco use, and oral contraceptive use.[95] After exposure to HPV, the incubation period is estimated at 1–3 months, but may be quite variable, making identification of the source of infection difficult for the patient.[96]

Diagnosis is made primarily by physical examination (Figure 71.1).[97] Lesions may appear on the external genitalia including vulva, perineum, and perianal skin, as well as on mucosal surfaces including cervix, vagina, urethra, and anal tissue. Lesions have a characteristic keratotic cauliflower-shaped appearance.[94] Biopsy and/or HPV testing is not required for diagnosis unless the diagnosis is unclear clinically.

Treatment is directed at elimination of all visible disease. There are multiple treatment options available, and the



FIGURE 71.1 Extensive bilateral Condylomata acuminata. (Reprinted from *Am. J. Obstet. Gynecol*., 189, 3 Suppl., Gunter, J., Genital and perianal warts: New treatment opportunities for human papillomavirus infection, S3–S11. Copyright 2003, with permission from Elsevier.)

treatment of choice will depend on the extent and the location of disease as well as patient preference. The first category of therapy is chemical destruction. Podophyllin and podophyllotoxin are antimitotic agents applied topically. The former is applied in the clinic by a physician once or twice a week while podophyllotoxin is applied by the patient with the following regimen: daily for 3 days with 4 days respite. This method is limited by neurotoxicity and chemical burns. It is contraindicated in pregnancy and on mucosal surfaces. Another method in the same category of chemical destruction is 80%–90% trichloroacetic acid. Again, this is irritating to the surrounding skin but may be used on mucosal surfaces and during pregnancy. Lastly, lesions can be treated with 5-fluorouracil gel, which acts as a pyrimidine antimetabolite. The second category of treatment is immune modulation. Imiquimod is a topical therapy that acts by induction of a cytokine response. It has both high clearance and low recurrence rates; however, it cannot be used on mucosal surfaces and it causes local erythema.[98] Interferon alpha is used for treatment of genital warts; however, it is not FDA approved for this purpose and is limited by its many associated side effects. Lastly, condyloma can be removed surgically using cryotherapy, laser, or excision. Excision allows examination of the tissue by a pathologist if there is concern for neoplasia or alternative diagnoses. Rate of recurrence after treatment is approximately 30%–70% after 6 months.[99]

Trichomoniasis vaginalis

Trichomoniasis is a form of vaginitis caused by the flagellated protozoa *Trichomoniasis vaginalis*. The incidence is around three to five million cases a year with higher rates in non-Hispanic black women and lower rates in non-Hispanic white women.[100] It is transmitted by sexual intercourse, although male partners have transient infection only. In vitro studies suggest that the incubation period is 4–28 days.[101]

Classically, patients present with green frothy malodorous vaginal discharge accompanied by pruritus and dysuria. Physical examination reveals discharge as described as well as punctate "strawberry hemorrhage" on the cervix.

Diagnosis can be made in the office with physical examination and wet mount microscopy, with the pH of the vagina elevated to 5.0–6.0. Saline microscopy reveals an inflammatory response with multiple leukocytes as well as mobile trichomonads. Trichomonads on wet mount may be absent in 30%–50% of cases.[102] If trichomoniasis is suspected but not confirmed with microscopy, culture may be sent on Diamond's medium or specimen may undergo rapid testing by DNA probe or monoclonal antibody depending on availability. Lastly, diagnosis may be made incidentally on liquid-based Pap tests. Although the sensitivity is low (61%), the specificity is high (99.4%) and thus a positive finding is an indication for treatment.[103]

Trichomoniasis is treated effectively with metronidazole or tinidazole.[104] Metronidazole regimens include 2 g orally once or 500 mg twice daily for 7 days. There are no established regimens for patients with allergies to 5-nitromidazoles and desensitization is recommended. Similar treatment regimens are used during pregnancy as metronidazole is not teratogenic although may cause significant nausea. Active trichomoniasis during pregnancy is associated with preterm delivery and preterm rupture of membranes; however, many clinicians do not treat asymptomatic pregnant women as this has not been shown to reduce these obstetric complications.[105]

Molluscum Contagiosum

Molluscum contagiosum is a viral skin infection caused by a virus in the *Poxviridae* family.[106] It can be transmitted by skin-to-skin contact and thus is commonly seen in school-aged children on exposed skin, although it avoids palms and soles. It is also transmitted during sexual activity resulting in genital and upper thigh lesions. There are few studies exploring the prevalence of molluscum as an STI. In patients with AIDS, there is a prevalence of 5%–18%.[107] Lesions are generally asymptomatic aside from cosmetic complaints. Physical exam reveals clusters of lesions that are 2–5 mm in diameter with a pearl appearance and central umbilication. Given their unique appearance, diagnosis is made clinically although skin biopsy may be used to confirm.

Providers have tried a variety of treatments including salicylic acid and tretinoin; however, no therapy has proven beneficial.[108] Lesions generally clear spontaneously in months in those with a healthy immune system. Individuals with immunosuppression are known to have a more recalcitrant infection. For this population, a provider may consider interventions similar to those available for genital warts, specifically topical imiquimod, optical podophyllotoxin, or excision.[109]

Pediculosis Pubis

Pediculosis pubis or pubic lice is caused by *Phthirus pubis*, the crab louse. The louse is 0.8–1.2 mm and may be seen with the naked eye upon close examination or more easily with microscopy (Figure 71.2).[110] Each louse lives for 3–4 weeks

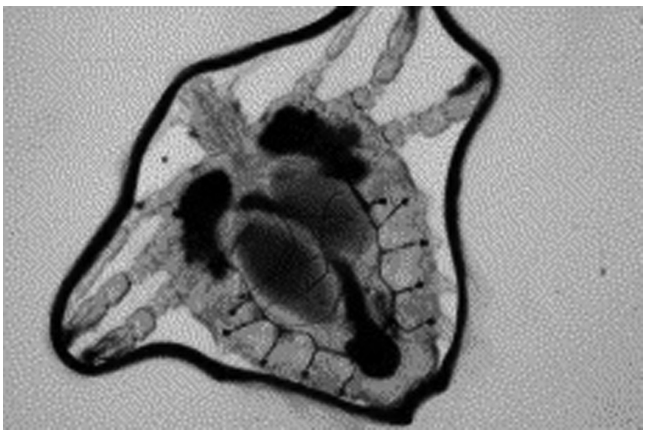


FIGURE 71.2 Crab louse in oil immersion. (Reprinted from *J. Am. Acad. Dermatol*., 50, Ko, C.J. and Elston, D.K., Pediculosis, 1–12. Copyright 2004, with permission from Elsevier.)

and lays approximately 25 ova. Pediculosis pubis is spread by sexual contact with an infected partner. Patients present with itching and occasionally maculae ceruleae, which are 5–10 mm bluish macules related to the bites of the louse. Diagnosis is made clinically with the assistance of microscopy. Treatment as recommended by the CDC consists of either topical permethrin (1%) or pyrethrins with piperonyl butoxide. Additionally, all bedding and clothing should be cleaned in hot water.

Chancroid

Chancroid is caused by a bacteria *Haemophilus ducreyi*, which results in painful genital ulcerations. Infection is rare; 14 women were diagnosed and reported to the CDC in 2008.[1] Lesions present after a 4–7 day incubation period. Lesions start as an area of erythema that evolves into a pustule and then into a non-indurated painful ulcerated lesion, approximately 1–2 cm in diameter. Women present with multiple vulvar lesions with a mean of 4.5 lesions, unlike men who generally present with a singular lesion.[111] Fifty percent of patients have tender unilateral inguinal lymphadenopathy. Occasionally, constitutional symptoms may be reported. Diagnosis is difficult as the *H. ducreyi* is difficult to culture, and few tests are commercially available. Culture has been the gold standard, but PCR is proving to be more sensitive (98% vs. 74%).[112] Given the difficulty of diagnosis, the CDC has developed guidelines for diagnosing definite versus probable disease.[113] Definite disease requires isolation of the organism whereas probable disease requires only an appropriate clinical history with confirmed exclusion of syphilis and HSV. Adequate treatment may be achieved with a single dose of either 1 g azithromycin orally or 250 mg ceftriaxone intramuscular. Given the high efficacy of these single-dose regimens, few providers are using multi-dosing regimens although they may be considered in the case of allergies or other contraindications.

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72 Maintaining a Healthy Pelvic Floor through Childbirth and Menopause

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CONTENTS

Introduction 899
Pelvic Anatomy 899
Urinary Incontinence 900
Stress Incontinence 901
Urge Incontinence 902
Mixed Incontinence 903
Pelvic Organ Prolapse 903
Interstitial Cystitis/Painful Bladder Syndrome 905
Conclusion 906
References 907

INTRODUCTION

Bladder health is an important part of healthy aging. Lifestyle factors such as weight and diet can affect bladder health, so the primary care provider should have a basic understanding of the pelvic floor and bladder-related disorders. As our population ages, bladder health issues are becoming more common, and they can greatly impact a healthy lifestyle. An estimated 24% of women in the United States have some type of pelvic floor disorder. Pelvic floor disorders included urinary incontinence, pelvic organ prolapse (POP), and pelvic pain syndromes.[1] This is probably a conservative figure given that these disorders are widely underreported by both patients and physicians. It is also estimated that 10% of women in the United States have surgery for urinary incontinence, POP, or both during their lifetime.[2] These disorders carry tremendous psychosocial, medical, and financial burdens to patients and society[3] and increase with each decade of life. Therefore, with the lengthening of women's lifespan and the aging population, the incidence and relevance of these problems increase. To fully understand the pathology and treatment of pelvic floor disorders, one must first understand the anatomy of the pelvis. Therefore, this chapter will begin with a review of basic pelvic anatomy. This will be followed by a discussion of the three major pelvic floor disorders: urinary incontinence, POP, and pelvic pain syndromes.

PELVIC ANATOMY

The female pelvis consists of a group of muscles, ligaments, vasculature, and nerves, which work together to provide support and function to the pelvic organs: the bladder, urethra, uterus, vagina, ureters, and rectum. The bony structures include the ilium, ischium, pubis, sacrum, and coccyx. Ligaments, muscles, and fascia attach to various points on the bony pelvis.

The pelvis is composed of the minor and major pelvis. The pelvic diaphragm resides in the minor pelvis. It is composed of the levator ani and coccygeus muscles. The pubococcygeus, puborectalis, and iliococcygeus muscles together comprise the levator ani muscles. The pelvic diaphragm stretches between the pubic bone and the coccyx. The arcus tendineus is a dense connective tissue structure from which the levator ani originates. It runs from the pubic ramus to the ischial spine, extending along the surface of the obturator internus. The muscles of the pubococcygeus and puborectalis form the urogenital hiatus through which the urethra, vagina, and rectum pass. The levator ani consists of both type I (slow-twitch) and type II (fast-twitch) fibers. This allows for constant baseline tone, which supports the pelvic viscera, and voluntary contractions. Enervation of the levator ani muscle is primary from the third and fourth sacral nerve roots via the pudendal nerve.[4]

The perineum is made up of a superficial and deep compartments separated by the perineal membrane that provides support to the vagina and urethra, which pass through it. The boundaries of the perineum are the ischiopubic rami, ischial tuberosities, sacrotuberous ligaments, and coccyx. The muscles of the perineum include the bulbospongiosus muscles, superficial and deep transverse perinea, ischiocavernosus muscle, and posterior vaginal muscularis.[5–7]

Pelvic organ support is primarily from the pelvic muscles, while the connective tissue stabilizes the organs in their correct position. DeLancey and others have described the various levels of connective tissue that support the vagina. Level I is the uterosacral/cardinal ligament complex attaching the cervix to the sacrum and lateral pelvic sidewalls. This maintains the vaginal axis nearly horizontal so the lavatory plate can

support it. Level II consists of the paravaginal attachments to the arcus tendineus keeping the vagina midline. Level III is the most inferior support of the vagina and includes the perineal body, the perineal membrane, the perineal muscles, and endopelvic fascia.[4]

URINARY INCONTINENCE

Normal urinary continence involves a complex interaction of neuronal signaling pathways and muscle activity. As the bladder fills, afferent signals activate the sympathetic pathways, which stimulate smooth and striated sphincters and inhibit detrusor contraction. Continence is also enabled by pelvic floor musculature, which compresses the urethra when intra-abdominal pressure increases.[8] Urinary incontinence is defined as the complaint of involuntary leakage of urine.[9] There are several different categories of urinary incontinence including stress, urge, mixed, and other. This section will discuss factors that are common to all types of incontinence and then focus on the three most common types: stress, urge, and mixed. There are several other types of incontinence that are rare and require specific intervention. These will not be addressed in this chapter.

The prevalence of urinary incontinence increases with age, as do most pelvic floor disorders. Approximately 25% of women less than 50 years old demonstrate urinary incontinence compared with 34% of women over 50 years of age. This is likely an underestimation, as the condition is often embarrassing for both patients and physicians to discuss. The disorder is three times more common in women than in men until approximately age 80 when the rates become nearly even.[10] The financial cost of urinary incontinence is estimated to be higher than other medical disorders including breast cancer and eating disorders.[11] In the year 2000, approximately $20 billion dollars was spent in the United States alone on this disorder.[12] There are also the psychosocial implications of incontinence for patients, with adverse effects on women's quality of life, productivity, sexual function, and emotional well-being.[3] Studies have shown that the severity of incontinence is associated with increasing incidence of major depressive disorder.[13]

Although incontinence can occur in any age group and population, there are several risk factors that are common to all types of urinary incontinence. Childbearing and obesity are both well-known risk factors for incontinence.[14,15] Similarly, functional impairment is a risk factor more commonly seen in the elderly and handicapped populations, which increases their likelihood of incontinence.[16] High-impact physical activity, chronic straining, diabetes, stroke, depression, fecal incontinence, episiotomy, estrogen depletion, gynecologic surgery, pelvic radiation, and a childhood history of enuresis are other factors that have been demonstrated in population studies to have significant association with having urinary incontinence.[17,18]

Age is a particularly strong risk factor for urinary incontinence, although this is thought to be secondary to several factors. First, it is known that there is increased detrusor overactivity in the elderly population. Similarly, detrusor contractility, bladder sensation, and urethral pressure decline with age.[19,20] The elderly suffer from striated muscle loss, which impacts pelvic floor muscles and sphincter tone. In addition, postmenopausal women are often in a chronic state of low estrogen levels. This has been theorized to lead to atrophy of the urethral mucosal epithelium creating an atrophic urethritis leading to symptoms of urgency and frequency and a theoretical risk of diminished urethral seal due to decreased vascular flow.[21] It is valuable to recognize a patient's risk factors when beginning an evaluation of urinary incontinence.

The assessment of patients with complaints of urinary incontinence begins with obtaining a thorough medical history, including comorbidities, medications, and any recent changes. Concomitant anorectal or sexual dysfunction should be queried at the same time. A voiding diary can also be helpful in diagnosis.[22] The physical exam should include calculation of patient's BMI and cardiovascular exam to search for evidence of volume overload. An abdominal exam is recommended to locate any hernias that may be a sign of tissue weakness, masses, or muscle abnormalities. A neurological exam is important to investigate sacral nerve deficits such as loss of anal wink or bulbocavernosus reflex as chronic neurologic disorders can also impact urinary continence. In elderly patients, ambulation and manual dexterity should be checked to identify any functional impediments to continence.[23]

During the genital exam, atrophy or milder hypoestrogenism should be evaluated. Skin irritation may suggest the presence of prolonged incontinence. Vaginal infections, or other disease states, such as lichen sclerosis or lichen planus, could also impact patient symptoms. Bimanual exam will demonstrate any masses or tenderness that could be causing urinary symptoms. The physician can also evaluate the pelvic floor strength and anterior or posterior wall defects. A tender, hypertonic pelvic floor should also be noted. Presence of prolapse or urethral diverticulum should also be assessed. The rectal exam will evaluate for sphincter tone, masses, or fecal impaction.[4]

There are several simple and inexpensive tests that can be performed in the office to further evaluate a patient with urinary incontinence. An empty supine stress test (ESST) can be carried out during the pelvic examination. With an empty bladder, the patient is asked to perform a provocative maneuver such as cough or strain either supine or standing. The physician then observes the urethra for any leakage of urine. A positive ESST has been thought to indicate increased severity of leakage. Immediate loss of urine may signify stress incontinence while a delayed leak often indicates uninhibited bladder contractions.[22] If there is a question, based on the history and physical, about whether the patient is in fact leaking urine, a pyridium pad test is also a simple and inexpensive way to distinguish between urine and other types of discharge. In this test, the patient takes oral pyridium and then wears a pad. She is asked to monitor her pad for orange staining indicating leakage of pyridium-stained urine. The Q-tip test is another inexpensive test that

can help look for urethral hypermobility. During this test, a lubricated Q-tip is inserted into the urethra to the level of the urethrovesical junction while the patient is in lithotomy. The angle between the Q-tip and horizontal is measured. The patient is asked to strain and the angle is measured again. Normal change is 30°. If the change is greater than 30°, this can suggest hypermobility of the bladder neck and therefore stress urinary incontinence (SUI). Although it can be helpful to quantitatively assess mobility, this test can be uncomfortable, and some women demonstrate hypermobility without incontinence symptoms.[24]

Checking a post-void residual volume in patients is a simple way to ensure that urinary retention of obstructive or neuropathic etiology is not the cause of the patient's incontinence. Volumes less than 50 mL are considered normal and greater than 100 mL are generally considered abnormal, although older women are often given more leeway and measurements up to 150 mL may be considered normal in some elderly patients. Volumes between 100 and 200 mL should be repeated. Finally, a urine analysis and culture is an inexpensive test to look for urinary tract infection (UTI) or other abnormality. A UTI can cause symptoms of urgency, frequency, and incontinence.

For more complicated clinical pictures, urodynamics can be utilized to provide further information on bladder function. Similar, cystoscopy can be considered if there is any concern of malignancy or other bladder abnormality, especially if symptoms are of sudden onset or accompanied by hematuria in the absence of UTI.[24] Urodynamics can be performed if a patient is contemplating surgery or there is a complicated clinical picture.

Therapy for incontinence varies depending on the type of incontinence. However, there are several noninvasive approaches that can be initiated regardless of the incontinence type. Weight loss, for example, has been demonstrated to help obese and overweight women suffering from urinary incontinence.[25] Dietary changes to eliminate known bladder irritants such as alcohol, carbonated beverages, coffee, and tea can also be helpful. Similarly, fluid intake modification may also address patients' complaints of frequency, urgency, nocturia, or nocturnal enuresis. Bladder retraining with timed, frequent voiding and learning pelvic mechanisms to inhibit urges are often useful in addressing incontinence.[26,27] Pelvic floor muscle physical therapy has been demonstrated to be helpful in the treatment of urinary incontinence in a variety of settings.[28] The success of physical therapy has been well demonstrated in women suffering from incontinence during pregnancy, postpartum, as well as other phases of life. The main obstacles with this therapy are often the time commitment required and locating a trained pelvic floor physical therapist in the area, as well as issues with adequate insurance coverage.[29,30] Setting up the environment for older women to facilitate access to the bathroom and prevent falls is also helpful.

Prevention is important and can make a difference in bladder health. Educating patients on good bladder habits and methods can prevent some urinary incontinence. This can begin with general lifestyle modifications, which improve their overall health. Weight loss, smoking cessation, increased exercise, dietary modifications, and treatment of chronic coughs and constipation are all helpful in the prevention of urinary symptoms. The patient can also perform pelvic floor muscle strengthening exercise such as Kegels as a preventive measure. Management or prevention of associated comorbidities, such as diabetes and other neurologic disorders, can also help prevent the development of urinary incontinence. Finally, instruction on healthy voiding habits is quite important, with an emphasis on adequate but moderate fluid intake, avoidance of straining with voiding or bowel movements, and regular soft bowel movements, which are all helpful in preventing the development of urinary incontinence in patients.[31]

STRESS INCONTINENCE

SUI is defined as the complaint of involuntary leakage of urine on effort or exertion, or on sneezing or coughing.[9] It is most often secondary to bladder neck hypermobility along with weakening of the striated sphincter with or without intrinsic sphincter deficiency.[24] During increased intra-abdominal pressure, the bladder and neck and proximal urethra drop below the retropubic space, and there is uneven distribution of abdominal pressure to the bladder but not the urethra due to loss of anatomic support. Often described as a hammock, the anterior vaginal wall and endopelvic fascia are attached laterally to the arcus tendineus and levator ani muscles creating a support structure for the urethra and urethrovesical junction. This hammock can be damaged during events such as childbirth. This leads to failure of optimal urethral compression with increased intra-abdominal pressure and resulting leakage of urine.[32] Intrinsic sphincter deficiency refers to failure of the urethral sphincter to close appropriately during times of stress. There are multiple factors that can cause this including trauma during childbirth, hypoestrogenism, neurologic disease, radiation exposure, scarring from prior surgery, and medications.[33]

The treatment of SUI varies depending on severity and patient goals. Conservative treatment can begin with the modifications mentioned earlier including treatment of medical comorbidities, decreased fluid intake to 2–3 L a day, avoidance of bladder irritants, and pelvic floor physical therapy. Biofeedback has not been demonstrated to produce any added benefit to physical therapy.[34] Elderly patients may elect to simply use absorbent pads.

Vaginal devices such as pessaries or urethral inserts are other treatment options for patients with SUI. The pessaries come in a wide range of styles and sizes; however, the ring type is often the most useful.[35] They sit under the neck of the bladder for support. Urethral occlusive devices are less popular, but can be inserted into the urethral meatus to achieve mechanical occlusion of the urethra. However, they can be irritating and pose a risk for infection. These options are often helpful for women who wish to avoid or delay surgical intervention.[36]

Medical management of SUI is another option although modestly effective. Although hypoestrogenation is thought to be a contributor to SUI in postmenopausal women, the data on estrogen replacement for treatment have been varied. Data on oral hormone replacement have demonstrated that it can actually worsen symptoms of urinary incontinence.[37] The role of topical estrogen remains unclear.[38] Alpha-adrenergics are a class of medications that act on sympathetic nervous system to increase the tone of the urethra and bladder neck. These have been associated with only modest improvements in symptoms and significant systemic side effects including hypertension, anxiety, headaches, and insomnia.[39] Duloxetine is a combination of serotonin and norepinephrine reuptake inhibitors, which had been shown to enhance the external urethral sphincter contraction.[40] However, a Cochrane clinical review demonstrated that any beneficial effects of the medication are transient and side effects can be quite serious.[41]

Urethral bulking agents are an attractive option for women who are not candidates for surgery or who have failed surgery. This can be done via local anesthesia in the office. The injections are transurethral or via paraurethral through perineal injections. There are multiple bulking agents available including silicone, saline, and collagen. Although the majority of women experience an initial relief of symptoms after treatment, many agents are biodegradable; therefore, the effect is transient.[42] Short-term cure rates are as high as 70%, and long-term rates fall to around 20%–30%. Women also require repeat injections.[43] When compared to surgical method of treatment, bulking treatment is less effective.[44]

Surgery for SUI is the most common treatment as it offers the most sustainable results. Several considerations should be evaluated prior to initiation of surgery. Coexistent urge incontinence is not a contraindication for surgical correction of SUI; however, patients should be counseled that the procedure could in fact worsen their other symptoms. In addition, women with concomitant POP should have both anti-prolapse and anti-incontinence procedures performed simultaneously because this will afford improved outcomes.[43–45]

There are a variety of surgical options available for women. Abdominal retropubic suspension procedures have been utilized for decades in the treatment of SUI. These surgeries work by elevating and fixing the bladder neck and proximal urethra in a retropubic position to enhance support. There are three main variations of the repair: the Burch, Marshall–Marchetti–Krantz, and paravaginal defect repair.[46] The most widely utilized approach is the Burch colposuspension; it also has the highest long-term success rates.[47] Given the higher success rates and lower complication rates, the Burch procedure is preferred to the Marshall–Marchetti–Krantz and paravaginal defect repair.

Vaginal approaches to SUI include anterior colporrhaphy with suburethral plication to elevate the bladder neck. This procedure has been shown to have limited long-term success rates.[24] Bladder neck needle suspension procedures are another option in which sutures are passed through the periurethral tissue near the bladder neck and then to the suprapubic space and rectus fascia. The sutures are tied over the rectus fascia to suspend the proximal urethra and bladder neck. This also has been shown to have poor long-term success rates and therefore is no longer a favored option of treatment. A Cochrane systemic review demonstrated that the open retropubic colposuspensions have lower failure rates than bladder neck needle suspensions, anterior vaginal repairs, and laparoscopic suspensions.[47] Other methods include bladder neck slings, mid-urethral slings, and injection of urethral bulking agents. The bladder neck slings involve placement of a sling under the bladder neck and urethra and fixation of the ends to the anterior rectus fascia.[24]

Tension-free mid-urethral sling procedures have been shown to be highly effective with minimal complications and are rapidly becoming the surgical treatment of choice for SUI, rapidly replacing Burch procedures. There are two different techniques: the tension-free vaginal tape (TVT) and the tension-free transobturator tape (TVT-O).[48] In the TVT procedure, small midline suburethral incisions are made in the vaginal mucosa. A synthetic polypropylene tape is placed at the level of the mid-urethra and extended bilaterally behind the pubic symphysis and through the fascia and suprapubic dermis using thin trocars. TVT-O differs by avoiding the retropubic space and passing through the obturator foramen. The latter method has been demonstrated to have lower rates of urinary tract injury, voiding dysfunction, and blood loss when compared with the TVT.[49] Mid-urethral slings are as effective as other surgical treatments for SUI but with shorter operative time and fewer postoperative complications, therefore the surgical treatment of choice for many surgeons.[48] Risks however include the risk of mesh erosion or infection as well as thigh pain with TVT-O.

URGE INCONTINENCE

Urge incontinence is defined as the involuntary leakage of urine accompanied by or immediately preceded by urgency. This differs from overactive bladder, which is a symptomatic diagnosis where patients have symptoms of urgency with or without urge incontinence.[9] This disorder is largely due to detrusor over activity.[50] A related disorder in the elderly is detrusor hyperactivity with impaired contractility. These patients experience urgency in combination with a high postvoid residual.[51]

There are multiple etiologies for urge incontinence. Neurologic diseases such as multiple sclerosis, Parkinson's disease, or spinal cord injuries can lead to detrusor hyperactivity. Local bladder or urethral irritants such as sutures or malignancies can be a cause. Medications, particularly parasympathomimetics, can cause a sensation of urinary urgency. Bladder outlet obstruction can also lead to symptoms of urgency; this is often seen in patients with advanced POP. Unfortunately, the vast majority of cases are due to an unknown etiology. There is likely a myogenic dysfunction of the detrusor muscles leading to spontaneous contractions.[52]

There are a variety of treatment options available for patients suffering from urge incontinence. Prior to initiating

treatment, patients should be counseled that up to 5.6% of patients suffering from urge incontinence experience spontaneous remission per year.[53] Intervention can be conservative at first with fluid management, bladder retraining, and physical therapy.[54] Pharmacologic therapy is primarily antimuscarinics, which increase bladder capacity and decrease urgency.[55] These medications have consistently been shown to be more effective than placebo in multiple randomized control trials, with a 40% or higher cure rate.[56] There is no definitive literature to suggest that one antimuscarinic is better than another.[57] Unfortunately, discontinuation rates are high, averaging around 60% at 6 months, given the multiple systemic side effects patients experience.[58] Common side effects include dry mouth, vision changes, tachycardia, drowsiness, and constipation. Constipation and dry mouth can often lead patients to increase fluid intake and strain, which may worsen their urinary symptoms. These medications are also contraindicated in patients with gastric or urinary retention and angle closure glaucoma. There is controversy regarding using this class of medication in elderly patients with dementia due to concern for aggravation of symptoms. If prescribed for the elderly, the lowest dosage possible should be utilized.[59]

Botulinum toxin A injected into the detrusor muscles is a newer therapy for urge incontinence patients with symptoms refractory to oral pharmacologic and behavioral therapy. The exact mechanism of action of botulinum toxin in the bladder is unclear, although evidence suggests that it may work by preventing the presynaptic release of acetylcholine from the parasympathetic innervations to the bladder and may have an effect on sensory mechanisms. The data are limited primarily to case series but results have been encouraging.[60] The concern with this treatment is urinary retention and need for intermittent self-catheterization; therefore, proper counseling of this risk is important prior to initiation of treatment.[61]

There are various neurologic stimulation therapies that can be utilized to treat urinary urge incontinence by stimulating or modulating pelvic and/or detrusor muscles. The most noninvasive option is a removable stimulation device in the vagina or the anus. It is thought to work by stimulating the periurethral striated muscles and the pudendal nerve, which thereby inhibits detrusor muscle activity. Results have been inconclusive with no clear benefit over behavioral therapy.[62]

Sacral nerve stimulation has had higher success rates. The stimulators are thought to act by innervation of afferent fibers to the detrusor, which inhibit spinal and supraspinal signals, leading to muscle relaxation. However, the exact mechanism of action is unclear. In this procedure, percutaneous electrodes are placed adjacent to the S3 dorsal roots. Patients then undergo a 1–2 week trial. If they have an improvement in their symptoms, patients return for permanent lead implantation and placement of a pacemaker-like stimulator under the skin of the buttock. Cure rates have been reported to range between 47% and 56% among patients who have failed other therapeutic options.[63] Unfortunately, the majority of the data available are from case series rather than randomized control trials. Adverse events are uncommon but include migration of the electrodes, pain, infection from placement, and occasional transient electric shock.[64]

Percutaneous stimulation of the tibial nerve stimulation is another alternative for patient refractory to other therapies. The data on the efficacy are limited. Most studies suggest limited benefit over pharmacologic management.[65]

Surgical treatment is generally not an option for patients suffering from urge incontinence as the procedures have limited success and high morbidity. For patients who have failed all other treatments, bladder denervation, bladder augmentation, and urinary diversion may be attempted. However, these are procedures of last resort, and their usefulness remains controversial.

MIXED INCONTINENCE

Mixed incontinence is the complaint of involuntary leakage of urine associated with urgency and also with exertion, sneezing, or coughing.[9] Patients exhibit components of stress and urge incontinence. It is often challenging to determine which therapeutic option is most appropriate for these patients. Treatment usually begins with conservative measures, which are common treatments for all types of incontinence, such as pelvic floor physical therapy. Electrical stimulation has also been shown to be helpful in this population.[66] The majority of these patients have one symptom that is more bothersome and generally receives treatment for that symptom, or a combination of treatments to address all their symptoms.

PELVIC ORGAN PROLAPSE

POP is defined as the herniation of one of pelvic organs (uterus, vaginal apex, bladder, rectum, or small bowel) from its normal location. The degree of prolapse is graded on a 0–4 scale in relation to the hymenal ring, with 0 being no prolapse and 4 complete prolapse often referred to as procidentia. There are various types of prolapse including upper vaginal prolapse (uterus or vaginal vault), anterior vaginal wall prolapse (bladder or urethra descent or pelvic fascia defect), or posterior vaginal wall prolapse (descent of the small bowel or rectum or perineal deficiency).[67] Twenty-four percent of women in the United States are estimated to suffer from POP.[1] There are an estimated 200,000 prolapse repair surgeries per year, with an annual cost exceeding $1 billion.[68,69]

There are multiple risk factors for POP. There appears to be a genetic predisposition to the disease. Parity, particularly vaginal births, occipital posterior position, and instrumental delivery are known risk factors.[70] There are some data that a cesarean delivery may be protective when compared to vaginal delivery; however, other data suggest that pregnancy itself, regardless of mode of delivery, is a risk factor.[71] Like many other pelvic floor disorders, obesity and advanced age increase the likelihood of developing POP.[72] Estrogen deficiency, connective tissue disorders, and prior pelvic surgery have also been associated with POP. Chronic increased intra-abdominal pressure such as chronic constipation or

cough (COPD) can also be associated with POP.[73] Women with hypermobile joints have been shown to have a higher prevalence than women with normal joints, suggesting that collagen abnormalities may contribute to prolapse.[74]

Patients exhibit a variety of symptoms depending on the location of prolapse. The most common complaint is a feeling of heaviness or pressure in the vagina. Urinary symptoms are often indicative of anterior wall prolapse, which comprise approximately 40% of prolapse.[75] Symptoms of defecatory dysfunction usually imply posterior wall prolapse, which occurs about 7% of the time. The majority (47%) of patients have a combination of anterior, posterior, or apical prolapse.[2]

Physical examination should be done with patients in both lithotomy and upright to visualize the maximal prolapse descent. The Pelvic Organ Prolapse Quantification system (POP-Q) is the standardized prolapse grading mechanism. Various points are recorded both at rest and with Vaslava to create a map to grade patients prolapse and measure treatment response. A rectovaginal exam should always be included to look for evidence of an enterocele, rectovaginal connective tissue defects, perineal deficiency, or masses.[76]

Prior to initiating treatment for POP, the clinician must first ascertain patient goals. The primary predictor of patient satisfaction is achievement of individual patient goals.[77] Mild prolapse has been shown to spontaneously resolve in some women or at least not be as symptomatic. Conservative management begins with weight loss, pelvic floor physical therapy, and behavioral modification including bladder retraining as needed and dietary modifications to improve bowel function and decrease chronic straining.[78]

There are multiple surgical options available for patients suffering from POP. The choice of procedure depends on the severity and location of prolapse, urinary or bowel symptoms, general health of the patient, sexual function of the patient, surgeon experience, and need for additional procedures. There are laparoscopic, vaginal, and abdominal techniques that can be utilized. One of the most common repair procedures is an anterior colporrhaphy. This entails placating the vaginal muscularis and adventitia overlying the bladder or plicating and reattaching the paravaginal tissue to reduce to the protrusion of the bladder and vagina. Cochrane review analysis has demonstrated that the anterior repair with the use of vaginal mesh may confer more successful repair than that without mesh.[67] However, vaginal mesh erosion rates have been reported between 2% and 11%, which can cause pain, bleeding, and need for reoperation. Therefore, it is imperative for physicians to counsel patients on the risks of the procedure prior to initiating surgery.[79]

Another option is a paravaginal repair. In this procedure, the detached lateral vagina is reconnected to the normal place at the level of the arcus tendineus. This can be accomplished vaginally or via a retropubic approach. Long-term results of these procedures have been disappointing.

Similar procedures are available for posterior defects. For instance, a posterior colporrhaphy is a procedure in which the tissue underlying the vaginal mucosa is plicated in the midline, increasing the fibromuscularis tissue in the midline of the posterior vaginal wall. A variant on this procedure is a site-specific defect repair. As the name implies, defects in the fibromuscularis are individually isolated and repaired. Graft augmentation is another variation to augment support of the posterior vaginal wall. Perineorrhaphy is often done with a posterior repair. During this procedure, the bulbospongiosus muscles and the transverse perineal muscles are plicated in order to recreate or fortify the perineal body.[67] These procedures are most helpful for localized defects or distal stool trapping requiring splinting.

Laparoscopic, vaginal, and abdominal approaches are possible for apical prolapse. Vaginal procedures offer relatively quick recovery when compared to abdominal procedures. The best studied vaginal procedure for apical prolapse is a sacrospinous ligament suspension. This procedure has a low failure rate (2%–11%) when performed for apical prolapse.[80] During this procedure, the sacrospinous ligament is sutured to the posterior vaginal muscularis.[81] The procedure is traditionally performed unilaterally. The most common complication is bleeding usually arising from the pudendal vessels, which are in close contact with ligament. Pain has also been reported due to the proximity of the pudendal and sciatic nerves. Subjective success rates have been reported to be as high as 90% from this procedure.[82] Iliococcygeus suspension is a similar procedure that secures the posterior vaginal muscularis to the iliococcygeus fascia rather than the sacrospinous ligament. It was thought that this procedure has less incidence of anterior vaginal wall prolapse recurrence than sacrospinous ligament fixation; however, studies have demonstrated that the two procedures have equal success and recurrence rates.[83] McCall culdoplasty is a technique often done at the time of vaginal hysterectomy to repair an enterocele and close the redundant cul-de-sac. It has also been shown to provide apical support by bringing the posterior vaginal cuff and peritoneum to the uterosacral ligaments bilaterally, thereby obliterating the dependent portion of the cul-de-sac. The most frequent serious complication of a McCall Culdoplasty is damage to the ureters.[24]

Uterosacral ligament suspension is another apical prolapse repair procedure in which the vaginal apex is elevated via attachments to the uterosacral ligaments. This procedure can be performed laparoscopically, abdominally, or vaginally. Subjective success rates have been reported up to 98% for apical prolapse.[84] A sacral colpopexy is the most common abdominal prolapse procedure and can also be performed laparoscopically. It is the most durable procedure due to the use of mesh for attachment and is considered by many to be the gold standard for prolapse repair. During this procedure, a Y-shaped graft is attached to the anterior and posterior vagina, and the arm of the graft is then attached to the anterior longitudinal sacral ligament. Success rates of up to 95% have been reported at 2 years postoperatively.[85] Various materials have been used for the graft in colpopexy, both natural and synthetic. Most studies indicate that cadaveric fascia is associated with a higher rate of recurrent prolapse than synthetic mesh (ref). However, increased durability comes with a 3%–4% mesh erosion and other mesh complications. Mesh

erosion rates can be as high as 14% when mesh is placed following a total hysterectomy.[22] For this reason, supracervical hysterectomy has become more common when planning for a sacrocolpopexy. Intraoperative complications are rare but can be serious such as bleeding, which can be difficult to control.[67] Also delayed bowel issues such as ileus, obstruction, or other intra-abdominal issues can be encountered with this route of repair.

With advancements in technology and surgical tools, more procedures formerly done via an abdominal incision are performed laparoscopically. This same trend is also evident with pelvic floor reconstructive procedures. Laparoscopic surgery offers the advantages of shorter hospital stay, decreased postoperative pain, and improved cosmesis.[86] Robotic surgery is another minimally invasive method to perform these procedures. There has been minimal prospective literature on this method; however, the results of numerous small studies on robotic sacrocolpopexy are encouraging.[86]

Vaginal mesh procedures have also been performed with increasing frequency. Although anatomic cure and durability are good, there remain questions on complications such as more common mesh erosions and intractable pain.

There are also obliterative procedures for women who do not desire future vaginal intercourse and/or have poor general health. In comparison with reconstructive surgery, postoperative patient satisfaction rates are similar.[87] The procedure consists of removing all the vaginal epithelium. The leading edge of prolapse is identified and successive interrupted sutures are used to reduce the prolapse until it lies above the levator plate, obliterating the vaginal canal. A wide perineorrhaphy is then created with a "butterfly"-shaped incision and the levator muscles are reapproximated, closing the area from above the rectum to the urethrovesical junction. Possible complications included SUI, which is likely secondary to incidentally pulling the posterior urethra down when suturing the anterior and posterior vagina.[88]

Studies comparing different surgical options demonstrate that each has its own strengths and weaknesses. For instance, a meta-analysis comparing abdominal sacral colpopexy versus vaginal sacrospinous colpopexy found that the abdominal procedure was better than the vaginal sacrospinous colpopexy in terms of recurrent vault prolapse, postoperative dyspareunia, urinary retention, and postoperative urinary stress incontinence. However, the abdominal procedure was also associated with longer operative time, recovery time, and increased cost.[89]

Given the multitude of surgical options, it is the responsibility of the provider to advise which procedure would be most appropriate for a particular patient with appropriate informed consent and to offer choices with regard to approach. For instance, a medically unstable patient who is not sexually active would most be best treated with an obliterative procedure. However, a young active women may prefer a laparoscopic sacrocolpopexy given its fast recovery time and durability. In addition, it is important to discuss potential complications and issues that are related to the use of mesh for pelvic reconstructive surgery.

INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME

Interstitial cystitis (IC) or painful bladder syndrome (PBS) is a poorly defined syndrome of bladder pain associated with filling and/or emptying and is usually accompanied with urgency, frequency, and nocturia.[90] It is a disease of exclusion with a poorly understood etiology, which has led to an unclear consensus on treatment.[91] It is difficult to estimate the incidence of the disorder given that there are variable definitions. Estimation of prevalence ranges from 10 to 865 cases per 100,000 people.[92] The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) attempted to create a standardized criterion in 1987. However, it is estimated that this criterion misses an estimated 60% of patients. The NIDDK criterion is primarily used in research settings, and often the diagnosis is made clinically using patient symptoms and exam findings.[93] IC/PBS patients are usually middle aged with a mean age of diagnosis of 42–45 years old.[94] However, patients can be of any age. There is also an association between IC/PBS and other chronic pain disorders including, endometriosis, vulvodynia, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and allergies.[95]

The pathophysiology behind IC/PBS is poorly understood. The etiology of IC/PBS is likely multifactorial; however, multiple theories exist. One hypothesis is that there are urothelial abnormalities, particularly a deficiency of the glycosaminoglycan layer (GAG), which are visualized on bladder biopsy, and these abnormalities lead to patient symptoms. However, it is difficult to establish a causal relationship and assume that the disease itself did not cause the urothelial abnormalities.[96] Another theory is that these patients have an increased sensory awareness making them more sensitive to normal bladder filling, as in allodynia. Central neurological upregulation and increased activation of bladder sensory neurons may initiate and propagate patient's symptoms and heighten sensitization.[97]

Patients suffering from IC/PBS often present with complaints of urgency, frequency, and pain around the area of their bladder. The pain may be modified by voiding habits, intercourse, or foods. It can wax and wane with periods of flair and remission. The first diagnostic step is to rule out other possible causes for the patients' symptoms including infections, mass, urinary stone, or malignancy. Tests to consider include a urinalysis with possible cytology and cystoscopy to look for any masses or physical abnormalities. In the past, hydrodistension was thought to be necessary to look for characteristic markers of IC including glomerulations and Hunner's patches. However, these findings are now considered to be nonspecific as they are found in 45% of healthy patients; therefore, hydrodistension is no longer necessary for diagnosis.[98] Similarly, the potassium sensitivity test is also no longer recommended for diagnosis given that the results are nonspecific. In this test, the bladder is filled with water, drained, and then filled with potassium chloride. Increased pain with potassium chloride is considered suggestive of IC/PBS. However, up to 46% of patients with negative

potassium sensitivity tests still have IC/PBS.[99] Therefore, given the lack of sensitivity and the discomfort associated with the test, it is no longer recommended.[100] Bladder biopsies are done if necessary to exclude other disorders.[101] Currently, investigations are under way to look for biomarkers that may help with diagnosis.[102]

Prior to initiating treatment, patients should be asked to complete a voiding diary and symptoms scale. The voiding diary will help establish a baseline for frequency, urgency, and bladder pain. A symptoms scale will help quantify the patient's symptoms and evaluate their response to treatment. There are various validated symptoms scales including the O'Leary IC Indices, the University of Wisconsin IC Scale, and the Pelvic Pain and Urinary Urgency and Frequency Scale.[24]

Currently, there is no "cure" for IC/PBS. However, treatment options are available that can effectively mediate symptoms and provide long-term relief. Given that this is a chronic pain disorder, many patients benefit from support groups. Patients can immediately begin with behavioral therapy such as bladder retraining with timed voiding for frequency symptoms. Avoidance of exacerbating triggers such as spicy foods or other patient-identified foods or activities can be initially helpful. Pelvic floor physical therapy has also been shown to be helpful in this patient population.[103]

Pharmacologic treatment modalities include pentosan polysulfate. This medication may be helpful in reconstituting the GAG layer, which is believed to be leaky in these patients.[103] Meta-analysis of randomized control trials of the agent has found it to be modestly more effective than a placebo. Another oral therapy used is amitriptyline. Often used to treat other chronic pain syndromes, several randomized control studies of this medication have demonstrated an improvement in patient symptoms.[104] Gabapentin is becoming increasingly used to treat pain in IC/PBS patients; however, data are still very limited on its efficacy.[105] Since some theories have suggested that mast cells cause the release of neuroactive and vasoactive agents responsible for IC/PBS symptoms, treatment directed at mast cells have been tried to alleviate this inflammatory response. However, recent data on medication such as hydroxyzine demonstrated that it has no clear benefit over placebo.[106] Cimetidine was found to have a minor benefit, but this was only seen in small studies.[107]

As hydrodistension has be used for diagnosis, it has also been used as a form of treatment for some patients. Thirty to fifty-four percent of patients have improvement of symptoms after hydrodistension of the bladder. Patients who have improvement for 6 months or greater are candidates for repeat therapy.[108] However, since symptoms often recur quickly and there have been concerns about distension injury to the bladder, hydrodistension is much less commonly used.

Bladder instillations are the next line of treatment for patients who fail oral therapy. The instillations are done via a catheter and usually left in the bladder for 20–30 min. Treatments are usually given once a week for a series of 6 weeks. Dimethyl sulfoxide (DMSO) is the only Food and Drug Administration-approved intravesical treatment of IC. It was shown to be beneficial in two randomized control trials reviewed in a review paper on pharmacologic treatment of IC.[109] DMSO has anti-inflammatory and analgesics effects. It is also thought to cause muscle relaxation and mast cell inhibition. It can be used alone or in combination with heparin, triamcinolone, and sodium bicarbonate.[110] Sodium pentosan polysulfate can also be used as a bladder instillation. This has equal efficacy as the oral method, although symptoms are relieved faster.[111] Steroids have also been utilized in this fashion with the thought that that they can help IC symptoms with their immunosuppressive properties. Heparin and local anesthesia can be used in combination or alone. Heparin may help replenish the GAG layer in the bladder's urothelium. Local anesthetics such as lidocaine produce a significant response but are generally short-lived improvement in symptoms. Instillations of various "cocktails" are often used for symptom relief. Patients who respond to these instillations can be taught to catheterize and administer them at home. Intravesical hyaluronic acid has shown to have a significant response rate for up to 6 months. It is thought to coat the lining of the bladder and protect it from irritating substances. Bacillus Calmette-Guerin is an immunogenic agent used to treat bladder cancer and is under investigation for instillation therapy. Randomized control trials fail to show a statistically significant improvement in symptoms among patients treated with the medication.[112] Botulinum A toxin has been utilized as a possible intravesical treatment option. In one study comparing hydrodistension versus hydrodistension with botulinum toxin, greater improvement in symptoms was found among patients treated with botulinum toxin. However, botulinum A toxin for IC remains investigational.[113]

Multiple small studies have investigated sacral neuromodulation as a treatment option for patients refractory to the earlier-mentioned treatment options. There have been mixed results with some prospective studies on sacral neuromodulation demonstrating promising results, while a prospective randomized control trial on tibial nerve stimulation demonstrating no difference from placebo.[114,115] Surgical therapy is considered a last resort for patient, given the morbidity and poor efficacy. Surgical options include laser fulguration of Hunner's ulcers, cystectomy, and bladder augmentation. All have low success rates and high rates of recurrence and morbidity.[24]

CONCLUSION

Pelvic floor disorders affect women of all ages, races, and backgrounds. This chapter focused on the preventive lifestyle and health modifications to maintain bladder health and the evaluation and treatment of the three most common pelvic floor conditions: incontinence, prolapse, and pain. These disorders have significant and important effects on the quality of life for many women. Simple preventive strategies include control of constipation, chronic coughs, or chronic straining. Pelvic floor muscle strengthening can also preempt these disorders. The treatments discussed in this chapter can be initiated only after the disorders are properly diagnosed. It is the responsibility of physicians to inquire about pelvic floor issues and symptoms as patients are often reluctant to report them.

Increased awareness and education of both physicians and patients about the frequency of these disorders, bladder health-related lifestyle modifications, and the array of available treatment options will bring increased prevention, detection, and effective treatment. As our patient population grows older, knowledge about bladder health can bring improved quality of life to healthy aging. Although significant advances have been made, more research is needed in the field to address the varied needs of the growing patient population.

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73 Risk Reduction and Screening for Women's Cancers

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CONTENTS

Introduction....911
Breast Cancer....911
Epidemiology/Risk Factors....911
Screening....912
Lifestyle....912
Intervention/Prevention....913
Ovarian Cancer....914
Epidemiology/Risk Factors....914
Screening....915
Lifestyle....916
Intervention/Prevention....917
Endometrial Cancer....917
Epidemiology/Risk Factors....917
Screening....919
Lifestyle....919
Intervention/Prevention....920
Cervical Cancer....921
Epidemiology/Risk Factors....921
Screening....921
Lifestyle....921
Intervention/Prevention....922
References....923

INTRODUCTION

Cancer is the second leading cause of death for women in the United States. Several women's cancers can potentially be caught early through screening. These include breast, endometrial, ovarian, and cervical cancers. Risk factors, guidelines for screening, and modifiable lifestyle factors are discussed.

BREAST CANCER

Epidemiology/Risk Factors

Breast cancer is the most common cancer among women in the United States, excluding non-melanoma skin cancer, and is the second leading cause of death from cancer. Approximately one in eight women will develop breast cancer during her lifetime.[1]

Various reproductive factors affect the risk of breast cancer, probably due to hormone exposure and changes in breast tissue as part of pregnancy and lactation. Delivering a child before age 30, increased parity, and increased duration of breast-feeding are all associated with reduced risk of breast cancer. By some estimates, every birth confers an approximate 7% reduction in risk, 4.3% with every year of breast-feeding.[2] Early menarche and late menopause are associated with an increased risk, with a relative risk of 2–3.[3]

There is a small increased risk of breast cancer with the use of oral contraceptive pills (OCPs), but this attenuates after discontinuation, and overall most experts agree that the risk does not outweigh the other potential benefits of oral contraceptive use (contraception and reduction of ovarian and endometrial cancer risk). A meta-analysis examined data from 54 studies with a combination of 53,297 women with breast cancer and 100,239 controls. Results demonstrated a relative risk of breast cancer of 1.24 in women currently taking contraceptive pills and in the 10 years after discontinuation of use, with attenuation of risk with years from use (e.g., relative risk of 1.16 at 1–4 years after stopping). However, at 10 years from discontinuation of use, risk returned to baseline with a relative risk of 1.01. Duration of use, age at first use, and type/dose of medication were not found to be significant.[4]

Similarly, use of postmenopausal hormone replacement therapy (HRT) confers a small increased risk of breast cancer that resolves with discontinuation of therapy. The same group analyzed a number of studies regarding the risk of breast cancer with use of HRT. Data on 52,705 women with breast cancer and 108,411 women without the disease from 51 different studies were analyzed. Among current or recent (within 1–4 years) users of HRT, relative risk for breast cancer was increased by 1.023 for each year of use. For those using HRT for 5 or more years, the relative risk was 1.35. Risk returned to baseline at 5 years from discontinuation of HRT.[5]

Screening

Screening for breast cancer is most commonly performed through mammography. In certain high-risk populations, additional imaging with ultrasound or breast MRI may be appropriate. Other modalities for the detection of breast cancer include breast self-exam and clinical breast exam by a physician.

Mammography is accepted as the current best method of early detection of breast cancer. Meta-analyses of randomized clinical trials demonstrated a 26%–27% reduction in breast cancer mortality. Another meta-analysis reported a sensitivity of 83%–95% and false-negative rates of 0.9%–6.5%, making it a good screening tool.[1] Results regarding the utility of clinical and self-breast examination are more equivocal. Data from the National Breast and Cervical Cancer Early Detection Program were analyzed with regard to clinical breast exams. In 752,081 clinical breast exams that were assessed, 6.9% were coded as abnormal. A total of 5 cancers were found per 1000 breast exams. A sensitivity of 58.8% and a specificity of 93.4% were reported.[6] For breast self-examination, efficacy is even less. A Shanghai trial randomized 266,064 women to either breast self-examination or a control group without any instruction in self-examination. The group instructed in self-examination received reinforcement training as well as reminders to perform self-examination and supervision of their technique during office visits. Mortality from breast cancer was the same in both groups, and women in the self-examination group underwent more biopsies for benign disease.[7]

The U.S. Preventive Services Task Force (USPSTF) recommendations regarding screening mammography include the following:

- At age 50, start routine biennial screening with mammography
- At ages 40–49, routine mammography screening not recommended
- At age 75 or older, insufficient evidence to assess risks/benefits of screening mammography
- Teaching breast self-exam not recommended
- Insufficient evidence to assess risks/benefits of the clinical breast exam

The rationale behind these altered guidelines was to attempt to reduce unnecessary additional testing and procedures for younger women, as false-positive results are higher.[8]

However, these guidelines are the source of some recent controversy. The USPSTF found that the net benefit for women is similar in their 40s and 50s, but that women in their 40s incur more harm through additional imaging and biopsies for abnormalities on imaging that are eventually found to be benign—and that this is potentially more common in younger women due to denser breast tissue. The American Cancer Society argues that when taking a broader view of the literature in existence, there is strong evidence to continue supporting the initiation of screening at a younger age, and more frequently. The American College of Obstetrics and Gynecology (ACOG) also endorses more frequent screening, and at a younger age.

The American Cancer Society recommendations for screening are as follows[9]:

- At age 40, start routine annual screening with mammography
- Clinical breast exam recommended at least every 3 years for ages 20–40, annually after 40
- Breast self-exam risks/benefits discussed, teach technique if a woman chooses to perform self-exam

The ACOG recommendations for screening are as follows[1]:

- Ages 40–49, routine screening with mammography every 1–2 years
- At age 50, routine annual screening with mammography
- Annual clinical breast exam for all women as part of the physical examination
- Breast self-exam may have some utility in detection of cancer, and may be recommended

Women with BRCA mutations should be screened earlier and more frequently than the general population. Currently recommended surveillance strategies include semiannual clinical breast examination, and both annual breast MRI and mammography, starting at age 25 or sooner, depending on family history and the earliest age of onset.[10] Please see the Section on Ovarian Cancer for a discussion of indications for BRCA testing.

Lifestyle

Some correlation has been found between obesity and the development of breast cancer, particularly in postmenopausal women. In a systematic review and meta-analysis examining the role of body mass and various cancers, a relative risk of 1.12 for postmenopausal breast cancer was found in obese women. The relative risk of premenopausal breast cancer in obese women from the study was 0.92.[11] A prospective cohort study within the Nurses' Health Study noted a relative risk of 0.43

for women who had lost 10 kg or more since menopause and maintained their lower weight.[12]

Data from the Nurses' Health Study supports the role of exercise in risk reduction of breast cancer. Baseline physical activity was assessed at the start of the prospective study, as well as at regular intervals. Over 16 years of follow-up, 3137 cases of breast cancer were identified, with 1036 premenopausal and 2101 postmenopausal. Women reporting higher levels of physical activity had a reduced relative risk of 0.82, when comparing those engaged in 7 or more hours of activity per week to those reporting less than 1 h of physical activity per week. There was a trend toward dose–response (higher levels of activity correlating with decreasing risk) that was statistically significant.[13] Another study looked at a large cohort of postmenopausal women as part of the American Cancer Society Cancer Prevention Study. In that study, 72,608 postmenopausal women completed a questionnaire, including assessment of physical activity, with 1,520 cases of breast cancer identified over 5 year follow-up. The women who were the most active had a 29% reduction in risk compared to the least active women. Measures of physical activity included both recreational and non-recreational activities, such as housework and gardening.[14]

Alcohol consumption, even in moderate quantities, has been linked to an increased risk of breast cancer. In the Million Women Study in the United Kingdom, 1,280,296 women were prospectively followed for the development of cancer and surveyed regarding various habits and characteristics. The authors estimated that for every additional drink per day (if consumed regularly), the risk of breast cancer increases by 11 per 1000 women.[15] The Women's Health Study in the United States found similar results. In that, 38,454 women provided dietary information and were followed for an average of 10 years, with subsequent diagnosis of 1484 cases of breast cancer. Analysis of the results found increasing risk of breast cancer correlating to increasing drinking, with a 9% increased risk for women consuming one drink daily and a 43% increase in those consuming more than three drinks daily.[16] A meta-analysis of 38 studies of alcohol consumption and its relation to breast cancer confirmed a modest increase in risk, with an 11% increased risk in women who consumed one drink daily.[17]

Smoking has also, in some studies, been correlated with an increased risk of breast cancer. However, a recent meta-analysis of 53 epidemiologic studies suggests that those results may have been confounded by alcohol use. Women who had smoked at any point in their lives were more likely to have higher alcohol intake. When smoking was analyzed separately from alcohol consumption, no increased risk was noted, with a relative risk of 1.03 for women who had smoked at some point during their lifetime and 0.99 for current smokers.[18]

High intake of dietary fat has been suggested to increase the risk of breast cancer. A review of the literature examined the available meta-analyses of various cohort and case–control studies. One meta-analysis reported a positive correlation between increased risk and both total and saturated fat intake. However, within another large study in Sweden, no association was found. Additional cohort studies did not report an association with total fat intake but did find a possible trend toward increased risk with higher saturated fat intake. However, in the same Swedish study, in subgroup analysis, women over 50 who had the highest consumption of mono- and polyunsaturated fats had a 50% reduction in risk compared to women with the lowest consumption. Overall, the evidence is mixed but suggests some role in reducing the risk of breast cancer through modification of certain fats within the diet.[19]

There is some evidence that vitamin D may be protective against breast cancer, but study results have been inconclusive. Generally, increased vitamin D intake or sunlight exposure proximal to the time of diagnosis has been more correlated with decreased risk when compared to assessed vitamin D status remote from diagnosis. However, vitamin D levels may be affected by hormonal status and may be affected by the cancer itself or by age. Additionally, most studies have been conducted in populations of Caucasian women and may not be applicable to other ethnicities.[20]

Soy products have been discussed as both possibly contributing to and protecting against the development or recurrence of breast cancer, due to estrogen-like activity. A recent meta-analysis of prospective studies showed a protective effect with soy consumption, but only in Asian populations, among whom the relative risk was 0.76. Western populations showed no effect, with a relative risk of 0.97.[21] Similarly, another meta-analysis that included case–control studies found a positive association between soy intake and reduced risk of breast cancer. The odds ratio for women in the lowest soy intake group was 0.88 and was 0.71 in the group with highest consumption, in Asian populations. Western population studies showed no effect, but the authors pointed out that in those studies, women in the highest soy consumption groups still consumed much lower quantities of soy isoflavones than the typical reported Asian diet. They suggested that high levels of soy, as in traditional Asian diets, may be protective against breast cancer.[22]

Evidence is mixed for other dietary factors, including green tea consumption. Some animal studies have demonstrated antitumor effects from compounds contained in green tea. A meta-analysis of studies examining a correlation between green tea intake and breast cancer reported heterogeneous results. A total of 5617 cases of breast cancer were studied. Case–control studies suggested a reduced risk with green tea consumption, with an overall odds ratio of 0.81. However, cohort studies found no association.[23] A review of meta-analysis examining the possible role of coffee in cancer reduction found no association with breast cancer.[24]

Intervention/Prevention

There is currently no role for the use of medications for prevention of breast cancer in the general population. However, for women at high risk, chemoprevention with tamoxifen (a selective estrogen-receptor modulator) has been approved

by the FDA. In a National Surgical Adjuvant Breast and Bowel Project study of 13,388 women at increased risk of breast cancer, tamoxifen reduced breast cancer risk by 49%–50% as compared to placebo. Tamoxifen does, however, have adverse effects such as increased risks of endometrial carcinoma and thromboembolic disease. For patients with known BRCA mutations, risk-reducing salpingo-oophorectomy, in addition to the reduction of ovarian cancer risk, also decreases the risk of breast cancer. Women with BRCA mutations, who undergo risk-reducing salpingo-oophorectomy, have been reported to have odds ratios of 0.44–0.57 for the development of breast cancer. Preventive measures in high-risk women, as they have other health ramifications, should be carefully considered, with full discussion of risks and benefits for the individual woman.[25]

OVARIAN CANCER

Epidemiology/Risk Factors

Ovarian cancer is the leading cause of death in women with gynecologic malignancies. Approximately 1.3% of American women will develop ovarian cancer during their lifetime. Its etiology remains poorly understood; proposed mechanisms include malignant transformation of cells engaged in turnover during ovulation, inflammation, and gonadotropin or hormonal influence.

Risk factors that have been identified fall into reproductive, genetic, and environmental categories. The most significant risk factor is a family history of breast and ovarian cancers, as up to 10% of women with ovarian cancer may have a hereditary predisposition. Women of Ashkenazi Jewish heritage are particularly at risk. Of women diagnosed with ovarian cancer, approximately 35%–40% of those with an Ashkenazi Jewish background have a BRCA mutation.[26]

For reproductive risk factors, parity seems to be the most significant. A large population, case–control study examined 563 cases of ovarian cancer in the New England area, with controls matched by age. Parity was associated with a reduced risk of ovarian cancer, as was having breast-fed. Increasing parity conferred additional risk reduction, but duration of breast-feeding did not. Women who had never had children had approximately twice the risk as women who had delivered a child. Early pregnancy losses and abortions were not found to be significantly associated with the risk.[27] A smaller case–control study in Taiwan also found an inverse association between ovarian cancer and parity, as well as trend toward protection with breast-feeding for over a year.[28] Early menarche and later menopause have been suggested as increasing risk of ovarian cancer. In at least one of the studies described earlier, those factors were not found to be significant although increasing age at menarche seemed to be protective among premenopausal women.[27] These identified reproductive risk factors lend credence to the theory of malignant transformation during cellular turnover, as many factors that seem to be protective suppress ovulation and subsequent turnover of ovarian epithelium.

For hormonal and gonadotropin effects, evidence regarding the risk for ovarian cancer is mixed. The Million Women Study was a UK study of women's health in those aged 50 or older. It reported a 2.2 per 1000 women incidence of ovarian cancer over 5 years in those not using HRT versus a 2.6 per 1000 women incidence in those using HRT (statistically significant), with a decrease in risk to that of controls with cessation of hormone use. Thus, the initial conclusion was that postmenopausal use of HRT was associated with an increased risk of ovarian cancer that could resolve with discontinuation.[29] However, a subsequent paper pointed out that the attributable risk for incidence of ovarian cancer associated with HRT use was only 4 per 1000 women and that the small increase in diagnosed ovarian cancer could be due to occult cancers that were then stimulated by hormone therapy and then able to be diagnosed.[30] The NIH-AARP Diet and Study Health Cohort examined over 90,000 women. Use of unopposed estrogen for fewer than 10 years was not associated with increased risk of ovarian cancer, although use for greater than 10 years conferred a relative risk of 1.89.[31] With regard to infertility and assisted reproductive therapy, a case–control study conducted in the southern United States found an increased risk for women diagnosed with infertility who had never had children. Among parous women, a history of infertility was not associated with an increased risk of ovarian cancer, nor was use of ovulation-inducing drugs. The reason that infertility would confer additional risk beyond nulliparity alone is unclear.[32] However, a recent Cochrane review of the use of clomiphene citrate (Clomid) for stimulation of ovulation noted that an up to threefold increase in ovarian cancer has been reported with the use for more than 12 cycles.[33]

Talc, used by some women as a powder in the genital area for personal hygiene, has been implicated in some studies as a risk factor for ovarian cancer. Structurally similar to asbestos, some have noted similarities in histologic characteristics between mesothelioma and serous adenocarcinomas. Inflammation and reactive changes in ovarian epithelium have been postulated to be a possible mechanism, with travel of talcum powder up the reproductive tract and to the ovaries. A meta-analysis examined 16 observational studies and found a statistically significant increased relative risk of 1.33 with the use of talcum powder, about a 33% increased risk of developing ovarian cancer. However, further analysis showed that hospital-based studies showed no association, whereas population-based studies did show an increased risk. Thus it is difficult to draw a clear relationship between talcum powder use and ovarian cancer.[34]

Endometriosis, polycystic ovarian syndrome (PCOS), and pelvic inflammatory disease (PID) are conditions in the literature that have also been associated with an increased risk of epithelial ovarian cancer. Endometriosis has particularly been linked to the endometrioid and clear cell histologic subtypes of ovarian cancer. One case–control study in Washington state found a threefold increase in risk of clear cell or endometrioid ovarian cancer with a history of endometriosis.[35] Studies have been mixed regarding the association between

PCOS and ovarian cancer, although the trend toward associated risk was stronger for those not using OCPs or who were thin.[36] A case–control study conducted in Canada found an increased risk of ovarian cancer with at least one episode of PID compared with never having had PID, with an increased risk if also associated with nulliparity or earlier diagnosis of PID.[37] Conversely, a similar Italian case–control study found no increased risk with a history of PID.[38]

Screening

A screening test should, ideally, be highly sensitive and highly specific and should uncover early disease at a point that intervention could result in a significant difference in morbidity or mortality. There is currently no recommendation for routine screening for ovarian cancer in the general population, as available screening methods neither have the required specificity to justify unnecessary procedures based on false-positive results nor are very successful at identifying early-stage disease.

Ovarian cancer generally presents at an advanced stage, and it was previously thought that women were asymptomatic until the disease became clinically apparent. This has been challenged; Goff et al. found in a survey of 1725 ovarian cancer patients that 95% reported having symptoms prior to their diagnosis, with 30% subsequently diagnosed as having stage I or II disease. This was a survey dependent on patient recall, but the results are still compelling. Only 11% of stage I or II patients, and 3% of stage III or IV, reported no symptoms prior their diagnoses. Symptoms were primarily abdominal or gastrointestinal (i.e., bloating, constipation, indigestion) rather than pelvic.[39] The study may have been affected by recall bias, but these types of symptoms should be noticed and could help triage patients to further testing.

Two modalities for testing are currently widely available—CA-125 serum level and transvaginal ultrasound. The University of Kentucky screened 25,327 women who were asymptomatic and either older than 50 or older than 25 with a family history of ovarian cancer, with annual ultrasounds from 1987 to 2005. Those who had an abnormal imaging study had CA-125 levels drawn and had a repeat ultrasound 4–6 weeks later. Of that, 364 (1.4%) eventually went on to have surgery, with 35 primary invasive ovarian cancers and 9 serous tumors of low malignant potential discovered. Of these, 64% were stage I, and the authors felt that transvaginal ultrasound could be an effective screening method. However, 313 (86%) of the masses removed were benign. Nine women developed ovarian cancer within 1 year of a negative screen, and three of those women died of their disease within the study period.[40] It has yet to be shown conclusively that transvaginal ultrasound identifies enough early-stage disease to justify the arguably unnecessary procedures for ultimately benign pathology.

CA-125 is a well-studied biomarker for ovarian cancer that, by itself, also has not been shown to be a valuable screening tool for asymptomatic women. It can be elevated by myriad other conditions including endometriosis and can also be affected by smoking, obesity, age, and race. CA-125 combined with transvaginal ultrasound has not been validated as a screening tool either, due to the high false-positivity rate leading to unnecessary procedures. For example, the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial screened women annually with CA-125 for 6 years and transvaginal ultrasound for 4 years. A total of 28,746 women were screened with either test; 1,675 abnormalities were found. Eventually, 566 surgeries were performed, with 18 invasive ovarian cancers detected. Then, 31.4 surgeries were performed for every cancer discovered, and 83% of the cancers discovered were advanced stage. This improved with subsequent screenings, but after four cycles of screening, the ratio of surgeries performed to cancers discovered was still 19.5–1, with 72% of the cancers already advanced.[41] There are ongoing studies examining the use of different algorithms to evaluate risk of cancer, rather than a one-time CA-125 measurement or imaging study. The Risk of Ovarian Cancer Algorithm (ROCA) is based on serial CA-125 levels taken at set intervals of time. By calculating the rate of change (slope), a risk assessment is generated; when the ROCA score exceeds a 1% risk of ovarian cancer, further evaluation is undertaken with transvaginal ultrasound. The ROCA is undergoing trials in the United States and the United Kingdom; data from the initial screening of 202,638 women are available, as part of the UK Collaborative Trial of Ovarian Cancer Screening. ROCA CA-125 screening with directed transvaginal ultrasound based on the ROCA score was found to have 89.5% sensitivity and 99.8% specificity, which was higher than the annual transvaginal ultrasound alone. The studies are ongoing to determine whether this algorithm will result in a clinically valid screening tool.[42]

Biomarker panels and proteomics represent another avenue of investigation into screening modalities. Mass spectrometric protein profiling and proteomic techniques have been used to identify differential patterns between cancer and control samples and subsequently to generate biomarker panels that could be used to identify clinically unapparent malignancies. These biomarkers include leptin, prolactin, and osteopontin, in addition to a variety of other markers in conjunction with CA-125. One example of a recently released biomarker panel is the OvaSure test, which was removed from the market after a few months due to lack of clinical validation. The Society of Gynecologic Oncologists has issued a statement regarding both OvaSure and OvaCheck, a similar panel, recommending additional clinical study of those and other new biomarker panels before making the tests widely available.[26]

The discovery of a genetic locus for familial breast and ovarian cancer syndrome has made a significant difference in the targeting of screening tests and prophylactic procedures. However, one should keep in mind that there may be unknown familial syndromes or other genetic foci that could confer risk. Testing should ideally first be performed in a family member who has breast or ovarian cancer. If the test is positive, then a family member subsequently testing negative can be more assured of a risk similar to that of the

general population. If the index family member with cancer tests negative for the BRCA mutations, then a negative result for your patient is less reassuring.

Additionally, risk for breast and ovarian cancers as part of the Lynch (or hereditary non-polyposis colorectal cancer/HNPCC) syndrome must be considered. Please see the Section on Endometrial Cancer for a discussion of indications for Lynch syndrome testing.

The ACOG guidelines for genetic evaluation are outlined in the following and are based on a Society of Gynecologic Oncologists Education Committee statement.[10]

Patients with the following characteristics have a greater than 20%–25% risk of having an inherited predisposition to breast and ovarian cancer, and testing should be recommended:

- History of both breast and ovarian cancer
- History of ovarian cancer and a first- or second-degree relative with ovarian cancer, pre-menopausal breast cancer, or both
- History of ovarian cancer and Ashkenazi Jewish ancestry
- History of breast cancer at age 50 or younger and first- or second-degree relative with ovarian cancer or male breast cancer at any age
- First- or second-degree relative with a known BRCA mutation

Patients with the following characteristics have a greater than 5%–10% risk of having an inherited predisposition to breast and ovarian cancer, and testing may be helpful:

- History of breast cancer at age 40 or younger
- History of ovarian, primary peritoneal, or fallopian tube cancer of high-grade, serous histology at any age
- History of bilateral breast cancer (particularly if first cancer diagnosed at age 50 or younger)
- History of breast cancer at age 50 or younger and a first- or second-degree relative with breast cancer at age 50 or younger
- History of breast cancer at age 50 or younger and Ashkenazi Jewish ancestry
- Breast cancer at any age and two or more first- or second-degree relatives with breast cancer at any age (particularly if at least one case was diagnosed at age 50 or younger)
- First- or second-degree relative that meets the aforementioned criteria

First- and second-degree relatives are parents, siblings, aunts, uncles, nieces, nephews, grandparents, and grandchildren.

There is no consensus regarding screening for BRCA or Lynch/HNPCC mutation carriers or those with a strong familial history of malignancy. However, some form of screening should be considered—one suggested method is pelvic exam, CA-125, and transvaginal ultrasound every 6 months starting at age 35 or 5–10 years before the youngest age of diagnosis in the family.[43] For women with a Lynch/HNPCC-associated mutation, current NCCN guidelines for screening are for annual transvaginal ultrasound, colonoscopy, and endometrial biopsy.[44]

Lifestyle

Various lifestyle and dietary factors have been implicated as risks for the development of ovarian cancer, but the evidence is mixed.

In terms of body mass, higher body mass index (BMI; overweight or obese) was associated with an increased risk of ovarian cancer in an Australian meta-analysis of case–control studies.[45]

Smoking, in meta-analyses, seems to be associated with an increased risk of mucinous tumors in particular.[46] However, there are some studies that did not find a correlation,[47] and others that noted an eventual return to baseline risk with smoking cessation.[48] Similarly, alcohol (heavy consumption) has been associated with mucinous tumors[49] but in several other studies has not been found to impact the risk of developing ovarian cancer.[50]

Population-based cohort studies of alcohol use and ovarian cancer have yielded mixed results. The Iowa Women's Health Study found a decreased risk, while the California Teachers Study did not find a correlation between total consumption and risk. However, having at least one glass of wine daily in the year prior to diagnosis was associated with a 43% risk of developing malignancy. Other cohort studies have reported no association. Some case–control studies have reported an increased risk, while others have found a reduced risk of ovarian cancer. Approximately half of case–control studies have found no correlation. Overall, there is no clear evidence to support alcohol consumption as a significant risk factor in the development of ovarian cancer.[51]

The effect of dietary patterns on ovarian cancer risk has also been found to be overall negligible. The European Prospective Investigation into Cancer and Nutrition (EPIC) study included 325,731 women from across Europe. At recruitment, patients were given country-specific food frequency questionnaires or diet histories. Subgroups of meat (fish, chicken, red meat) and dairy products (milk, cheese, and yogurt) were examined. None of the food groups was found to be associated with a significant change in risk, despite previous case–control studies suggesting a link between red meat consumption and development of ovarian cancer.[52] Although some studies have also suggested a reduced risk with the consumption of antioxidants, fiber, and carotene, results from the Women's Health Initiative (WHI) suggest otherwise. Assessment was done on 133,614 women enrolled in the WHI for intake of carotenoids and antioxidants, including vitamins A, C, E, and selenium using food frequency questionnaires. An eventual 851 cases of ovarian cancer were identified over approximately 8.5 years of follow-up, with no significant association found between dietary intake and development of ovarian cancer.[53]

A prospective cohort study of 49,613 Canadian women administered food frequency surveys did not find any correlation between dietary fiber intake and subsequent development of ovarian cancer.[54]

A recent study examined exercise among those diagnosed with ovarian cancer in Washington State. 812 patients were interviewed, with exercise level assessed both by average number of hours and by metabolic-equivalent (MET) hours per week, as well as the number of years during which the patient engaged in regular recreational activity. The risk of invasive ovarian cancer, but not borderline tumors, was reduced among active women as compared to those who denied performing regular exercise during adulthood. Higher-intensity activity (greater MET hours) was associated with greater risk reduction, with the most active women having 60% the serous invasive ovarian cancer risk as nonactive women. However, that same group of women was noted to have an increased risk of endometrioid and clear cell invasive tumors, making the results inconclusive.[55] Another prospective study did not find an overall significant association between exercise and risk of ovarian cancer, although there was a trend toward inverse association.[56]

A meta-analysis of studies investigating the relationship between soy (which contains phytoestrogens that have been postulated to have an estrogen-like effect on tissues) and gynecologic cancer reported a protective effect. The odds ratio for the development of ovarian cancer was 0.52 when comparing those in the highest soy intake group versus the lowest. The authors concluded that there could be a protective effect from soy intake and that additional prospective studies are needed to investigate this further.[57]

Caffeine has been reported to increase, decrease, and have no effect on the risk of ovarian cancer. Tea, due to its antioxidant properties, has been suggested as having a beneficial effect.[58]

Intervention/Prevention

OCP use has been strongly associated with a decreased risk of ovarian cancer, presumably through the inhibition of ovulation.[59–61] The duration of use required and the length of protection conferred have been more clearly delineated by recent studies. As part of the U.S. Nurses' Health Study, OCP use as well as other contraceptive methods was investigated for an association with ovarian cancer in 107,900 participants. Follow-up extended for 28 years, with 612 cases of invasive epithelial ovarian cancer. In attempting to adjust for other influencing factors, women with a greater than 10 year history of OCP use were more likely to be parous, to have had tubal ligation, and to have used postmenopausal HRT as compared to women reporting no OCP use. Increasing length of OCP use was associated with decreased ovarian cancer risk, with benefit seen after at least 5 years of use. Age at use was not significant when adjusted for duration of use. The authors reported an approximate 38% risk reduction with 10 years or greater of OCP use. There was a trend toward decreasing benefit with greater length of time since discontinuation, particularly with a period of more than 20 years since last OCP use. The study also found a 34% risk reduction in women reporting a history of tubal ligation.[62]

Tubal ligation has been associated with risk reduction for ovarian cancer, perhaps by preventing the transmission of environmental/inflammatory factors from the lower genital tract into the abdomen.[63,64] Prophylactic, or risk-reducing, salpingo-oophorectomy confers at least an 80% risk reduction for BRCA mutation carriers,[65,66] although the incidence of incidentally found invasive ovarian, fallopian tube, or primary peritoneal carcinoma found during that surgery ranges from 2% to 17%[67,68] in various studies. Removal of the ovaries also confers a risk reduction for ovarian cancer, of up to 70%.[69,70] The benefit of hysterectomy is not as clear; in theory, there could be residual tubal tissue left at the cornua of the uterus, which increases the risk. However, studies have yet to show a clear correlation with remnant tissue on the uterus developing into malignancy in those undergoing risk-reducing salpingo-oophorectomy. By contrast, women with a Lynch/HNPCC-associated mutation clearly benefit from hysterectomy with bilateral salpingo-oophorectomy due to their increased risk of endometrial cancer, with a risk reduction of nearly 100%.[71] Risk-reducing surgery should be offered at the completion of childbearing or by age 40 for those with a BRCA or Lynch/HNPCC-associated mutation or with a very strong familial history.[26]

ENDOMETRIAL CANCER

Epidemiology/Risk Factors

Endometrial cancer is the most common female genital tract malignancy, with an estimated 2.62% of women in the United States developing uterine cancer within their lifetime. The majority of those diagnosed with endometrial cancer will present at an early stage, as abnormal or postmenopausal bleeding is an early manifestation of the malignancy. Approximately 72% of women will be diagnosed with stage I disease. The most common histologic type of endometrial cancer, the endometrioid subtype, is clearly associated with several risk factors, largely related to increased circulating levels of hormones. The more aggressive papillary serous and clear cell subtypes are not clearly associated with defined risk factors. Risk factors include older age, nulliparity, menstrual irregularities, diabetes, and obesity.[72]

For example, an Australian case–control study surveyed women younger than 50 regarding their medical and reproductive histories. A total of 156 cases were matched to 398 controls. Women with PCOS, which is associated with anovulation and menstrual irregularities, had a fourfold increase in the risk of endometrial cancer as compared to those without PCOS. This risk decreased when adjusted for BMI but was still elevated with an at least twofold increased risk.[73]

The following list describes relative risk of the provided factors for the development of endometrial cancer[74,75]:

Nulliparity	2–3
PCOS	2–3 (evidence mixed)
Obesity (BMI > 27)	2–4
Diabetes (independent from BMI)	1.3–2.7
Late menopause (after 55)	2
Hormone replacement therapy (unopposed estrogen)	4–5
Tamoxifen therapy	1.7–2.5

Most women diagnosed with endometrial cancer will be postmenopausal. However, in various studies, 5%–30% will be younger than 50 years of age at the time of diagnosis. A retrospective cohort study conducted at the MD Anderson Cancer Center examined characteristics of 1531 patients treated for endometrial cancer between 1989 and 2003 at the institution. Of these 12% were younger than 50, with an average age of 41 at diagnosis 58% had a BMI of 30 or greater, 55% were nulliparous, and 39% reported irregular menstrual cycles—these factors may be the most significant when evaluating the risk of endometrial cancer, particularly in younger women.[76]

The use of HRT confers an increased risk of endometrial cancer, particularly therapy with estrogen alone. In a meta-analysis analyzing HRT, women receiving estrogen alone had a relative risk of 2.3 for the development of endometrial cancer, as compared to women not taking hormones. If use was continued for 10 years or greater, relative risk increased to 9.5 and remained elevated even after the discontinuation of estrogen therapy for approximately 5 years. However, if progesterone was given in combination with estrogen, relative risk was reduced to 0.8. Another study found that if progesterone was given for 10 days/month, there was no increased risk of endometrial cancer, nor if combined HRT was given continuously.[77]

Approximately 5% of all cases of uterine cancer can be attributed to a hereditable cause.[78] Careful attention should be made to family history and the possibility of an inherited predisposition to malignancy, especially Lynch/HNPCC (hereditary non-polyposis colorectal cancer) syndrome. The presence of a Lynch/HNPCC-associated mutation confers an approximate 40%–60% lifetime risk of endometrial cancer, in addition to (most commonly) colon and ovarian cancers. The syndrome also predisposes to gastric, small bowel, ureter, and renal cancers classically, in addition to several others such as bladder, brain, and skin.[72] The Amsterdam criteria, originally created in 1991 and revised in 1999, can be used to aid in identifying individuals whose family history could indicate a high index of suspicion for Lynch/HNPCC syndrome.

The Amsterdam criteria are as follows:

1. At least three relatives with Lynch/HNPCC-associated cancer (colon, endometrium, small bowel, renal pelvis, or ureter).
   a. Of note, not included in this list is stomach, ovary, bladder, brain, or skin.
2. One affected person is a first-degree relative of the other two.
3. At least two successive generations are involved.
4. One person was diagnosed below the age of 55.
5. Familial adenomatous polyposis has been excluded.
6. Tumors have been verified by a pathologist.

In at least one study, a sensitivity and specificity of 72% and 78%, respectively, have been documented. However, the Amsterdam criteria do not take into account patients who present with a gynecologic malignancy or who have small family pedigrees, and this should be taken into account when considering referral for genetic counseling and/or testing.[79]

Guidelines for genetic testing, incorporating both family and personal history, are outlined in the following and are based on a Society of Gynecologic Oncologists Education Committee statement.[80]

Patients with the following characteristics have a greater than 20%–25% risk of having an inherited predisposition for colon, endometrial, and other malignancies and genetic testing should be recommended:

1. Endometrial or colon cancer and with the criteria listed in the following:
   a. At least three relatives with a Lynch/HNPCC-associated cancer (colon, endometrial, ovarian, small bowel, ureter, renal) in one lineage
   b. One should be a first-degree relative of the other two
   c. At least two successive generations affected
   d. At least one cancer diagnosed before age 50
2. Synchronous or interval development of endometrial and colorectal cancer with the first cancer diagnosed before age 50
3. Colorectal or endometrial cancer with evidence of a mismatch repair defect
   a. Microsatellite instability
   b. Immunohistochemical loss of expression of MLH1, MSH2, MSH6, or PMS2
4 First- or second-degree relative with a known mismatch repair gene mutation

Patients with the following characteristics have a greater than 5%–10% risk of having an inherited predisposition for colon, endometrial, and other malignancies, and genetic testing may be helpful:

- Endometrial or colorectal cancer diagnosed prior to age 50
- Endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch/HNPCC-associated tumor at any age
- Endometrial or colorectal cancer and a first-degree relative with a Lynch/HNPCC-associated tumor diagnosed prior to age 50

- Colorectal or endometrial cancer diagnosed at any age with two or more first- or second-degree relatives with Lynch/HNPCC-associated tumors regardless of age
- First- or second-degree relative that meets the aforementioned criteria

First- and second-degree relatives are parents, siblings, aunts, uncles, nieces, nephews, grandparents, and grandchildren.

Screening

Routine screening in the general population, if asymptomatic, is not currently recommended as early endometrial cancer is generally symptomatic, with abnormal or postmenopausal bleeding the most common presenting sign.

As the risk of endometrial cancer increases with age, particularly after age 35, any woman over the age of 35 with irregular bleeding should have the endometrium evaluated. Consideration should be given to those younger if risk factors are present, using clinical judgment. Any postmenopausal woman with vaginal bleeding should be evaluated for endometrial cancer. With any type of abnormal bleeding, other etiologies should be considered, such as lesions of the cervix or vagina. Imaging with transvaginal ultrasound prior to endometrial sampling is reasonable; blind office endometrial biopsy is useful for detecting a process that globally involves the endometrium, but may miss focal lesions. If a thin, distinct endometrial echo of 4 mm or less is present on imaging, the ACOG guidelines report a very low (1 in 917) risk of endometrial cancer and state that endometrial biopsy is not necessary. If the endometrium is globally thickened, then an office endometrial biopsy is warranted. However, if the endometrium appears to be focally thickened, visual evaluation with hysteroscopy and removal of the lesion and/or curettage would be appropriate. Sonohysterography is a valuable adjunct if the endometrial cavity is difficult to define or if there is a question of a focal lesion, such as a polyp.[81]

For asymptomatic women with incidentally found endometrial thickening or endometrial polyps, there is evidence to support expectant management, as the risk of underlying malignancy has been found to be quite small in the absence of symptoms, depending on the actual thickness of the endometrium. An analysis was conducted of studies examining postmenopausal women over 50, not on hormone therapy, who had transvaginal imaging to assess the endometrial echo (sometimes referred to as the stripe). In a postmenopausal woman without vaginal bleeding, the risk of malignancy with an endometrial strip of <11 mm was estimated at 0.002%, whereas risk was assessed to be around 6.7% with a thickness >11 mm. For postmenopausal women with vaginal bleeding, a concerning endometrial thickness is >5 mm, although consideration for biopsy should be given for any symptomatic woman.[82] Another study found that in 82 women with an incidentally found suspected endometrial polyp on imaging, who subsequently underwent evaluation with operative hysteroscopy, no malignancy was found. Sixty-eight polyps were found, of which one contained simple endometrial hyperplasia. No premalignant conditions such as complex atypical hyperplasia were found. The overall complication rate reported was 3.6%.[83] A larger study examined 1152 women who underwent hysteroscopic removal of polyps found during sonohysterography. The women were all asymptomatic and postmenopausal. There was one endometrial cancer in a polyp (<0.1%) and three other endometrial cancers that were not in a polyp but were found to by polypoid in appearance and focal and were thus mistakenly thought to be a polyp (<0.3%).[84] Thus in the absence of bleeding, an incidental finding on imaging does not need to automatically trigger further evaluation, but this should be adjusted based on the individual patient and her risk factors for malignancy.[81]

For women with Lynch/HNPCC syndrome, some form of screening should be undertaken. The average age that women with the syndrome develop endometrial cancer is 48, and ultrasound evaluation of the endometrial stripe can be limited in premenopausal women due to cycle variations. The National Comprehensive Cancer Network currently recommends annual endometrial biopsy for screening, based on expert opinion.[78]

Lifestyle

Obesity is one of the most significant risk factors for endometrial cancer, hormone dependent/endometrioid particularly, and is a potentially modifiable factor. Some estimate that up to 70%–90% of patients with hormone-dependent endometrial cancer are overweight or obese. Other comorbid conditions, such as hypertension and diabetes, also put patients at increased risk of mortality after treatment for endometrial cancer.[75] A recent meta-analysis found a strong correlation between increasing BMI and the risk of endometrial cancer.[11]

Conversely, a recent meta-analysis showed a correlation between increasing physical activity and decreased risk of endometrial cancer. Physical activity has been postulated to be protective both by maintenance of a healthy body weight with increased lean body mass (decreased aromatization of circulating hormones to estrogen in adipose tissue) and increased serum levels of sex-hormone-binding globulin (increased binding of estrogen and thus less active circulating estrogen). The meta-analysis did not examine the effects of exercise independent of BMI, as a reduction in BMI is a likely mechanism for the benefits and found that increased physical activity was highly correlated with reduced risk.[85] A case–control study matched 472 cases to controls and assessed approximate lifetime physical activity. In general, patients with endometrial cancer had an overall lower level of physical activity, were nulliparous, or were obese. Risk decreased in proportion to the level of physical activity, although when results were stratified by BMI, the risk reduction was limited to overweight and obese women.[86]

A cohort study from the Swedish Twin Registry investigated the effects of various lifestyle factors, including dietary intake, smoking, and alcohol consumption, on the risk of endometrial cancer. In the study, 133 cases of endometrial

cancer were observed. Increasing physical activity was associated with a significant risk reduction, with women in the highest exercise category having a relative risk 0.2 in comparison with women reporting little or no regular exercise. There was a trend toward very low fruit and vegetable intake increasing risk, but this did not reach significance. There was no clear association between smoking or alcohol consumption and endometrial cancer risk.[87] A meta-analysis suggested an inverse relationship between vegetable consumption and the risk of endometrial cancer. The study included both cohort and case–control studies and reported overall risk reduction with vegetable consumption, particularly cruciferous vegetables (broccoli, cauliflower, bok choy), but not as significant of an association with fruit intake. The pooled odds ratio was 0.71 for those in the group of highest vegetable consumption compared to those in the lowest.[88] An Italian case–control study found that in 454 women treated for endometrial cancer, as matched to 908 controls, there was an increased risk associated with consumption of red meat and decreased risk associations with consumption of coffee and vegetables.[89] However, a prospective study examined the possible preventive effects of fruits and vegetables on the development of endometrial cancer and did not support those results. In the study, 41,400 postmenopausal women were surveyed regarding their dietary habits and were then followed for approximately 10 years, with one survey to update dietary information in the intervening time. There were 435 cases of endometrial cancer, with no association found with fruit or vegetable consumption.[90]

A recent analysis of several cohort studies suggests a reduced risk of endometrial cancer correlated with soy intake, with an odds ratio of 0.67 for the development of endometrial cancer in the group of women reporting the highest soy intake, with a trend toward inverse dose–response.[57]

A recent meta-analysis examining coffee consumption and the risk of various cancers found a consistent association between coffee consumption and a reduced risk of endometrial cancer. In the aforementioned Italian case–control study, endometrial cancer risk in the group of women with the highest consumption was approximately half that of women with the lowest consumption.[89] A Japanese study found a linear inverse relationship correlating coffee consumption with reduced risk, with increasing reduction in risk as the number of cups consumed per day increased. Additional Swedish and Japanese studies also found statistically significant associations between coffee consumption and reduced risk, with reports of a relative risk of 0.4 with a consumption of three or more cups of coffee per day.[20] Another Japanese case–control study found an inverse, dose–response relationship between the consumption of green tea and the risk of endometrial cancer. In this study, endometrial cancer cases were specifically limited to the endometrioid subtype. The decreased risk of endometrial cancer was observed even when analysis was controlled for other factors such as obesity and menopausal status.[91]

A recent study summarized the results of various studies examining the effect of alcohol consumption on gynecologic cancers. Cohort studies in North America, Sweden, and the United Kingdom did not show a consistent correlation between alcohol consumption and the development of endometrial cancer. One study, the Iowa Women's Health Study, showed a reduced risk in alcohol users as compared to those who did not drink. In the Multiethnic cohort, however, those who drank two or more drinks per day had a significantly increased risk. Other cohort studies showed no correlation. Results from case–control studies were similarly inconsistent. Sixteen studies carried out in North America, Japan, and Western Europe were examined. In 10 of the studies, no significant association between alcohol consumption and endometrial cancer was observed. Several other studies showed a trend toward increased risk with alcohol consumption, with one study reporting a decreased risk with alcohol users compared with those who abstained. Overall, there is no clear evidence that alcohol use increased the risk of endometrial cancer.[51]

Intervention/Prevention

Use of OCPs is protective against endometrial cancer. A recent review compiled information from 4 large cohort studies and over 15 case–control studies that demonstrated an overall 50% reduction in the risk of endometrial cancer with the use of combined oral contraceptives. This is reported to be independent of pill formulation, and risk is overall reduced in correlation with duration of use. A meta-analysis found that reduced risk of 50% remained at 5, 10, and 20 years after cessation of use. Of note, these results were found with combined OCP users. In the studies that address the subgroup, users of progesterone-only contraceptive pills were too small in number to generate significant findings.[92]

The use of intrauterine devices (IUDs) can also be protective against endometrial cancer. The two IUDs currently available in the United States are a nonhormonal copper IUD (Paragard) and a progesterone-containing/levonorgestrel IUD (Mirena). Several studies, including the Cancer and Steroid Hormones study of the Centers for Disease Control and Prevention, showed an association between reduced risk of endometrial cancer and use of the nonhormonal IUD.[93] The levonorgestrel IUD was approved by the FDA in 2000, so long-term data are not available. However, there are several studies examining its use in the treatment of endometrial hyperplasia and as a means of preserving fertility and treating early-stage endometrial cancers in young women. A European study, where a similar device was approved earlier, recently released follow-up results after 15 years of IUD use to treat endometrial hyperplasia. Patients having all forms of hyperplasia, from simple to complex/atypical, were included. Of that, 94% had regression to atrophic endometrium based on tissue sampling at the end of treatment.[94] In recent case series from Australia, three patients with early endometrial cancer were treated with the Mirena IUD, nine patients were treated with the IUD and an oral progesterone, and four were treated with an oral progesterone only. A 63%

response rate was reported.[95] Endometrial hyperplasia, particularly atypical/complex hyperplasia, is a precursor to malignancy. Studies demonstrating a response to treatment with the progesterone-containing IUD, whether hyperplasia or cancer, suggest that there may be a protective effect on the endometrium.

Several retrospective studies have demonstrated the value of risk-reducing surgery for women with Lynch/HNPCC syndrome. For 210 women who did not undergo hysterectomy, 69 developed endometrial cancer compared to no endometrial cancers in 61 women who did have a hysterectomy. Additionally, 12 ovarian cancers developed in women who did not have concurrent bilateral salpingo-oophorectomy, while no ovarian cancers were diagnosed in those who did, although those results did not reach statistical significance.[78]

CERVICAL CANCER

Epidemiology/Risk Factors

Cervical cancer in the United States has steadily declined in recent years, largely due to improved access to screening with the Papanicolaou, or Pap test, and a long preinvasive disease phase that is treatable. However, cervical dysplasia still represents a significant burden to health care in the United States, and worldwide cervical cancer continues to cause significant morbidity and mortality as the second most common cancer among women.[96]

The link between human papillomavirus (HPV) and cervical cancer has now been well established. Up to 75% of women will be infected with HPV in their lifetime. However, many younger women will clear their infection, and there are myriad strains of HPV, some of which are associated with malignancy and some of which are associated with genital warts, with strain distribution depending on the population. Risk reduction of cervical cancer is aimed at reducing factors that could contribute to persistent infection, decreasing acquisition of high-risk strains, and establishing guidelines for regular screening.[97]

The predominant risk factor for HPV infection is the number of lifetime sexual partners. Young age is also a significant factor, with the highest prevalence of infection in the early 20s, decreasing until around age 35, with a plateau and then a further decrease after age 50. The pattern is reflective of a sexually acquired infection, with the second decline at age 50 perhaps reflective of immunity or decreased exposure.[98] There may be different risks for high-risk versus low-risk HPV. Non-oncogenic HPV may be more associated with short-term sexual activity, as the infections tend to be more transient, while high-risk HPV is more associated with cumulative behaviors.[99]

Vulvar and vaginal cancers, while uncommon, may be associated with similar risk factors as those for cervical cancer, including HPV infection and smoking. Women with lichen sclerosis and other inflammatory skin disorders of the vulva are also at increased risk of malignancy.[100]

Screening

The 2009 screening guidelines for Pap testing from the ACOG are outlined as follows[101]:

Screening should begin at age 21

1. Women aged 21–29, screening every 2 years
2. Women aged 30 or older, with 3 consecutive normal tests, screening every 3 years
3. More frequent screening is indicated if the following factors are present:
   a. HIV
      i. Twice in the first year after diagnosis and annually thereafter
   b. Immunosuppression
   c. History of diethylstilbestrol (DES) exposure in utero
   d. Women previously treated for CIN 2, 3, or cervical cancer
      i. Annually for 20 years post-treatment or after post-treatment surveillance
4. May discontinue screening at age 65–70
   a. If three consecutive normal tests, no abnormal test in >10 years
5. May discontinue screening post-hysterectomy if for benign disease, no history of CIN 2 or 3
   a. If history of CIN 2 or 3, or undocumented screening history, continue screening
6. Women who have received vaccination should be screened according to the same guidelines
7. HPV testing may be used to stratify risk for women with ASC-US or LSIL results
8. HPV testing may be used for women older than 30 as a co-test with the Pap smear
   a. If both results are negative, testing should be spaced to every 3 years

Women with cervical dysplasia and HPV infection are also at risk for vulvar and vaginal dysplasia and cancers, and attention should be paid to those areas during examination. There is no routine screening for vulvar and vaginal cancers, but clinicians should have a high index of suspicion if lesions are noted.

Lifestyle

Genital HPV is transmitted sexually, through contact with skin, body fluids, or mucous membranes of an infected individual. Genital HPV subtypes have been isolated from the skin and nails of those with genital warts; transmission may be possible through manual–genital or non-penetrating genital–genital contact.[102] Condom use is protective, as a latex condom covers many areas of the male genitalia where HPV tends to reside. However, any area of genital skin, or bodily fluids, may harbor HPV and thus a condom is not completely protective, particularly if it should slip or break.[103] Studies examining the efficacy of condoms have been mixed,

probably because HPV infection can be latent and intermittently nondetectable, making it difficult to assess whether an infection is newly acquired. Protection has been shown for non-oncogenic subtypes and genital warts, but for a reduction of cervical dysplasia, the evidence has been mixed.[97]

Parity and oral contraceptive use have been reported to be associated with cervical dysplasia. In a study that pooled data from eight case–control studies, women with invasive or in situ cervical carcinoma, with HPV, were compared to controls. Increasing parity was directly associated with increasing risk of squamous cell carcinoma of the cervix (the most common sub-type), while not correlated with adenocarcinoma. The odds ratio for a woman with—one to two term pregnancies was 2.3, and for a woman with greater than seven term pregnancies, it was 3.8.[104] A meta-analysis of cervical cancer and oral contraceptive use studies showed a relative risk of 1.9 for those using oral contraceptives for more than 5 years versus those who had never used them. The risk was noted to decline after cessation of use and to return to baseline after approximately 10 years. While the study adjusted for age, number of sexual partners, age at first intercourse, parity, smoking, and screening, it did not address HPV infection.[105] A Swedish case–control study looked at those with cervical intraepithelial neoplasia (CIN) 2 and 3 and controlled for past and present HPV exposures during the study. Women diagnosed with CIN 2 or 3 through the local screening program, and who had been tested for HPV, completed questionnaires regarding sexual and reproductive history, dietary intake, smoking, and use of oral contraceptives. A significant period of oral contraceptive use (>5 years) was associated with an increased risk of CIN 2 or 3, but this finding disappeared after adjustment for age, smoking, and HPV infection. In the adjusted analysis, a history of pregnancy was associated with increased risk. A dose-dependent significantly increased risk with smoking was reported, which was found to be present even after adjustment for HPV exposure.[106]

Tobacco smoking has been implicated as a significant risk factor in the development of high-grade cervical dysplasia and cervical cancer. This may be mediated either by direct carcinogenic activity on cervical cells or through suppression of the immune system's ability to clear HPV infection. A 10 year prospective study in Oregon enrolled 1812 identified to have infection with high-risk HPV at enrollment and completed a survey regarding smoking, oral contraceptive use, and reproductive history. Oral contraceptive use and parity were not associated with the development of high-grade dysplasia (CIN 3) or cervical cancer. Final analysis demonstrated an increased risk of CIN 3 or cervical cancer for current or former smokers, with odds ratios 2.9–4.3, with the highest risk in those smoking more than 1 pack per day.[107]

Several cohort studies have examined alcohol use and risk of cervical cancer and found increased risk; however, many did not adjust for confounding factors such as HPV infection, number of sexual partners, smoking, or access to Pap screening. Several of those studies were also performed in select populations (waitresses, alcohol abusers). In the Million Women Study, which was conducted in the general population and controlled for the aforementioned confounding factors, reported no association between alcohol consumption and risk of cervical cancer. Case–control study results have been mixed, with no overall clear association but a positive trend toward increased risk with increased alcohol consumption.[51]

In prior studies, higher intake of fruits and vegetables and certain micronutrients has been associated with a decreased risk of cervical dysplasia, although the evidence is largely from observation and is not overwhelming. A recent case–control study compared 231 women diagnosed with CIN 3–453 controls. Significantly reduced fruit and vegetable intake was noted when those with CIN 3 were surveyed, compared with controls. Smokers in both groups reported lower overall fruit and vegetable consumption. Sexual history and reproductive factors were similar among both smokers and nonsmokers in the CIN 3 group. Lower fruit and vegetable intake was associated with an increased risk of high-grade cervical dysplasia, with an odds ratio of 1.14. However, smokers with a higher intake of fruits and vegetables had a higher risk, with an odds ratio of 1.83. The study suggests a weak association with dietary intake, but a stronger effect of smoking on the development of cervical dysplasia.[108] There have been some studies showing benefit from vitamins C and E, carotene, and lycopene in ameliorating HPV persistence. Additionally, folate, retinol, vitamin B_{12}, lutein, and cryptoxanthin have been discussed as protective against cervical neoplasia. However, most analyses do not demonstrate strong evidence for dietary protection when HPV is taken into account.[109]

Intervention/Prevention

A recent development in the prevention of cervical cancer has been the introduction of the vaccines Gardasil and Cervarix. Both are protective against the high-risk HPV strains 16 and 18, which have been implicated as being the most frequent strains associated with cervical cancer in the United States. Gardasil adds additional protection against HPV strains 6 and 11, which are low risk for the development of cervical cancer but cause genital warts. In approximate 3 year follow-up of the vaccines, the efficacy of Gardasil has been reported to be near 100% for HPV 16 and 18 CIN 2/3, adenocarcinoma in situ, vulvar intraepithelial neoplasia 2/3, and vaginal intraepithelial neoplasia 2/3 (high-risk dysplasia or carcinoma in situ). Similarly, 99%–100% efficacy for genital warts was reported. Cervarix was found to have a rate of 93% protection for HPV-16 and -18-associated lesions. Both have also demonstrated cross-protection for several other strains of HPV. Even if sexual activity has been initiated, it should not preclude administration of the vaccine, as women may not have been exposed to any or all strains of HPV covered by the vaccines. The vaccines are currently approved for routine vaccination of girls aged 11–12 years, at the physician's discretion at ages 9–10, and for catch-up vaccination at ages 13–26. Gardasil has also been approved for males aged 9–26 for the prevention of genital warts, but could potentially also reduce the burden of HPV transmission.[110]

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74 Preventing Medical Errors in Obstetrics and Gynecology

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CONTENTS

Introduction 927
Error: Missing an Ectopic Pregnancy 928
Error: Abnormal Cervical Cancer Screening Tests Lost to Follow-Up 928
Error: Failure to Suspect Cancer Based on Ultrasound of the Ovaries 930
Error: Incomplete Workup of Postmenopausal Bleeding 931
Error: Palpable Breast Lump, Normal Imaging, Lost to Follow-Up 932
Error: Unsafe Medication Prescribing 932
Putting Theory into Action 934
References 935

INTRODUCTION

Helping patients achieve and maintain a healthy lifestyle includes allowing them to be equal partners who take ownership of their health care. Such a partnership has benefits for both patient and physician and has the potential to decrease medical errors, which in turn enhances health. In the course of a busy day, the average clinician has many opportunities to make mistakes. While only some of these will lead to harm, the value of error prevention in delivering health care is unquestionable. If left only to the skill, alertness, or memory of individuals, there would be little hope of preventing medical errors. But by redesigning systems to eliminate the occasion for errors, danger can be averted.

The focus of this chapter will be the use of thoughtful and efficient systems that can make women's health care safer. Several common errors related to screening and preventive health care for women are explained, along with algorithms to improve outcomes. These serve as examples for other situations when clinicians are poised to identify vulnerabilities and embed systems into their everyday workflow. Such systems will prevent errors and put women's health care in the vanguard of sound practice by placing the patient at the center of her own care.

In his "Swiss cheese model," the psychologist James Reason asserted that adverse events can be traced to one or more levels of failure: organizational influences, unsafe supervision, preconditions for unsafe acts, and the unsafe acts themselves.[1] In Reason's thinking, the ideal system is like a stack of Swiss cheese slices, each slice a different step in the process, each hole another opportunity for errors to creep in, and the cheese itself a defensive wall that prevents errors from reaching the patient. An error that passes through one layer is usually caught at the next step, where the holes are in different places. For harm to occur, the holes need to be lined up in a way that allows a persistent error to pass through and reach the patient. Thus, if a system allows all the holes to line up, the system is the problem. For Reason, a well-designed system has many defenses to stop errors (i.e., many slices of Swiss cheese) and few opportunities for error (small holes in the cheese).

Reason's model considers both active and latent errors. Active errors include the unsafe acts that can be directly linked to an adverse event, such as administering a medication to a person with a known allergy. Latent failures are features of a system—such as ineffective communication, fatigue, inadequate supervision, or illegible handwriting—that may lie dormant until they collide to produce a catastrophic result. Adverse events do not occur because of one failure; they occur when several problems come together in a way that allows errors to persist—when all the holes in the Swiss cheese line up. Only well-designed systems can prevent multiple levels of failure, individuals alone cannot.

Consistent with Reason's thinking, the patient safety movement has emphasized system correction, not individual punishment.[2] At the root of this philosophy is the belief that embedding good systems can lead to widespread improvement in a way that targeting individuals never will. The medical community's attitude toward the value of systems began to change in 2000 when the Institute of Medicine (IOM) published its seminal report, "To Err is Human," which estimated that 98,000 Americans die each year as a result of medical errors.[3] A year later, the IOM followed up with a proposal to redesign the health care system for the new millennium.[4] It saw the patient as a potential defensive barrier who could protect against error and suggested that shifting control to her was a pivotal step toward a safer health

care environment. To that end, the report recommended that patients be provided with information and the opportunity to control decisions that affect them. Patients, then, provide an additional defense against error—another slice of Reason's Swiss cheese.

Women's health care presents an ideal arena in which to push forward with patient safety, because women often function as caregivers for the people they live with or for other relatives or friends. One out of four people is a caregiver for a family member or friend; in the absence of an able spouse, a daughter or daughter-in-law is most likely to assume the role of caregiver.[5] Approximately 75% of caregivers for older family members and friends are female.[6] Of the 2.4 million grandparents who live with and are responsible for grandchildren, 63% are women. Clearly, women have a huge footprint in the health care network and are well positioned to provide a safety net for their nuclear and extended families.[7]

ERROR: MISSING AN ECTOPIC PREGNANCY

Whether a pregnancy is planned or unplanned, confirming an intrauterine gestation is a key initial step for the clinician and patient. Life-threatening ectopic pregnancy remains a possibility until this takes place.

It is estimated that approximately 2% of pregnancies in the United States are ectopic.[8] If not addressed, ectopic pregnancy can lead to hemorrhage, transfusion, and death. The approach to minimizing risk related to ectopic pregnancy rests on two principles: engaging the patient in her own care by educating her about early warning signs and understanding the ability of different tests to discriminate between normal and abnormal early pregnancies.

Patients who present for preconceptual counseling or initiate care early in the first trimester provide an opportunity for the clinician to discuss, among other things, early warning signs of abnormal pregnancy. Such signs may include pain, bleeding, or light headedness. Alerting the office to these symptoms, should they occur, may help to prevent complications of ectopic pregnancy.

If pregnancy is diagnosed by urine or serum testing, the clinician should review the patient's history to identify risk factors for ectopic pregnancy. These may include endometriosis, tubal infection, cigarette smoking, previous history of ectopic pregnancy, or the presence of an intrauterine device. After a physical exam, the remainder of the evaluation and plan is dependent on the quantitative level of serum human chorionic gonadotropin (beta-HCG).

The discriminatory threshold (or cutoff) is that level of beta-HCG at which evidence of an intrauterine gestation can be visualized by transvaginal ultrasound, with sensitivity approaching 100%.[9,10] The discriminatory threshold is determined by individual institutions based on experience and expertise and is commonly between 1500 and 2500 IU/L. When no evidence of intrauterine gestation is seen on transvaginal ultrasound, and the beta-HCG level is above the discriminatory threshold, ectopic pregnancy should be suspected. Treatment of ectopic pregnancy may include medical or surgical options, but prompt attention is crucial.

In order to detect an ectopic pregnancy, offices must have tracking systems for pregnancy tests. When a pregnancy test is ordered, an electronic or paper alert should be sent to the clinician, who contacts the patient. If risk factors for ectopic pregnancy are present, and quantitative HCG is above the discriminatory threshold for an intrauterine gestation, an ultrasound should be performed.

If quantitative HCG is below the discriminatory threshold for pregnancy, and risk factors for ectopic pregnancy exist, the patient should be evaluated promptly. It is also important to engage the patient in her own care, including a clinician–patient agreement to monitor beta-HCG levels until reaching the discriminatory threshold.

Below the discriminatory threshold, serial measurements of quantitative beta-HCG, along with monitoring of patient signs and symptoms, may help confirm a normal intrauterine pregnancy (thus, excluding an ectopic pregnancy). In a normal pregnancy, the beta-HCG concentration doubles about every 2 days. An increase over 48 h of at least 66% is commonly used as a cutoff for normalcy.[11–14] However, this must be viewed within the clinical context, as Barnhart et al.[15] found that some patients with a 53% increase in serum beta-HCG levels over 48 h were later found to have a viable intrauterine pregnancy. Thus, caution is required when using serial beta-HCG measurements below the discriminatory threshold to monitor a desired pregnancy, as one risks incorrectly diagnosing nonviability.

A clinical pathway that involves both patient and provider in the confirmation of normal early pregnancy will prevent unrecognized ectopic pregnancy. Figure 74.1 is an example of such a clinical pathway.

ERROR: ABNORMAL CERVICAL CANCER SCREENING TESTS LOST TO FOLLOW-UP

Cervical cancer screening, or the PAP test, is a routine yet important aspect of well-woman care. However, providers can be inundated with results of these tests. An estimated 30.2 million PAP tests were ordered at physician offices and hospital outpatient departments in the United States from 2003 to 2005.[16] The follow-up of PAP test results is particularly susceptible to error; lost in a sea of normal results, the lone abnormal finding goes easily unnoticed unless every test is tracked in a closed-loop system that begins the moment the test is ordered.

Revised recommendations in recent years for follow-up of abnormal cervical cancer screening tests have altered the schedule and the volume of tests that are performed.[17] Additionally, the clinician may now be presented with not only cytologic information, but also data regarding the human papillomavirus (HPV) carrier status of the patient. Any additional piece of information received, as well as changes in recommendations for follow-up, presents opportunities for confusion, miscommunication, or lack of communication with patients and eventually losing track of patients.

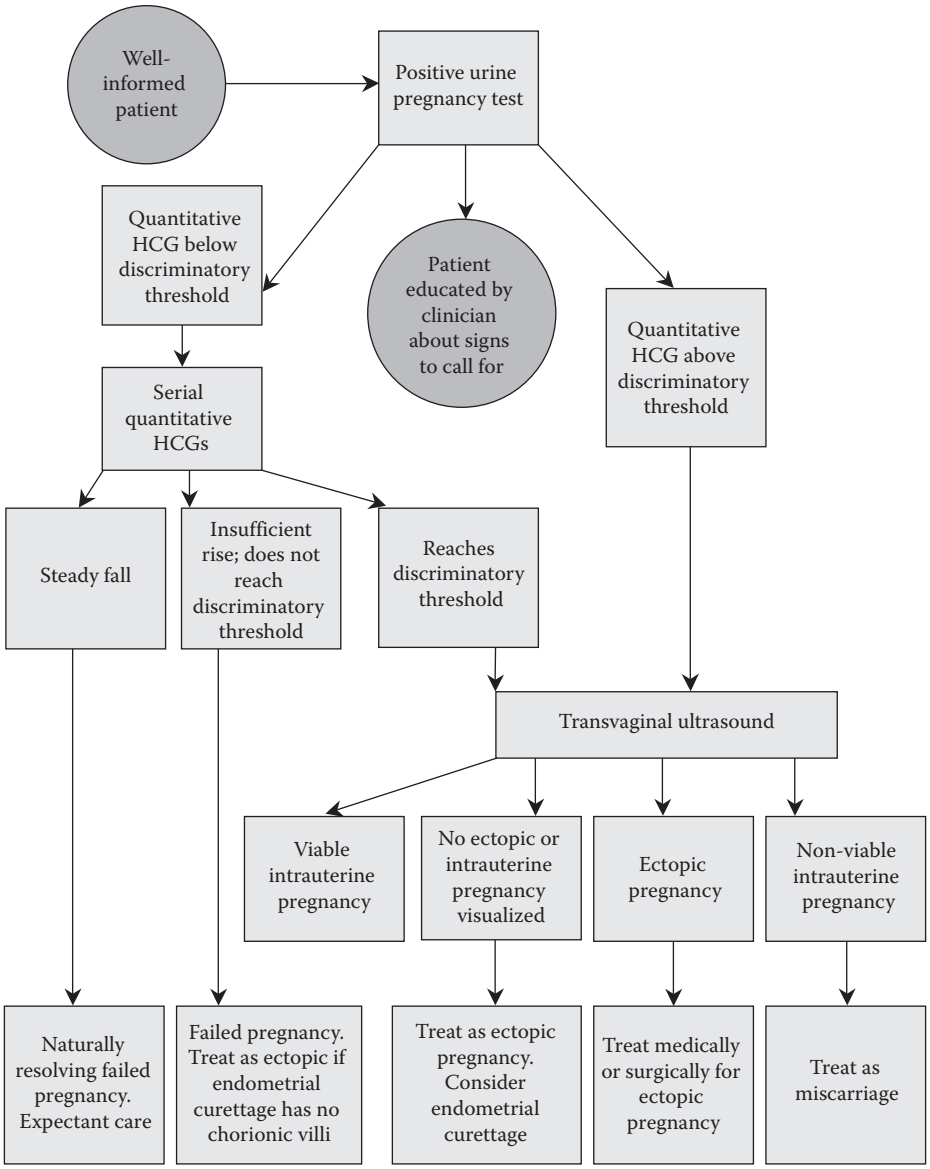


FIGURE 74.1 Example algorithm to prevent missing an ectopic pregnancy.

Engaging the patient in the prevention of cervical dysplasia and cervical cancer begins before the initiation of cervical cancer screening. This discussion should include details about safer sex practices and vaccination for the prevention of HPV infection.

The Centers for Disease Control and Prevention recommend vaccination for HPV at age 11 or 12. Therefore, at a time when adolescents are on the cusp of beginning sexual activity and may be receptive to information about potential hazards of unsafe sexual practices, a discussion regarding vaccination for HPV may be most productive. HPV vaccines are most effective for both males and females when given before exposure to HPV through sexual contact. HPV4 (quadrivalent vaccine) or HPV2 (bivalent vaccine) is recommended for the prevention of cervical dysplasia and cancers in females, while HPV4 is recommended for the prevention of cervical, vaginal, and vulvar precancerous lesions and cancers, as well as genital warts in females. Vaccinations are a routine part of preventive care; the HPV vaccine is no exception.[18]

Regardless of whether a patient has received the HPV vaccine, an abnormal PAP test or positive test for HPV needs to be explained to the patient. Patient care is at risk when communication breaks down; according to the American College of Obstetricians and Gynecologists, these breakdowns can include delay in care, failure to follow up on abnormal results due to workload, and failure to establish a tracking system.[19]

Once a patient is screened for cervical cancer, an office reminder system must be triggered in order to provide the patient with timely, accurate follow-up recommendations. This system should not rely on an individual's memory, but must be incorporated in a sustainable way into office workflow. While effective tracking can be accomplished either electronically or manually, recent data suggest that electronic tracking is preferred in an at-risk urban population because it accelerates the resolution of abnormal results and increases

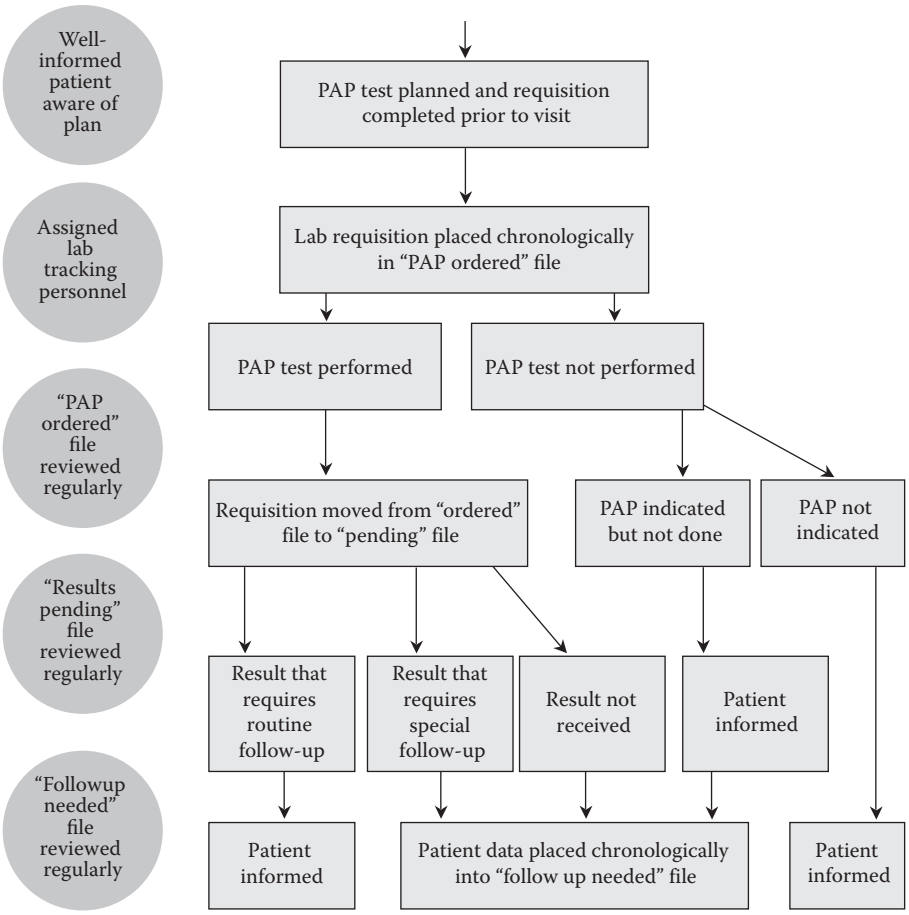


FIGURE 74.2 Example algorithm to prevent abnormal cervical cancer screening tests lost to follow-up. Note "PAP" refers to cytologic or HPV testing. The circles at left represent necessary background conditions and organizational structure that must exist in order for the algorithm to prevent error.

the number of women who achieve diagnostic cure.[20] For the many offices without access to an electronic system, however, paper tracking is possible and effective. Tracking systems for cervical cancer screening tests may be adapted according to the individual office's patient population, the level of the provider monitoring the tracking, and the anticipated lag time in the receipt of results. Figure 74.2 is an example of such a tracking system.

ERROR: FAILURE TO SUSPECT CANCER BASED ON ULTRASOUND OF THE OVARIES

There currently is no effective way to screen for ovarian cancer. However, clinicians are often faced with interpreting pelvic ultrasound results in order to determine which ones might be suggestive of ovarian cancer. The vast majority of pelvic ultrasounds reveal either entirely normal findings or findings suggestive of a benign process; as an example, several studies have shown that simple cysts (those without internal echoes on ultrasound) up to 10 cm are highly likely to be benign, with malignancy rates of less than 1%.[21–23] However, there is evidence that women with ovarian cancer whose care is managed by a physician with advanced training, such as a gynecologic oncologist, have improved overall survival rates when compared with those treated without such collaboration.[24–26] The challenge, then, is to properly utilize the information from a torrent of ultrasounds and avoid missing or under treating ovarian cancer by failing to refer the case to a specialist.

There are specific ultrasound results that warrant surgical consultation. For those women who are experiencing symptoms including, but not limited to, pelvic pain or abnormal uterine bleeding, surgery may be indicated even if the suspicion for cancer is very small. Likewise, for those women with solid tumors diagnosed on ultrasound, prompt surgical consultation is absolutely necessary.

The more difficult decision-making involves the patient who is not experiencing symptoms and does not have a solid tumor, but an adnexal cyst is discovered incidentally on pelvic ultrasound. The Society of Radiologists in Ultrasound convened a panel of specialists in 2009 from gynecology, radiology, and pathology to arrive at a consensus regarding the management of ovarian and other adnexal cysts imaged sonographically in asymptomatic women. Its consensus statement guides management diminishes the likelihood of overlooking cancer and identifies the characteristics that are most worrisome for malignancy (thick septations 3 mm or more, solid elements with flow at Doppler ultrasound, and focal

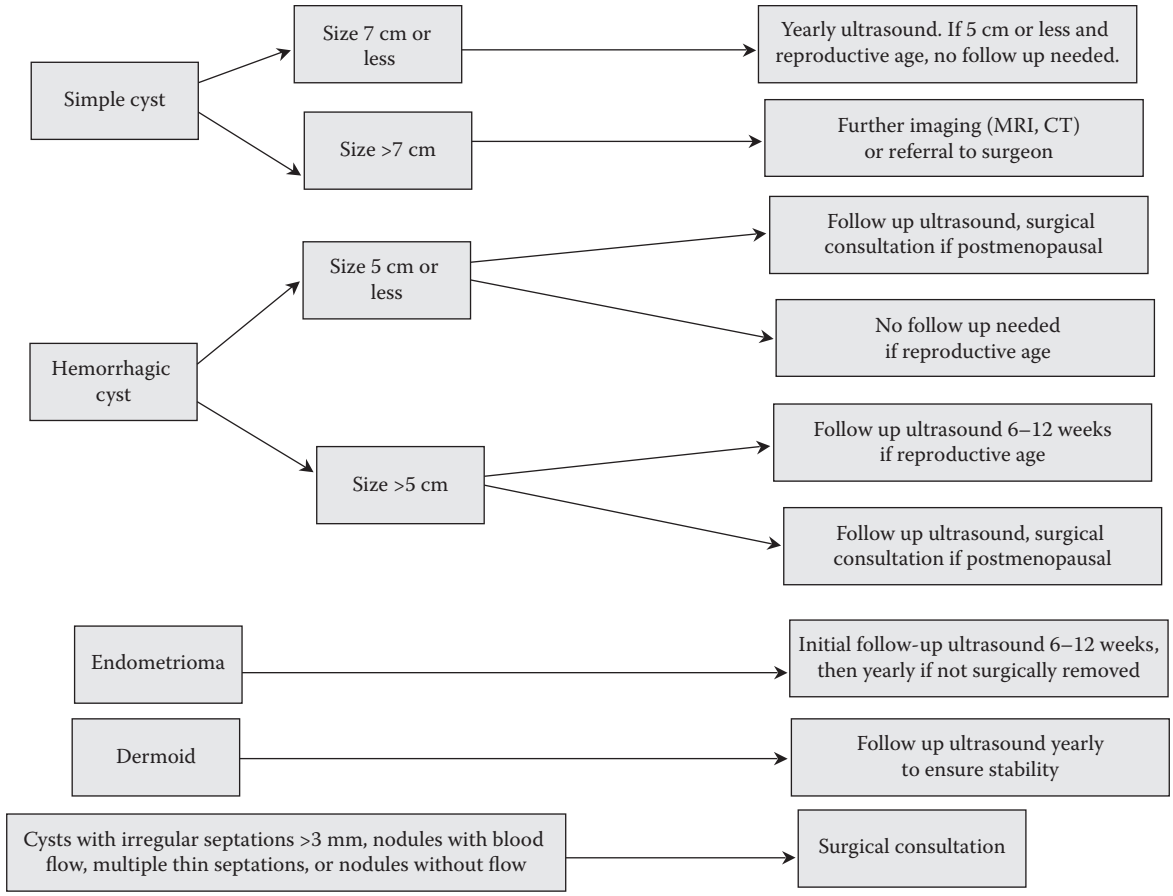


FIGURE 74.3 Example algorithm to prevent failure to suspect ovarian cancer based on ultrasound, based on recommendations from the Society of Radiologists in Ultrasound Consensus Conference Statement. (From Levine, D. et al., *Radiology*, 256(3), 943, 2010.)

areas of wall thickening 3 mm or more).[27] With these parameters, it is possible to effectively triage the management of asymptomatic adnexal cysts in order to minimize the risk of undetected cancer and maximize patient safety.

A clinical pathway that engages the patient in her follow-up after pelvic ultrasound, particularly in the asymptomatic patient who may be less likely to advocate for herself, will help with the timely detection of ovarian cancer. Such a pathway begins with ordering the ultrasound. A patient should be instructed to expect a result, and the clinician must have a system to trigger this, either electronically or on paper. The ultrasound exam should be considered incomplete until a patient is informed of the result, regardless of how she is feeling. Figure 74.3 is an example of such a clinical pathway.

ERROR: INCOMPLETE WORKUP OF POSTMENOPAUSAL BLEEDING

One of the most common reasons women seek medical attention is because of a change in their uterine bleeding pattern. Cancer of the endometrium is the most common type of gynecologic cancer in the United States, and bleeding is the presenting sign in more than 90% of postmenopausal patients.[28] Menopause is defined as the absence of menstrual periods for 1 year not due to pregnancy or medication, and bleeding that occurs after menopause must prompt a workup. Several modalities are available to investigate.

The ability of transvaginal ultrasound to diagnose or exclude endometrial cancer has been extensively studied and found to have an extremely high negative predictive value.[29–33] As a result, transvaginal ultrasound can be used to exclude the diagnosis of endometrial cancer for postmenopausal women who experience bleeding. An endometrial thickness of greater than 4 mm, however, does not yield a specific diagnosis and cannot be relied on to exclude pathology.[34]

Endometrial biopsy may be used as part of the workup for postmenopausal bleeding. However, studies have demonstrated that entrance to the uterine cavity may not always be possible, and attempts at retrieval of sufficient tissue for pathologic diagnosis are prone to failure.[35] In such cases, a normal transvaginal ultrasound demonstrating an endometrial thickness equal to or less than 4 mm may eliminate the need for more invasive testing; however, the problem must be addressed again if bleeding recurs or persists.

Postmenopausal bleeding can have a variety of clinical presentations, ranging from brown spotting to frank blood. Failure to investigate this complaint squanders an opportunity for early detection of cancer, and it is an error. Figure 74.4 is an example of an algorithm for the workup of postmenopausal bleeding.

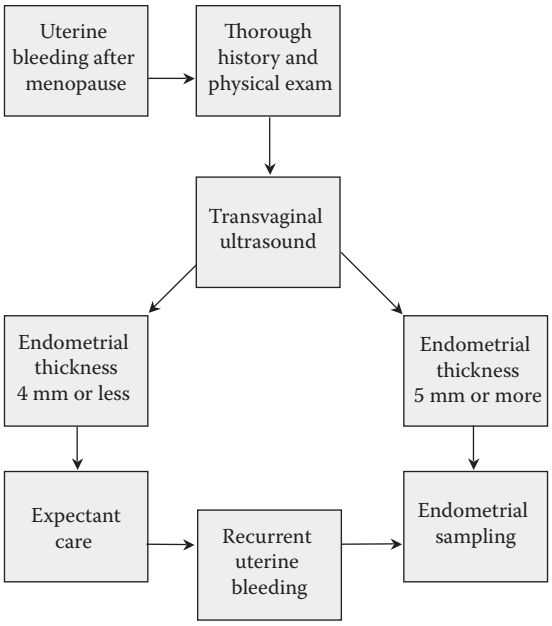


FIGURE 74.4 Example algorithm for the evaluation of postmenopausal uterine bleeding.

ERROR: PALPABLE BREAST LUMP, NORMAL IMAGING, LOST TO FOLLOW-UP

Breast cancer is the single most common female malignancy and a leading cause of cancer deaths in the United States.[36] Screening and early detection can make a difference in outcomes. Breast cancer may be detected during a clinician breast exam, through imaging, or sometimes, by the well-informed patient herself.

Commonly, women seek medical attention when they detect a change in their breast through self-examination. This is a cause of great anxiety, and patients look for immediate reassurance from a clinician's exam, or from mammography or ultrasound. This is the opportunity to educate the patient that the evaluation of a breast mass, particularly in a woman over 30, does not stop with imaging. As the patient leaves the office, she should expect to need an additional diagnostic workup for a palpable breast mass—even if imaging results are reassuring. The prevalence of breast cancer among women with a breast lump is relatively high (10%) compared with those who are asymptomatic, and about 15% of women with palpable cancer have a diagnostic mammogram that is normal.[37]

In women under 30 who have dense breast tissue, evaluation of a mass may begin with an ultrasound performed by a practitioner with training and expertise in breast imaging. For older women, the evaluation of a breast mass should include diagnostic mammography and may be augmented with breast ultrasound. With a palpable breast lump, screening mammography is inadequate as a single test to exclude cancer.[38,39] Therefore, if a patient is found to have a breast mass, workup should proceed even if she has had a recent normal screening mammography.

In order to obtain the most valuable information from breast imaging, a careful history and physical examination should be performed; any pertinent positive or negative findings should be conveyed to the patient and the imaging professional.[40] Important pieces of information include the timing of onset of the mass, changes in its size or shape, changes in skin texture, and the relationship of these changes to the menstrual cycle.[41]

Physical exam findings should be conveyed to the imager as precisely as possible. Noting the location of the mass by its clock-face location and distance in centimeters from the nipple, as well as its diameter, mobility, texture, and presence or absence of tenderness, can aid the imaging professional in arriving at a likely diagnosis. This is important when ordering either ultrasound or diagnostic mammogram. The patient herself must be fully informed and prepared to describe the location of a palpable breast lump to the imaging professional; without such information, the quality and usefulness of a report may be limited.

Communication with the patient in this clinical setting is paramount. According to the Risk Management Foundation (RMF) of the Harvard Medical Institutions,[42] several steps should be part of a system to make sure the patient understands the importance of follow-up for breast abnormalities. These include making follow-up or test appointments before the patient leaves the office, creating a system to recall and track patients who need follow-up, and reducing noncompliance by reminding patients of their appointments. Many radiologists are able to inform the primary provider when a patient does not appear for a scheduled test. Redundant safety steps can assure that no patient with a palpable breast lump is lost to follow-up so that breast cancer can be detected early.

Complete evaluation of a breast mass includes a well-informed patient, a thorough history and physical exam, precise interdisciplinary communication in a closed-loop fashion, high-quality imaging, the possibility of a return office visit to confirm resolution, and often a cytologic or histologic diagnosis. Figure 74.5 is an example of an algorithm for the evaluation of the palpable breast mass.

ERROR: UNSAFE MEDICATION PRESCRIBING

Safe prescribing and use of medications is a vital part of health care. The frequency of medication errors and preventable adverse drug events is a very serious cause for concern. The Institute of Medicine estimated in a 2006 report on preventing medication errors that approximately 450,000 preventable adverse drug events occur each year and that the rate of medication errors in hospitalized patients is approximately one medication error per patient per day. The report emphasized that medication safety is everyone's responsibility, and it proposed a move toward a patient-centered system. There should be openness—including with patients and families—regarding errors and problems, and information is made available to patients and their families that anticipates their needs and allows them to make informed decisions when choosing among alternative treatments.[43]

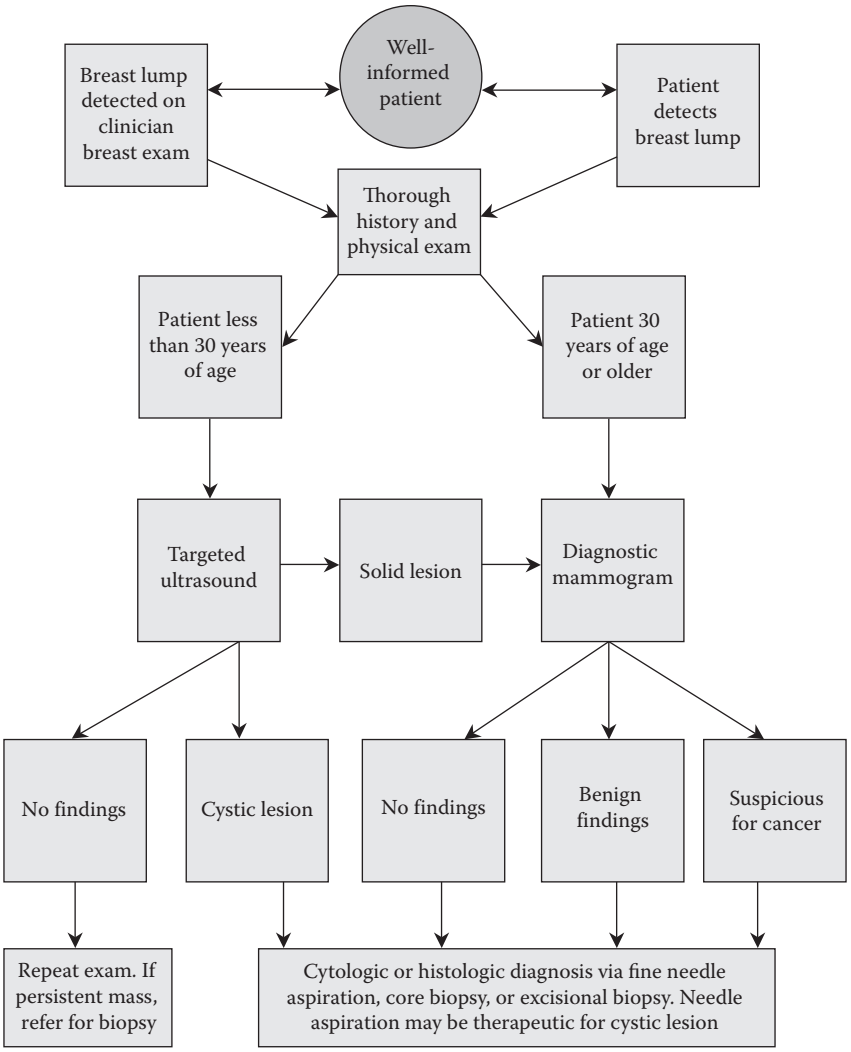


FIGURE 74.5 Example algorithm for evaluation and investigation of palpable breast mass.

In the labor and delivery setting, there are ample opportunities for errors in the transitions from triage to pre-procedure areas, labor rooms, and operating rooms, then to recovery and postpartum units. These mistakes may include poorly chosen drugs, inappropriate dosing, improper dosing intervals, or failure to prescribe a medication when it is indicated (an error of omission). The fatigue, stress, and production pressure that often accompany obstetric emergencies add to the vulnerability when using medications to care for patients with massive hemorrhage, sepsis, or fetal compromise. Often, such medications are ordered verbally and administered rapidly.

Similarly, medication errors are also common in ambulatory practice. Evidence reveals a preventable adverse drug event rate of 3 per 100 patients.[44] In the outpatient setting, medication orders are not usually checked, either in an electronic system or on paper, by pharmacists or nurses before dispensing and administration. Ambulatory practices often do not have policies for prescribing high-risk medications such as insulin or methotrexate, and there is no infrastructure to ensure read-back of prescriptions phoned into pharmacies or for deciphering illegible handwriting.

An additional hazard in the ambulatory women's health practice involves the risk of unknowingly prescribing a contraindicated medication to a patient with an undiagnosed pregnancy. While many medications can be used safely during early gestation, some drugs are preferable to others based on longevity of use and the historical lack of proof of human teratogenicity. The overbooked office schedule, task disruption, and burdensome outpatient documentation expectations increase the possibility of making such an error; however, an empowered patient who feels part of the care team and is therefore more likely to volunteer information, along with enhanced provider awareness and caution, will decrease the likelihood of unsafe medication practices.

In order to improve medication safety, providers need to take an active role. It should be routine to verify the patient's current medication list during each visit to ensure that it is accurate and up to date. Patient education before prescribing, allowing time for questions and answers, is essential. The name of the medication, a basic description of its mechanism of action, side effects, dosing schedule,

and drug–drug interactions should be reviewed. In this way, partnering with patients and engaging them in the medication-use process serve as a safety net in the ambulatory care practice.[45,46]

In many inpatient settings, and some outpatient, electronic prescribing is available. These systems ensure prescription completeness and are often able to be sent electronically to an outpatient pharmacy. They may be printed out, avoiding dispensing errors from illegibility. Many electronic prescribing systems are capable of decision support and can be integrated into the patient's electronic medical record. This creates an additional barrier to an incorrect medication or dosing interval or a potentially dangerous drug combination.

Medication safety in women's health rests on several key systematic preventive measures: routine and thorough patient education, attentive medication reconciliation and identification of allergies, scrutiny during the prescribing and dispensing process, and, most importantly, engagement and empowerment of the patient so that she becomes a valued member of the care team.

PUTTING THEORY INTO ACTION

As long as human beings are the ones who provide health care, the possibility of errors will exist. Concentrating only on those human errors, though tempting, is exceedingly unlikely to lead to a safer environment. Learning from error and creating sustainable systemic improvement are possible only when one steps back and looks at error in a different way.

All too often, those responsible for quality oversight, root cause analysis, and regulatory compliance function much like a firefighter. Caught in a barrage of everyday problems, well-intentioned nurses, physicians, medical assistants, and their managers focus on individual events or incidents. They quickly determine an immediate cause and eliminate it, exactly the way the firefighter responds to a desperate 911 call with a huge shower of water. The first responders cannot worry about whether the fire was caused by an unattended cigarette or an outdated electrical wiring system—the fire just needs to be extinguished. It is someone else's job to determine the reason for the fire; still others decide whether to update building codes or step up inspections that might help prevent a similar fire.

The health care analogy follows naturally: an elderly patient has a urine culture ordered at an office visit, the result never finds its way to a clinician's desk, and no antibiotics are prescribed. Three weeks later, the patient develops pyelonephritis and urosepsis, necessitating a prolonged intensive care unit admission. A likely reaction is to look at the clinician's habits, advise him or her to be more careful, and care for the patient's complication. The analysis and corrective action ends there; everyone is just too busy to look at this any differently, and bystanders are likely to say, "That wouldn't happen to me." A more holistic analysis of this error, though, would include consideration of the lab-reporting system, the office's paper reconciliation process, and the general approach toward educating the patient about being on the alert for notification of results. All would be considered aspects of process improvement. When the event is viewed this way, and improvements are aimed at root causes, the next patient will be less likely to be harmed by a similar mistake. Learning should be expected to follow errors or adverse outcomes.

In order to learn from an adverse event or error and make improvements, one must first understand how it happened. The error may be discovered through voluntary reporting or from analyzing a process or adverse event. One study in women's health that looked at voluntary reporting of medical errors showed that in a large tertiary care hospital, 38 of 82 medical errors reported during the study period represented potential adverse events.[47] The important point is that, in order to truly be successful at process improvement, errors and adverse events must be looked at as opportunities for generalized learning, not as things to be feared. There must be a change in the collective attitude.

Sharing the details of events is an important part of changing that attitude. Debriefs are a way to share information after an adverse or sentinel event has occurred, or even on a routine basis following a typical day's work. Debriefs are generally facilitated rather than led and work best when conducted within an organization that embraces a "just culture," originally described by David Marx, an attorney and expert in human error management[48]:

> It is through the lessons of our everyday errors that we can design our work environment to be less error prone and more error tolerant. Few people are willing to come forward and admit to an error when they face the full force of their corporate disciplinary policy, a regulatory enforcement scheme, or our onerous tort liability system. To collect productive investigative data, we must promote a culture in which employees are willing to come forward in the interests of system safety.

Debriefs are practical ways to gather information. They do not substitute for careful analysis but will facilitate corrective actions. Often, well-conducted debriefs will provide information that might, in another setting at another time, go undetected.[49]

Once the facts are known, through a debrief or other means, a simple way to analyze an event and elicit potential learning points and improvements is to utilize a question-asking method called "The 5 Whys." This technique developed by Sakichi Toyoda has been used within the Toyota Motor Corporation and the now-famous Toyota Production System, which is widely respected for its focus on continuous improvement, respect for people, and belief that the process that leads to the root cause of a problem will produce the right results. When faced with an adverse event, answers to "The 5 Whys" will uncover systemic

issues and lead to process improvement. The following example illustrates the technique:

1. The problem: The patient had emergency surgery and a fallopian tube was removed.
   a. Why? She had a ruptured ectopic pregnancy.
   b. Why? She did not phone the doctor when she had increased pain 3 days earlier.
   c. Why? She was not given instructions to call for this symptom when an early pregnancy was diagnosed and an ultrasound failed to show a normal pregnancy 2 weeks earlier.
   d. Why? The patient did not speak English and an interpreter was not available.
   e. Why? It was a weekend when she was initially diagnosed with a pregnancy, and interpreters do not work on the weekend.

Looking only at the outcome in this example, one can see the temptation to blame the provider. However, a quick analysis yields a few opportunities for systematic improvements: making interpreters available on the weekend, perhaps by telephone, having printed instructions available in a variety of languages, and creating a callback system for patients diagnosed with early pregnancy when follow-up is critical. When viewed in this way, it is apparent that although the provider did not adequately follow up with the patient, there were systematic deficiencies that enabled the whole mistake to happen.

We must look at the way we provide care in a way that points us toward continuous improvement, not continuous blame. In *Chasing the Rabbit*, Steven Spear, a senior fellow at the Institute for Healthcare Improvement, suggests ways to start process improvement projects that are likely to successfully reduce error and avoid adverse events[50]:

- Start with a small project. Improve a process that you know well and is in the control of just a few people; in this way, the chance for sharing ideas as improvements are made will be high.
- Solve a problem that really matters. Do not pick something people do not care about.
- Real learning comes to life as you walk through a process. As you decide to make improvements, do not just stand by—get involved and know the work.
- Stay safe. Improve things in a way that does not put anyone at risk.
- Budget time every day for designing a work process in order to see its problems, for solving those problems, and for sharing what you learn with others to whom the new insights may be useful.

Women's health care presents countless chances for mistakes, but it also offers an ideal environment for systems that can prevent error and improve in both inpatient and outpatient settings. A commitment to examining error in a nonpunitive way, addressing adverse events as opportunities to learn and improve, and reworking systems deliberately and persistently will create a safer environment for women.

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Part XIV

Dermatology

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75 Nutritional Deficiencies, Diseases, and the Skin

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CONTENTS

Overview 940
Change in Dietary Habits 940
Nutritional Guidelines and Supplementation 940
Vitamins Important for Healthy Skin 941
Vitamin C 941
Vitamin E 942
Vitamin A 942
Vitamin K 943
Vitamin B Complex 943
Vitamin B_1: Thiamine 943
Vitamin B_2: Riboflavin 944
Vitamin B_3: Niacin 944
Vitamin B_5: Pantothenic Acid 944
Vitamin B_6: Pyridoxine 944
Vitamin B_7: Biotin 944
Vitamin B_9: Folate/Folic acid 945
Vitamin B_{12}: Cyanocobalamin 945
Vitamin D 945
Essential Fatty Acids 945
Omega 3 946
Omega 6 946
Antioxidants Important for Healthy Skin 946
Lycopene 946
Grape Seed Extract 947
Coffeecherry Extract 947
Polypodium leucotomos 947
Cocoa Powder 947
Green Tea/Black Tea/White Tea 947
Alpha Lipoic Acid 947
Resveratrol 947
Curcumin 948
Pomegranate 948
Trace Elements and Minerals Important for Healthy Skin 948
Zinc 948
Selenium 948
Copper 948
Silicon 949
Ubiquinone/Idebenone 949
Chromium 949
Calcium 949
Conclusion 949
References 950

OVERVIEW

The skin is a vital organ in the human body, and as with any other organ, proper nutrition can help improve function and longevity. Improper diet can exacerbate or cause disease states that can severely impact the skin and the entire body. The appearance of the skin can also be significantly affected. Therapeutic and preventative dietary measures are important for skin health just as they are for other bodily organs. For example, people with heart conditions carefully monitor salt intake and balance other nutritional requirements in order to control their cardiac disease and to improve their prospects of healthy longevity. Even people without a diagnosed cardiac condition are attempting to be more "heart smart" in order to prevent the development of cardiovascular disease. Being "skin smart" is also very important because the skin is constantly bombarded with environmental stressors like UVA and UVB radiation, and the nutritional requirements needed to prevent skin damage and increase the overall health of the skin should be considered. The internal ravages of smoking and its ability to cause lung cancer are well known, but it is also easy to see the impact of smoking in a smoker's lax and wrinkled skin. So both health and beauty of the skin are influenced by dietary choices.

The concept that a healthy inside is equal to a healthy outside is gaining momentum, and evidence is growing daily that the presence or absence of certain foods in the diet can improve or worsen skin conditions [1]. The appearance of the skin is also reflected by nutritional state, and just as people aspire to "healthy longevity" for their body, another useful goal is to achieve a lifetime of healthy skin. While encompassing the diseases related to skin nutrition, this chapter will also attempt to give a broader understanding of why certain nutrients are needed in the skin and where they can be obtained in the diet.

Change in Dietary Habits

In modern society, "fast" food is abundant. Foods are highly processed and chemicals are added to them on a routine basis to act as preservatives, artificial flavorings, or colorings. Dietary fat and sugar intake is high, and overindulgence of fried foods and sweetened drinks and snacks is common. In short, people are eating more and more of the wrong things and less of the beneficial things needed to promote healthy skin. A recent review of the food consumption in America over the last 100 years (1909–2008) by the USDA demonstrated the average citizen eats 37% more processed food now than they did 100 years ago. Even more disturbing is the consumption levels of high-fructose corn syrup, which is the predominant sweetening agent in processed foods. It is estimated that the average consumption of high-fructose corn syrup, as of 2003, is 61 lb/year, the average sugar consumption is 142 lb/year, and the average soft drink consumption is 46 gal/year [2]. The average consumption level (in pounds of food per year) has also increased from 177 to 251 lb. As of 2008, the average American on a 2000 cal diet consumes 130% of the recommended grain servings and 120% of the recommended meat servings per day. To go along with this overconsumption of meat and grain, the average consumer gets only 70%, 60%, and 40% of the recommended vegetable, dairy, and fruit servings per day [3].

As previously stated, the most common outward appearance of premature aging and poor skin nutrition is characterized by loose, wrinkled, and dyschromic skin (often appearing as spots of hyperpigmentation). However, aging skin is also a combination of genetics, disease, progressive deterioration, body composition, and environmental stress [4]. The importance of nutrition in skin and overall health can be seen in a recent study for caloric restriction in monkeys. The study demonstrated that calorically restricted monkeys had not only better looking skin and fur (in both texture and fur color) but also reduced amount and severity of disease as the monkeys aged [5]. By contrast, a longtime rhesus monkey researcher said the (at one time) largest monkey on record, "Fat Albert," ate nothing but the American Heart Association-recommended diet [6]. This illustrates that one diet may not work for all situations and that optimal nutrition for skin health will take into account all factors and attempt to provide the proper nutrients in the proper amount to keep the skin healthy and all defensive and repair mechanisms running smoothly.

Nutritional Guidelines and Supplementation

The most popular set of nutritional guidelines is the recommended daily allowance or RDA. The RDA was created in 1941 by the Food and Nutrition Board and was designed to represent values that would be acceptable to 97%–98% of the healthy population in each group based on gender, age, and health stage. The RDAs were generally updated every 5–10 years. More recently, there have been a number of other additions to the nutritional guidelines for different purposes, which we will summarize here. The reference daily intake (RDI) is used for nutrition labeling by the FDA and was initially based on the highest 1968 RDA value to ensure that the needs for all groups were met. The most current nutritional guidelines (as of November 2010) in use are the dietary reference intake (DRI) established by the Food Nutrition Board of the Institute of Medicine. The DRI is composed of several measurements: (1) the estimated average requirements, which is expected to satisfy the needs of 50% of the selected age group based on the review of the scientific literature; (2) the RDA (previously described); (3) the adequate intake, which is an intake level believed to cover all members of the group and is used where no RDA exists; and finally (4) the tolerable upper intake level, which is the highest level of consumption that the current literature or data show to be safe. It should be noted that the DRIs are currently based on pooled opinion and literature review and not on randomized, controlled clinical studies [7]. So, as evidenced here, most people use general guidelines, which, while ensuring that basic nutritional levels are met for most healthy individuals, have little focus on the unique needs of an individual based

on the many previously mentioned factors. In general, under the current system of guidelines, an elite athlete or a chronically ill person would require the same nutrient levels as an average, healthy person. While this will keep the individuals free from disease caused by deficiency, it is obvious the nutrient requirements are vastly different.

It is currently estimated that per year use of dietary supplements and the dietary supplement production and sales of over 150 million Americans is a $26.9 billion industry. The industry is regulated by the FDA and the Federal Trade Commission through the Dietary Supplement and Nonprescription Drug Consumer Protection Act [8]. The sheer volume of products competing in the marketplace almost assures varying levels of efficacy. Consumers need to be aware of how products are tested and what the results of those tests truly mean for them. For instance, products containing conjugated linoleic acid showed the ability in vivo and in animal studies to produce a loss of fat mass and increase in lean muscle tissue. In human trials, little evidence was found of reducing body weight or repartitioning of body fat and fat free mass; it is possible that the increase in LDL:HDL ratio may result in an adverse effect on human health, in this case a higher cardiovascular risk [9]. The final variable found in dietary supplements is that the actual nutritional content may vary from what is described on the label, sometimes at levels over the upper limits or at reduced levels [10].

VITAMINS IMPORTANT FOR HEALTHY SKIN

Vitamin C

Vitamin C is the common terminology for L-ascorbic acid or L-ascorbate. It is a vitamin, antioxidant, and enzymatic cofactor in at least seven important cellular reactions, several of which involve the synthesis of collagen, which is vital in maintaining skin health. Collagen synthesis, aside from its importance in skin appearance and health, also plays a vital role in the healing of wounds (Office of Dietary Supplements, 2010) [11]. The most severe symptoms of scurvy (a disorder caused by vitamin C deficiency) stem from inability to synthesize collagen. Vitamin C is made internally by most organisms, with humans and primates being the most notable exceptions. Synthesis of vitamin C requires L-gluconolactone oxidase (GLUO), which is lacking in the human and primate body, making it essential that enough vitamin C be taken in through the diet. Vitamin C functions in an antioxidant role in the body. As L-ascorbic acid, it has reducing agent properties and is converted to L-dehydroascorbate (oxidized vitamin C). This molecule is then recycled to active L-ascorbate through enzymatic reactions involving glutathione [12].

Vitamin C is absorbed from consumed food via the intestine through sodium-dependent active transport and simple diffusion. The mechanisms regulating the bioavailability of vitamin C are complex and not fully understood. After absorption from food, any excess vitamin C is excreted in the urine making vitamin C toxicity a rare occurrence, but reinforcing the need for meeting the daily requirements for good health and healthy skin. Relating to healthy skin, it has been shown that outer layers of the skin itself (epidermis) store vitamin C at higher levels than deeper layers, such as the dermis [13]. Other areas of the body that demonstrate higher levels (100× more than in serum) of vitamin C are the adrenal gland, pituitary gland, thymus, corpus luteum, and retina. The brain, spleen, lung, testicles, liver, lymph nodes, small intestinal mucosa, leukocytes, pancreas, kidney, and salivary gland demonstrate levels of vitamin C 10–50× greater than serum [14].

There are multiple forms of vitamin C, both natural and synthetic, and the bioavailability and rate at which they are absorbed through the skin can often vary. One form is ascorbic acid 2-phosphate, which when given to human dermal fibroblasts increased the gene expression levels of genes associated with DNA replication and repair, showed faster repair of oxidatively damaged DNA, and increased proliferation and cell motility in the context of wound healing. This is a good indication that a topical application of a stable vitamin C derivative can serve to protect the main components of skin from reactive oxygen species (ROS) and aid in repair/wound healing [15]. Percutaneous absorption of vitamin C studies have shown that the L-ascorbic acid form demonstrates over 400-fold greater absorption than vitamin C palmitate or Mg ascorbyl phosphate [16]. There are ways to increase the absorption of vitamin C through the skin: one such method demonstrated that pretreatment with lasers can increase the amount of vitamin C derivatives across the dermis by 82- to 117-fold in the case of 3-*O*-ethyl ascorbic acid and 181- to 277-fold in the case of another derivative, ascorbic acid 2-glucoside [17]. Bioavailability of vitamin C is another factor that can vary, particularly in amount available following an oral dose. It has been demonstrated that vitamin C in doses of 15 mg has an 89% bioavailability, at 100 mg there is 80%, at 200 mg there is 70%, at 500 mg there is 63%, and at 1250 mg there is 46% bioavailability, indicating that increased dosage does not ensure a greater amount of bioavailable vitamin C [18].

The highest recorded concentrations of vitamin C have been found in Kakadu Palm, CamuCamu, rose hip, acerola, and sea buckthorn. Other plant sources with good vitamin C concentrations include green chili pepper, guava, black currant, red pepper, papaya, strawberry, orange, kale, garlic, cauliflower, and raspberry. Animal sources of vitamin C are less common and have a much lower concentration than plant sources, but some examples are raw oysters and fried livers (raw beef, chicken, and calf livers contain more vitamin C, which is damaged during cooking, but raw liver is far less palatable than cooked). If not enough vitamin C is obtained through the diet, a deficiency can result. The most recognizable disorder tied to vitamin C deficiency is scurvy. Scurvy left untreated is fatal and is incredibly rare in modern times since all that is needed for treatment is to resume adequate levels of vitamin C. The symptoms of scurvy demonstrate the significance of insufficient collagen synthesis on the health of the skin. It commonly causes dry and splitting hair; gingivitis and other gum inflammations; rough, dry, and scaly skin; easier

bruising; and decreased wound healing rate. Other symptoms not directly related to skin include anemia, nosebleeds, swollen and painful joints, decreased ability to fight infection, and possible weight gain through slower metabolism [19].

Vitamin E

Vitamin E is the collective name for a group of important fat-soluble antioxidants. There are eight chemical forms: alpha, beta, gamma, and delta tocotrienol and a coinciding set of tocopherols with varying levels of biological activity. Originally, alpha tocopherol was thought to be the only form recognized as able to meet human requirements, but it is the preferred form in the body [20]. The American diet consists of mainly gamma tocopherol, while the European diet is mainly alpha tocopherol, which is also the primary form used in nutritional supplements. While alpha tocopherol is predominantly thought to be the "best" form, new research is pointing toward the applications of other forms like delta tocopherol, which has recently been shown to be more active than the alpha or gamma forms at inhibiting tumorigenesis in an in vivo mouse model. Delta tocopherol was shown to reduce oxidative DNA damage while enhancing apoptosis in tumor cells to a greater degree than either alpha or gamma tocopherol [21]. Vitamin E, particularly in alpha tocopherol form, primarily functions as a peroxyl radical scavenger; by doing this, it maintains the integrity and bioactivity of long-chain polyunsaturated fatty acids found in cell membranes and damaged through oxidative stress [22]. The tocotrienol forms of vitamin E are a new area of research, but are thought to be even more potent antioxidants than the tocopherols, as well as being more active against cancer, cholesterol, and brain cell damage.

The primary use of vitamin E in relation to skin health is in the area of UV protection. As early as 1985, researchers discovered that vitamin E could confer some protective effects against UV exposure [23]. Topically applied vitamin E has a significant effect on protecting from UVB radiation, but has not been shown to have a large effect on UVA radiation. A 5% vitamin E cream applied to the skin prior to a 30 J UVA exposure demonstrated no change in the melanin index over the 12 week study [24]. However, when skin with topically applied vitamin E is exposed to UVB radiation, it demonstrates reduced erythema, less sunburn cells (SBCs), reduced chronic UVB-induced skin damage, and photocarcinogenesis in most studies. It was also determined that only high oral doses of vitamin E show a significant photoprotective effect, but a synergistic effect between vitamin C and E does exist [25]. This synergy for skin protection is demonstrated even further in a study of 45 volunteers supplemented with vitamin C, vitamin E, and vitamin C + E exposed to UVB radiation. The minimal erythemal dose (MED) in subjects with vitamin E supplementation increased from 60 to 65 mJ/cm^2, and in the vitamin C + E group the MED increased from 50 to 70 mJ/cm^2 [26]. As previously described, vitamin E contributes to healthy skin mainly in its role as an antioxidant by protecting skin from UVB damage and raising the overall photoprotective level. It can also help regulate the levels of vitamin A in the body and shows some anti-inflammatory capacity through the regulation of PKC. These anti-inflammatory properties are why it has been used, with varying degrees of success, to treat inflammatory skin disorders like psoriasis.

The best sources of vitamin are nuts, seeds, and oils, more specifically wheat germ oil, sunflower seeds, almonds, hazelnuts, sunflower oil, and saffron oil. Another effective source is fortified breakfast cereals which have been shown more effective than some capsule supplements [27]. Common plant sources include tomatoes, mangoes, spinach, broccoli, and kiwi fruit. Animal sources are generally poor sources for vitamin E.

Vitamin E deficiencies in the American and European diets are rare, but diseases that prevent the absorption of fat, such as Crohn's disease, cystic fibrosis, or liver disease, may interfere with the absorption and ability to process vitamin E and may require supplementation. When deficiencies do occur, they can cause neurological conditions stemming from impaired nerve conduction and anemia/hemolysis. The effects on the skin can include decreased sun protection (which results in higher levels of oxidative stress, DNA damage, and the like) and easier bruising.

Vitamin A

Vitamin A is a generic term for a number of related compounds collectively known as retinoids and carotinoids. The compounds are composed of retinyl groups, and the most commonly known is beta carotene, which comprises two joined retinyl groups. One of the compounds under the vitamin A umbrella is retinoic acid (a converted form of retinal aldehyde), which is important in skin health. It regulates gene expression levels that allow keratinocytes to mature into endothelial cells. It (in the form of all *trans* retinoic acid) has also been shown to reduce the activity of collagen-degrading enzymes like MMP-1 by reducing the post-UVB activity of the transcriptional factors AP-1 and NFKB [28]. It is this stimulation of immature skin cells that has led the cosmetic industry to use retinoic acid for the improvement of fine lines and wrinkles, as well as to treat psoriasis. The mechanism of retinoid action on skin health is not well known, but they remain popular in the treatment of many skin-related diseases. For example, 13-*cis*-retinoic acid, commercially known as Accutane, is used to reduce the size and activity of the sebaceous glands. A second prescription retinoid, called tazarotene, is approved for use in the treatment of acne, psoriasis, and sun-damaged skin. It is commonly sold in a gel or cream form at concentrations of 0.05% or 0.1%. The effects of vitamin A compounds are not limited to the skin; another compound, retinol alcohol, accumulates in the retina and plays a role in the formation of the visual pigment rhodopsin. Vitamin A is also involved in cellular differentiation, differentiation of white blood cells, the integrity/function of skin/mucosal cells, and the expression of growth hormone [29].

The precursor of vitamin A is beta carotene, and this compound is also a singlet oxygen quencher, which has been shown to inhibit MMP-1 and MMP-10 expression in keratinocytes [30]. Vitamin A is a lipid-soluble vitamin, and excess vitamin A is not easily removed from the body, which can allow buildup to toxic levels. Dietary vitamin A is obtained from preformed vitamin A (i.e., retinyl esters from animal foods, fortified foods, and pharmaceutical supplements) as well as from provitamin A carotenoids from plant sources. Preformed vitamin A is efficiently absorbed and utilized by humans at absorption rates of 70–90% (Penniston K., Tanumihardjo S., [31]. However, the intake of dietary fat needs to be evaluated as studies have had conflicting results indicating improved vitamin A absorption [32] and other studies that indicated no noticeable effect of dietary fat intake on the absorption levels [33]. Disregarding the dietary fat effect on absorption, the most common plant sources for vitamin A compounds are carrot, sweet potato, kale, spinach, pumpkin, collard greens, cantaloupe, mango, and butternut squash. Animal sources are also viable sources of vitamin A and can include milk, butter, eggs, liver (beef or poultry), and cod-liver oil.

Vitamin A deficiencies can be either a primary deficiency, in which not enough vitamin A is consumed in the diet, or a secondary deficiency where the individual cannot absorb lipids or is in a state of continuous exposure to oxidative stress (e.g., cigarette smoking or alcoholism). Vitamin A deficiencies are unfortunately quite common in children under the age of 5 around the globe and can result in blindness. These instances are highest in Southeast Asia and Africa, where hunger and malnutrition continue to be problems [34]. The good news is that simple supplementation with vitamin A can decrease the mortality levels of these children by 23% [35]. Along with its effect on children, vitamin A is also important in prenatal care, but should come from whole sources and not supplements [36]. This is due to high oral doses having been shown to affect the developing fetus, resulting in side effects ranging from a serious disruption of cephalic neural activity to a transient carotenodermia or orange-yellow tinting of the skin.

In adults, vitamin A can be over- or underconsumed, with both states resulting in disorders and disease states. Toxic levels of vitamin A symptoms include muscle weakness or pain, nausea, irritability, blurry vision, and headaches. A chronic state of excess often leads to dry skin, fever, fatigue, bone fractures, hair loss, and diarrhea. Deficiencies in adults commonly cause blurred vision, night blindness (even actual blindness), and lowered protection from ROS and oxidative stress. This reduction in ROS protection leads to an increase in the photodamage to the skin and poor bone health.

Vitamin K

Vitamin K is another fat-soluble vitamin, which has two types of natural versions, K_1 or K_2, and three synthetic versions, K_3, K_4, and K_5 (commonly used in the food industry). Both natural forms are naphthoquinone derivatives, with K_1 being obtained from outside the body and K_2 is synthesized in the gut by normal intestinal flora. Vitamin K is primarily responsible for blood clotting, but is also involved in the posttranslational modifications of proteins and metabolic pathways for bone and tissues. It also converts glutamate in proteins, which then bind calcium and affect the previously described pathways [37]. Oral vitamin K absorption occurs in the intestinal tract and is mediated by the amount of free bile present. Penetration of vitamin K into the skin is low, with the majority of the penetrated molecule located in the stratum corneum and a lesser portion being found in both the dermis and the epidermis 12 h post-topical application [38].

Vitamin K_1 is obtained through the diet primarily from green leafy vegetables. Viable sources of vitamin K_1 are spinach, Swiss chard, beet greens, asparagus, broccoli, collard greens, kale, parsley, and olive, soybean, and canola oils (although the oils would require too large a caloric intake to give the full RDA) [39]. It is thought that cooking sources of vitamin K with fat increases the bioavailability of vitamin K. Vitamin K_2 sources are found primarily in animal sources like meat, eggs, and dairy products [40].

Vitamin K, while being fat soluble, has no known toxic levels (K_1 and K_2), but deficiencies can occur. Though they are rare in adults, they are more common in newborns due to their underdeveloped intestinal flora. Deficiency causes easy bruising and bleeding (particularly from the gums), which can be severe and life-threatening in infants. Lack of sufficient vitamin K in the skin can result in dark circles under the eyes and increased ease of bruising. Vitamin K in conjunction with retinol is used in antiaging regimens. It has been used to treat rosacea and can be applied topically after cosmetic injections to help prevent or reduce the severity of bruising.

Vitamin B Complex

Originally thought to be 1 vitamin, it was later determined that there are many different chemical structures (roughly 28) that are often present in the same food. Vitamin B must be obtained from the diet as it is not synthesized by the body. There are eight major forms of B vitamin that are often referred to as the B complex. The following eight compounds form the B complex:

Vitamin B_1: Thiamine

Used primarily for protein binding, most serum thiamine is bound to albumin in erythrocytes. Vitamin B_1 is absorbed through carrier-mediated transport at low concentrations and passive diffusion at high concentrations. Sources of vitamin B_1 are commonly whole grains. Most of the thiamine is found in the germ layer, which is removed in the processing of rice and flour. To combat this, most Western countries must put the thiamine back into processed white rice and bread. Other sources of thiamine are other fortified grains (common in breakfast cereals), lean pork, milk, oatmeal, asparagus, cauliflower, and kale [41].

Thiamine deficiency results in a disease called beriberi, which can be termed "dry," "wet," or "infantile." It is not common for beriberi to have skin effects other than a slight

rash or swelling in the extremities; however, it is possible. Dry beriberi affects the nervous system and causes symmetric impairment sensory, motor, and reflex functions in the distal limbs. Wet beriberi not only affects the cardiovascular system but can also cause neuropathy, tachycardia, edema, mental confusion, muscular atrophy, and congestive heart failure. Infantile beriberi affects babies who are being nursed by thiamine-deficient mothers (who may not themselves show symptoms of thiamine deficiency) and has symptoms akin to wet beriberi, which can result in death if not treated.

Vitamin B_2: Riboflavin

Vitamin B_2 is what imparts the yellow color common to the vitamin. It is the main component of key oxidoreductase cofactors (FAD and FMN), which are vital to the energy metabolism of fats, proteins, and carbohydrates. Riboflavin is destroyed by exposure to light. Vitamin B_2 is naturally found in milk, cheese, tomatoes, almonds, mushrooms, and green leafy vegetables [42]. It is also removed in the processing of grains, flours, and cereals and must be added back post-processing. Items that have had the riboflavin added back in are labeled as "enriched."

Riboflavin is a water-soluble vitamin, so it is continuously excreted in the urine. Dietary insufficiency can easily lead to a deficient state known as ariboflavinosis. Common in alcoholism, one of the symptoms is angular stomatitis, which is cracking of the lips and edges of the mouth. In addition, the skin can be affected in other ways, such as seborrheic dermatitis (particularly around the scrotum or labia majora). Other symptoms common to riboflavin deficiency are glossitis (purple, atrophied tongue) and redness/swelling of the mucosa in the throat and mouth. Riboflavin deficiency in pregnant women is 4.7 times more likely to cause preeclampsia or hypertension due to pregnancy [43].

Vitamin B_3: Niacin

This vitamin exists in two alternate forms, nicotinamide and inositol hexanicotinate, which have different physiological effects than niacin. Niacin is important in metabolism, nervous function, and production of sex- and stress-related hormones. Recently, niacin has been used to lower elevated LDL levels and raise HDL levels [44]. Niacin is most often found in dairy products, lean meats, fish, nuts, eggs, and legumes and, like many other vitamin B compounds, is added back to processed grains, flours, and cereals. A niacin deficiency, also known as pellagra, is caused through dietary insufficiency or inability to absorb the vitamin. This is common in alcoholism and gastrointestinal disease sufferers. Symptoms of pellagra include scaly skin sores, mental confusion, delusions, diarrhea, and inflamed mucous membranes [45].

Vitamin B_5: Pantothenic Acid

Pantothenic acid is essential to all forms of life and is found in cells as coenzyme A. Coenzyme A is a cofactor in energy metabolism, synthesis of essential fats, steroids, acetylcholine, and heme. Heme is a component of hemoglobin, which binds oxygen in the blood. The main function coenzyme A performs in the previously mentioned processes is acetylation of key compounds [46]. Vitamin B_5 has been shown to accelerate the closure of wounds and increase the strength of the scar tissue in animals. In human skin fibroblast cultures, it has demonstrated increased number and speed of wound migrating skin cells, but clinical trials in humans remain inconclusive to date [47]. Coenzyme A is primarily found in animal muscle tissues, the outer layer of whole grains (which is often lost through processing and not added back in items labeled enriched), mushrooms, avocados, and broccoli [48].

As essential as coenzyme A is, deficiencies are not only fortunately rare but also poorly understood and studied. There is a broad range of symptoms associated with lack of vitamin B_5 in the diet. Typical of most B vitamin deficiencies, it results in lower energy output due to the important role coenzyme A plays in energy metabolism. This decreased energy output manifests as fatigue, apathy, or irritability. There can also be neurological symptoms like numbness, stinging of the feet or hands, muscle cramps, nausea, and in a few rare instances, adrenal and hepatic problems [49].

Vitamin B_6: Pyridoxine

Pyridoxine, again like most B vitamins, plays a role in the energy metabolism of food. Additionally, it also aids in the formation of red blood cells, antibodies, and proteins and in maintaining the integrity of healthy skin. Vitamin B_6 is most common in fortified, ready-to-eat cereals. It can be found in potatoes, bananas, garbanzo beans, pork loin, roast beef, trout, salmon, tuna, and chicken breast [50]. Like vitamin B_5, deficiencies of pyridoxine are also uncommon, although it most frequently appears in alcoholics due to their impeded ability to absorb the enzymes and overall diet deficiency. Vitamin B_6 deficiency is also noted in infants, manifesting as seizures or irregular EEG patterns. In more severe cases, the lack of proper vitamin B_6 in the body can also cause irritability, confusion, and sores/ulcers of the skin and at the corners of the mouth [51].

Vitamin B_7: Biotin

Biotin is essential for cell growth and production of fatty acids, plays a key role in the citric acid cycle, and assists carbon dioxide transfer. One of the biological activities of vitamin B_7 is the biotinylation of histones, which may have a role in affecting replication and transcription of DNA [52]. While it is required by all organisms, it is synthesized only by bacteria, yeast, molds, algae, and some plant species [53]. Vitamin B_7 comes from a variety of sources, but very few would be considered "biotin rich." Egg yolks have high biotin content when raw, but cooking and consumption with the egg whites mitigates the bioavailability. Other sources include yeast, raspberries, avocado, pork, salmon, and cauliflower [54].

Since biotin is synthesized in the body by intestinal flora, deficiencies are uncommon. In the rare instance the intestinal flora does not produce enough biotin or enough is not taken in from the diet, disorders can result. The symptoms, other than the neurological and energy metabolism-based ones, are

common to the skin. Biotin deficiency, as exhibited in the skin, has been known to cause alopecia (including the eyelashes); scaly, red rash around the mucous membranes; and unusual fat distribution in the face. Systemically, it can cause numbness in the extremities, lethargy, depression, and even hallucinations [55].

Vitamin B_9: Folate/Folic acid

Vitamin B_9 occurs naturally as folate, and not folic acid. The biologically activating step of folate occurs in the liver and involves the transformation of folate into dihydrofolic acid [56]. Bioactive vitamin B_9 is important in the synthesis, methylation, and repair of DNA. It also has a key role in the production of red blood cells and recently has been shown to potentially prevent changes that are commonly associated to lead to causation of cancer [57]. Supplementation of folate in pregnant women has been shown to significantly reduce the risk of neural tube defects [58]. Green, leafy vegetables and citrus fruits are excellent sources of folate. Other common sources include asparagus, lentils, and lima beans. The FDA has also required addition of folic acid to any already enriched and refined grain products like pasta, rice, or bread in an effort to ensure that the proper nutrient levels are met for the population [59]. Folate deficiency is more common than the other B vitamin deficiencies and occurs most commonly when an increased need for folate is not matched through the dietary intake. States requiring a higher folate intake include pregnancy/lactation, alcoholism, and kidney dialysis. Medications can also interact and cause a need for folate, particularly anticonvulsants, barbiturates, and drugs used to control inflammation in Crohn's disease or colitis [60].

Vitamin B_{12}: Cyanocobalamin

Vitamin B_{12} is the most common and air-stable form of vitamin B, found in some foods but commonly used as a food additive in most others. Vitamin B_{12} is not actually usable by the body, but can be converted into active cofactors like methylcobalamin and 5′-deoxyadenosylcobalamin [61]. Through these and other cofactors, vitamin B_{12} is involved in the formation of red blood cells and of genetic material (commonly DNA) and is an important cofactor in methionine synthesis. Methionine is required to create compounds that serve as methyl-donating species in over 100 reactions in the body. When taken orally at a 1 mcg dose, approximately 56% of the dose is absorbed. The absorption of vitamin B_{12} decreases drastically when the capacity of the intrinsic factor is exceeded, usually around 1–2 mcg of B_{12} [62].

Sources of vitamin B_{12} are lean meats (turkey, mutton, liver, and chicken demonstrated average bioavailability from 40% to 89%), milk, shellfish, eggs, tea leaves/drinks, cabbage, spinach, celery, broccoli, soybeans, and edible algae, aka nori in Japanese cooking [63]. B_{12} is also added to fortified cereals, like many of the other B complex vitamins. Vitamin B_{12} deficiency is more prone to occur in vegans/vegetarians since the primary natural sources are meat based. A deficiency can also be caused through malabsorption, common in disorders like gastritis. Symptoms include anemia and neuropathy [64]. Cutaneous manifestations can be hyperpigmentation, vitiligo, angular stomatitis, hair loss/changes, and unresolving/unexplained skin lesions [65].

Vitamin D

Vitamin D is a fat-soluble vitamin that must be metabolized into biologically active forms and is synthesized in the skin following UVB exposure. The vitamin D (D_3 or cholecalciferol) synthesized in this fashion must be obtained through the diet if UVB exposure is low, as vitamin D is a key component in maintaining normal calcium metabolism, which is important for bone growth and bone density and in keeping serum calcium levels in the narrow range required for proper nervous system function [66]. Vitamin D can also function as an immunomodulator and promoter of cellular differentiation and proliferation.

Aside from being generated by sunlight in the skin, vitamin D, since not many foods contain vitamin D, can also be obtained in the diet by supplements or with more difficulty through consumption of egg yolks; salmon, mackerel, and sardines; and fortified milk, cereals, and juices. Severe deficiencies of vitamin D have been known to be serious for a long time, but lesser states of deficiency can exist, and knowledge of risk factors for vitamin D deficiency is becoming more important. The known risk factors involved in vitamin D deficiency are infants who are exclusively breast-fed (they do not receive the vitamin in fortified milk), people with dark skin (since less UVB radiation penetrating the skin means less D synthesis), fat malabsorption syndromes, inflammatory bowel disease, aging, and lack of sun exposure (due to covering the skin or using sunscreens whenever outside). A sunscreen of SPF8 will reduce the amount of vitamin D synthesis by as much as 95% [66]. Recently, the American Academy of Dermatology (AAD) has released a position paper reinforcing both the need for getting vitamin D through the diet and preventing UV radiation overexposure.

In fact the AAD recommends

> an adequate amount of vitamin D should be obtained from a healthy diet that includes foods naturally rich in vitamin D, foods/beverages fortified with vitamin D, and/or vitamin D supplements. Vitamin D should not be obtained from unprotected exposure to ultraviolet (UV) radiation [67].

Severe vitamin D deficiency is also known as rickets in infants and children and osteomalacia in adults. Both disorders affect the bones; in the case of rickets, the bones continue to grow, but without adequate mineralization they become bowed. In adults the bones lose minerals and density and can become painful.

ESSENTIAL FATTY ACIDS

Essential fatty acids are labeled as "essential" because they are not made by the body or intestinal flora and must be taken in from the diet. The human body lacks the enzyme

required to place a *cis* double bond at the *n*-3 (omega 3) or *n*-6 (omega 6) position on the chemical structure of a fatty acid. Essential fatty acids are macronutrients indicating they need to be obtained in far larger quantities per day than vitamins or other micronutrients, often in gram amounts per day. Also known as "good fats" or polyunsaturated fats, they are involved in the maintenance of cell membrane integrity and the transfer of waste and water through those membranes. The ratio of omega 3 to omega 6 fatty acids in the early human diet was 1:1, but in the modern Western diet, that ratio is more like 10–30:1, mainly due to the increase in the use of vegetable oils and the reduction in fish consumption [68].

Omega 3

The parent version of the omega 3 fatty acid is alpha-linoleic acid (ALA) and is an 18-carbon fatty acid with the first *cis* double bond located at position *n*-3. ALA is hydrolyzed from fats by pancreatic enzymes before being absorbed in the small intestine [69]. ALA functions in the cell itself by being incorporated into phospholipids that compose the bilayer of the cell membrane. This adds structural support, while still retaining the membrane's ability to be flexible and permeable and to affect the activity of membrane-bound enzymes. Docosahexaenoic acid (DHA) is synthesized from ALA and has critical roles in vision through the regeneration of rhodopsin. Rhodopsin is required to convert the light signals received on the retina to visual images in the brain; therefore, it is not unexpected that DHA is highly concentrated and conserved in the retinal cell membrane [70]. DHA is also present in high ratios in the phospholipids of the gray matter in the brain indicating a function in the central nervous system, quite possibly regulating the availability of neurotransmitters and function of ion channels or membrane receptors. There is also evidence that both omega 3 and omega 6 fatty acids can regulate gene expression relating to inflammation and fatty acid metabolism by interacting with PPAR and LXR receptors. Omega 3 addition results in the suppression of NFkB, which results in the inhibition of inflammatory cytokines [71], and a second study confirmed the anti-inflammatory potential of omega 3 fatty acid [72]. ALA is currently being used in the oral treatment of arthritis and in products designed for skin health and acne. It is this anti-inflammatory effect, and possibly related increase in blood flow, that will keep the skin producing elastin and collagen, which can prevent sagging and wrinkle formation. Meta-analyses have also shown that ALA supplementation decreases overall mortality and mortality due to myocardial infarction and sudden cardiac death in patients with cardiovascular disease [73].

Sources of omega 3/ALA include walnuts, flaxseed, canola oil, and tofu [74]. Other plant sources of omega 3s are lingonberry, black raspberry, pecans, and hemp. The most common animal sources for obtaining omega 3 are generally fish and fish oils, with a higher proportion being found in fish from cold-water climates. The fish most associated with ALA content are salmon, flounder, grouper, herring, shark, oysters, sardines, trout, and tuna. If enough omega 3 is not ingested, there are many health issues that can result, although not all of them have solid research behind the association. Some of the issues associated with less than sufficient levels of ALA include acne, prematurely aging skin, arthritis, Alzheimer's disease (clinical trials are currently under way to determine whether ALA supplementation can help [75]) cancer, depression, eczema, vision disorders, rheumatoid arthritis, ulcerative colitis, psoriasis, obesity, and mental illness. Vision problems can occur in infants if the mothers do not receive enough ALA during pregnancy, while in adults, the most common symptoms are fatigue, depression, dry skin, poor circulation, and memory.

Omega 6

The parent form is linoleic acid and consists of an 18-chain fatty acid that has the first double bond at the *n*-6 position and absorbed by the body and converted into di-homo-gamma linoleic acid (DGLA) and arachidonic acid (AA). Conversion of GLA to DGLA requires other nutrients like magnesium, vitamin B_3 and B_6, vitamin C, and zinc. These are then converted into prostaglandins (PGE1 or 2, respectively). These prostaglandins are involved in the inflammatory response, with PGE2 being responsible for clotting and having pro-inflammatory effects, and PGE1 prevents clotting and is anti-inflammatory. When the levels of AA or PGE2 are out of balance with PGE1 and PGE3, the pro-inflammatory nature of PGE2 becomes evident. In most Western diets, the majority of the omega 6 is of the AA form and this pro-inflammatory boost is causing poor skin health and inflammatory diseases.

The sources of omega 6 commonly found are unheated and unprocessed vegetable oils, like corn, sunflower, sesame, and soy. Another common set of plant sources are legumes, nuts, gooseberry, black currant seeds, evening primrose, raw nuts, and leafy greens. Most problems associated with omega 6 fatty acids are caused by overconsumption and not a deficiency. Overconsumption leads to excess production of eicosanoids, which is associated with heart attacks, thrombotic stroke, arthritis, osteoporosis, inflammatory disease, mood disorders, cancer, and obesity [76]. Most medications treating these conditions focus on curtailing the efficacy/activity of arachidonic acid, which forms the basis for the mechanism of action for the COX1 and 2 anti-inflammatory medications [77].

ANTIOXIDANTS IMPORTANT FOR HEALTHY SKIN

Lycopene

Lycopene is a nonessential carotenoid, but it has no vitamin A activity. It is fat soluble, absorbed in the stomach (so ingesting with oil aids in the absorption process), and is transported by lipoproteins through the blood. Lycopene in tomato products, unlike most other vegetables, has increased bioavailability when processed. Lycopene may be one of the

most powerful quenchers of singlet oxygen (the primary form of oxidative stress and cause of skin aging) following exposure to UV radiation. UVA-generated singlet oxygen mediates photoaging-related mitochondrial deletions [78]. Studies have shown the antioxidant activity of lycopene to have some effect on cancer, diabetes, cardiovascular disease, sunburn cell formation (following a 10 week placebo-controlled study, the lycopene supplemented group had lower numbers of SBC following 2 MED of UVA/UVB radiation), and skin texture. Relating to skin texture, a recent study demonstrated that higher levels of the antioxidants in the skin may correlate to lower levels of skin roughness/wrinkles [79]. While rarely deficient in most diets, overconsumption can cause lycopenodermia, a reversible orange-yellow tinting of the skin.

Grape Seed Extract

Grape seed extract is rich in proanthocyanidins, a class of flavonols. Flavonols generally correlate to high ORAC (oxygen radical absorbency, which is a measure of the ROS quenching ability of a compound commonly measured in trolox equivalents/unit) values. When administered to Japanese women suffering from chloasma, 83% of the women demonstrated improved skin lightening and melanin index scores at 6 months [80].

Coffeecherry Extract

An extract made from the actual semi-ripe fruit of the coffee plant (the flesh surrounding the bean). Coffeecherry extract contains a multitude of antioxidant compounds such as chlorogenic acid, caffeic acid, quinic acid, and ferulic acid. Processed coffee is the most common antioxidant source in adults, and it is estimated that 1300 mg of antioxidants in 1.6 cups of coffee, on average, are consumed daily.

Polypodium Leucotomos

Polypodium leucotomos is a fern that contains phenolic antioxidant compounds, including *p*-coumaric, ferulic, caffeic, vanillic, and chlorogenic acids. The antioxidant-rich extract is taken orally and has been found to reduce the erythema, sunburn cell counts, DNA damage/dimers, and mast cell infiltration following UV exposure [81]. It has also been shown to inhibit MMP and may reverse the loss of elastic fibers through intrinsic aging in fibroblast and keratinocyte cultures exposed to UV radiation. It is currently being used as treatments for psoriasis and vitiligo.

Cocoa Powder

When dry and unsweetened, this powerful antioxidant has a total ORAC score of 80,933 µmol TE/100 g. The processing of chocolate removes the naturally high flavonol content from the raw cocoa product and renders it less effective at protecting from ROS-induced damage. A good quality cocoa can deliver 5000 ORAC units in about 20 g/day. Processed chocolate also has antioxidant capacity (the higher cocoa content the better), but to a lesser extent than the raw form.

Green Tea/Black Tea/White Tea

Green, black, and white tea all come from the *Camellia sinensis* plant, but at varied stages of crushing and drying; green tea is unprocessed. All are excellent sources of antioxidants in the form of polyphenols and flavonols, primarily catechins, epicatechins, and thearubigins. There has been evidence showing that green tea polyphenols can cause an increase in IL-12-mediated DNA repair, which aids in preventing the formation of UVB-induced skin tumors [82].

Alpha Lipoic Acid

Alpha lipoic acid (LA), aka thioctic acid, is synthesized in the mitochondria of plants and animals from octanoic acid. It functions as an enzymatic cofactor in several mitochondrial complexes for energy production and is important in the catabolism of alpha keto and amino acids [83]. It also functions as an antioxidant by directly scavenging free oxygen and nitrogen radicals (demonstrated in vitro, but not confirmed in vivo) and indirectly through acting as a reducing agent for other oxidized free radical scavengers, chelating ROS forming metal ions, and inducing glutathione synthesis, particularly in aged animals [84]. LA is commonly found in food bound to the protein lysine forming lipoyllysine. Food sources with larger amounts of LA include organ meats, spinach, broccoli, tomatoes, peas, and Brussels sprouts. Supplements of alpha lipoic acid contain unbound or "free" lipoic acid and typically contain far greater amounts than can be obtained through the diet. There have been no known instances of lipoic acid deficiency since the body seems capable of synthesizing enough on its own or getting enough through the diet. Toxic levels are also not known, but higher doses of oral supplementation have demonstrated some cases of gastrointestinal problems and allergic reactions (hives, skin rashes, etc.).

Resveratrol

A polyphenolic compound present in red grapes, red wine, peanuts, and some other berries, resveratrol is a stilbene, which is produced by some plants in response to stress, injury, fungal infection, or UV radiation. This compound is fat soluble, has direct antioxidant activity (through free radical scavenging and inhibition of LDL oxidation), and is well absorbed orally, but the bioavailability is low since it is rapidly metabolized. Resveratrol has demonstrated the ability to induce cell cycle arrest, inhibit proliferation, and induce apoptosis in cancer cells [85]. Resveratrol has a wide variety of effects on cells in culture, such as inhibition of inflammatory enzymes, inhibition of at least one type of metalloproteinase, stimulation of eNOS activity, and increase in the activity of NADPH:quinone reductase. Not all of these in vitro findings have been repeated in vivo, and cultured

cells were not exposed to the metabolites of resveratrol (as would occur in the body) and often in levels much higher than would be found in circulation. However, in yeast, fruit flies, and nematodes, resveratrol supplementation extended the lifespan of the organisms in a manner similar to caloric restriction [86]. Resveratrol supplementation (usually in the form of red wine extract or *Polygonum cuspidatum* extract) is still in the early stages, and very few controlled clinical studies have been conducted. There are currently no known adverse effects of high-dose resveratrol, but pregnant women are advised to avoid alcohol as a means for resveratrol supplementation and individuals suffering from estrogen-dependent cancers should also avoid resveratrol as little is known about the estrogenic activity of resveratrol.

Curcumin

A yellow, curcuminoid (polyphenolic compound) found in the rhizomes of a member of the ginger family, curcumin is what gives the spice turmeric its yellow color. While studies have shown that the bioavailability of curcumin is low, it is possible to achieve biologically active levels in the gastrointestinal tract through oral supplementation. Curcumin, in vitro, has demonstrated free radical scavenging ability of both ROS and RNS, inhibition of inflammatory enzyme activity, and increase of glutathione synthesis [87]. Like resveratrol, curcumin is being studied for its anticancer potential, and clinical trials are still in the very early stages. It is also being used to treat skin disorders like scleroderma, psoriasis, skin cancer, and possibly wound healing [88]. There have been no recorded instances of serious adverse effects in individuals on high doses of curcumin, and it is generally recognized as safe by the FDA.

Pomegranate

The juice of the pomegranate aril (the water-laden pulp surrounding the seed) contains large amounts of vitamin C, vitamin B_5, potassium, and polyphenols. The juice contains a wide variety of polyphenols like, ellagitannins, punicalagins, catechins, gallocatechins, and anthocyanins. One of the compounds, egallic acid, is metabolized very quickly in the body when taken orally. This same compound when applied topically to SKH-1 hairless mice exposed to UVB radiation demonstrated diminished production of pro-inflammatory cytokines, blocked macrophage infiltration, and attenuated UVB-triggered skin wrinkle formation and epidermal thickening [89]. Using the same mouse model, a study involving oral supplementation of pomegranate fruit extract, prior to UVB radiation, inhibited edema, hyperplasia, leukocyte infiltration, peroxidation of lipids, peroxide generation, and ornithine decarboxylase (ODC) activity, indicating a substantial protective effect to UVB-induced photodamage [90]. A final study using cultured human skin fibroblasts demonstrated that pomegranate extract increased synthesis of collagen and decreased synthesis of MMP-1 [91]. Preliminary data exist indicating that pomegranate extract has a positive effect on several types of cancer, coronary artery diseases, oxidative stress, diabetes, and the common cold.

TRACE ELEMENTS AND MINERALS IMPORTANT FOR HEALTHY SKIN

Trace elements are only needed in small amounts in the diet, and toxic levels could easily result through overconsumption.

Zinc

Zinc must be ingested daily as it is not stored by the body. The most common source of zinc is red meat or poultry, but is also found in pumpkin seeds, beans, nuts, and whole grains (but it is most highly concentrated in raw oysters). Zinc is involved in many body processes including wound healing, DNA synthesis, protein synthesis, cell growth and division, and catalytic activity for enzymatic reactions. Zinc is currently found in sunscreens since it physically blocks UV rays, it is also used to treat acne, seborrheic dermatitis, and dermatitis herpetiformis. Another study has shown possible use as a treatment for age-related macular degeneration [92]. Toxic levels can result despite the inability of the body to store excess zinc, and the result is usually gastrointestinal injury, fever, and kidney failure [93].

Selenium

A nonmetal trace element related to sulfur, selenium forms selenoproteins in the body, such as glutathione peroxidases (five types) and thioredoxin reductase. These enzymes are key mediators in the reduction of damaging ROS, like hydrogen peroxide or lipid hydroperoxides, and in the regeneration of antioxidants like vitamin C, making it vital in the pro-oxidant/antioxidant balance. It is a known stimulator of the immune response [94]. The richest known sources of selenium are Brazil nuts, followed by organ meats and seafood such as crab, shrimp, salmon, and halibut. Selenium doses over 400 μg/day can result in toxicity, which can cause shakiness, vomiting, redness of the face, irritability, brittle hair/nails, and possible cardiac arrest [95].

Copper

Copper is an important metal involved in creating energy for the cell inside the mitochondria through interaction with the copper-dependent enzyme cytochrome c oxidase. Copper also plays a vital role in the scavenging of free radicals and in redox reactions as a part of superoxide dismutase (SOD). Copper is required in the cross-linking of collagen and elastin fibers and aids in myelin formation, neurotransmitter synthesis, and melanin formation [96]. Copper-rich foods include organ meats, oysters, clams, cashews, crabmeat, hazelnuts, almonds, and raw mushrooms. Copper toxicity, while possible, is rare, and copper deficiency often presents as anemia since copper functions as a key mediator in iron

absorption. Wilson's disease is another form of copper toxicity, which is caused by abnormal copper accumulation from birth, although the first symptoms often do not occur until late childhood or early adolescence. The primary damage is usually to the liver, and this is reflected in the skin by the appearance of jaundice, hypermelanotic pigmentation, and other signs of liver disease like spider veins.

Silicon

Silicon is a common metalloid found in apples, raw cabbage, cereals, peanuts, carrots, onions, cucumber, pumpkin, honey, and oranges. Its status as an important trace element is currently being debated with proponents listing many yet-to-be-accepted benefits like preventing brittleness in hair and nails, strengthening the connective tissues in the skin (silicon is most commonly found in skin connective tissue), and reduced skin wrinkling (silicon plays a role in collagen synthesis).

Ubiquinone/Idebenone

Ubiquinone is also known as coenzyme Q10 and is an oil-soluble compound vital to the mitochondria and production of ATP. The majority of the body's energy is generated through the electron transport chain, and coenzyme Q10 serves a critical role as an electron carrier from complex I to complex II. It also serves a function as an antioxidant through its ability to undergo redox reactions in the cell and is very effective against the damaging singlet oxygen radical. Food sources include organ meats, pork and beef, sardines, salmon, tuna, soybean oil, peanuts, parsley, and avocado. Deficiencies can be caused by reduced biosynthesis due to aging, increased utilization by the body, disease conditions like cancer, or insufficient dietary intake. There are no known skin-specific symptoms of ubiquinone deficiency, but supplementation has been shown in some studies to increase the longevity of rats and nematodes through reduced oxidation and DNA damage [97].

As a synthetic version of coenzyme Q10, idebenone must be obtained as a supplement because it does not occur in nature. It has been shown to have an antiaging effect and, like ubiquinone, when applied topically, can improve the appearance of photodamaged skin [98]. It has also been used orally in the treatment of many neurological disorders like Alzheimer's disease and Friedreich's ataxia [99].

Chromium

Found commonly in nature as trivalent chromium (III) or hexavalent chromium (VI) and generally recognized as an essential mineral, the actual mechanism or function of chromium in the body is poorly understood. The reason for the uncertainty on chromium function is the lack of sensitive and accurate testing methods for its nutritional status. Chromium III is commonly found in food sources and is the bioactive form preferred by the body; while chromium VI is convertible to usable chromium III, it is thought to be an irritant and carcinogen. Chromium interacts with insulin and aids in glucose metabolism in the body. Common chromium sources include processed meats, whole grain products, broccoli, grape juice, green beans, apples, and bananas. A chromium deficiency has rarely been reported; however, inhalation of chromium VI has been shown to increase the risk of lung cancer, and exposure to the skin has demonstrated the ability to cause dermatitis. There has been no known risk associated with chromium III, but caution against long-term high-level intakes is encouraged.

Calcium

As the most common mineral found in the human body, calcium interacts with a number of other compounds and biological systems. Primarily forming the bones and teeth, calcium is also important in the maintenance of voltage-sensitive ion channels in cell membranes and muscle function, and the binding of calcium activates vitamin K-dependent clotting of coagulation [100]. Calcium in the skin (epidermis) is believed to help regulate the turnover of skin cells, affect skin color through stimulation of melanocytes, help control inflammation, and keep the skin full and healthy as skin cells without calcium can result in fragile, thin-appearing skin. Calcium is most commonly found in dairy products like milk, yogurt, and cheeses. It can also be obtained in tofu, white beans, rhubarb, and spinach. Supplementation of calcium is usually reserved for certain nutritional disorders as most health care providers encourage individuals to get the required amounts of calcium from natural sources and foods because natural calcium is often accompanied by other nutrients that help the body utilize calcium more efficiently. Calcium deficiency is usually associated with osteoporosis, but can also be related to parathyroid malfunction, chronic kidney failure, and vitamin D deficiency. It is reflected cutaneously by dry skin and brittle hair and nails. Toxic levels of calcium can be achieved and is known as hypercalcemia. Cases of mild hypercalcemia can show no symptoms or include nausea, vomiting, constipation, frequent urination, dry mouth, and thirst, while more severe hypercalcemia can be characterized by confusion, delirium, coma, and death if left untreated. Increased secretion of calcium in the urine, called hypercalciuria, can result in a greater likelihood of kidney stone development.

CONCLUSION

A lifetime of healthy skin begins on the inside through proper diet and nutrient intake. Optimizing mitochondrial function and having the proper nutrients available for repair of environmental damage and chronologic aging keep the skin looking youthful and resilient and minimize the risk of preventable diseases. As this chapter has shown, proper nutrition must take into account many factors in an individual's lifestyle such as age, activity level, current health status, and environmental/oxidative stress level. To do this, it is important to understand the function of the more important nutrients for skin health as well as the bioavailability

and structural form required for each. Most experts agree that natural food sources are generally ideal, but that there is also an important role for proper supplements. Another important factor is selection of the nutrient source and preparation for consumption. In some instances, processing or improper cooking method can damage or remove potential health benefits, but this is not always the case. For example, with regard to total ORAC levels, a raw, unprepared sweet potato has an ORAC of 902 µM TE/100 g, while a sweet potato that has been baked in the skin has a total ORAC of 2115 µM TE/100 g [101]. Finally, bear in mind that most nutritional guidelines are set at the intake level required to prevent a deficiency or disease for 95% of the population and is not tailored to an individual, so there are instances where more of a specific nutrient or supplementation may be required (in the case of alcoholism or malabsorption disorders). So these nutritional guidelines to prevent disease are not the guidelines for producing optimal skin health.

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76 Aging and the Skin

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CONTENTS

Intrinsic Skin Aging 953
Mechanisms of Intrinsic (Chronologic) Aging of the Skin 953
Epidermis 954
Dermis 955
Hypodermis 956
Glands and Nerves 956
Hair 957
Menopause and the Skin 957
Photoaging 957
Mechanisms of Photoaging 958
Signaling 958
Mitochondrial Damage 959
Protein Oxidation (Smoking) 959
Neoplasia 960
Infections 960
Conclusion 961
References 961

Life expectancy in both developed and developing nations is continuing to increase as advances in health care and accessibility continue to expand. This means that across the world, the proportion of older people is increasing. By 2030 in the United States, 31% of the population is expected to be 55 years of age or older [1]. As a result, it will be indispensable for physicians and health care providers to recognize and address age-related changes in every organ system of the body, including the skin.

Aging in the skin reflects an interaction between two processes: intrinsic aging and photoaging. Intrinsic aging occurs throughout the entirety of the skin and is caused by several factors including gradual oxidative damage and reduction in the rate of skin cell replication. Photoaging is the result of chronic, lifelong exposure to ultraviolet radiation, which superimposed on intrinsic aging, causes most of the visible age-related changes in the skin [2]. In addition to gradual skin aging, several dermatologic disorders increase in incidence with age, including cutaneous neoplasms and certain skin infections [2].

INTRINSIC SKIN AGING

Intrinsic skin aging, caused by the passage of time alone, is considered universal and unavoidable. This type of aging results in characteristic histologic, functional, and physical changes in the skin. In the epidermis, histologic changes are numerous and include flattening of the dermal–epidermal junction (DEJ), variable or decreased thickness, variable cell size and shape, and fewer melanocytes and immune cells; in the dermis, there are fewer fibroblasts, fewer mast cells, fewer blood cells, and atrophy [2]. Functional changes include reductions in barrier function, DNA repair, immune responsiveness, mechanical protection, cell replication, vitamin D production, and wound healing [3]. Physical changes include dryness, roughness, wrinkling, delayed healing, and an increased incidence of cutaneous malignancies [2].

Mechanisms of Intrinsic (Chronologic) Aging of the Skin

Several theories have been proposed to explain the specific mechanisms behind the intrinsic aging of skin. A major and widely accepted theory [4] involves the formation of free radicals and their deleterious effects on cellular integrity of the skin. Cellular aerobic metabolism continuously exposes skin cells to reactive oxygen species (ROS) that gradually damage biomolecules, including DNA. The accumulation of this damage increases the risk of tumorigenesis and results in apoptosis or senescence causing skin aging.

ROS and oxidative stress cause upregulation of inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF)-alpha [2]. These immune-modulating molecules [5] are thought to play a major role in cellular aging partly through stimulating expression of matrix-degrading metalloproteins [6].

In addition, oxidative stress affects terminal portions of chromosomes in eukaryotic cells known as telomeres. They consist of a repetitive sequence of nucleotides that are conserved within a species. As a cell replicates, telomeres are gradually shortened due to inability of DNA polymerase to fully replicate the end of a linear strand of DNA, known as the end-replication problem [7]. The telomerase enzyme replenishes telomeres; however, its expression is reduced dramatically with age resulting in gradual erosion of telomeres [7]. As telomeres shorten with each replication cycle, they reach a critical length that signals for cell death or senescence [7]. One mechanism by which oxidative stress may cause damage to telomeres and ultimately result in cutaneous aging is through activation of these same signaling pathways [8,9]. Under normal conditions, the 3′ end of a telomere is longer than the 5′ end and is "buried" and protected beneath the loop configuration of the telomere [7]. It is believed that during the repair of oxidation-induced telomere damage, as well as when telomeres reach their critically short length, the 3′ end of the telomere becomes exposed, activating a cellular signaling cascade involving p53 that eventually results in apoptosis or senescence [8,9].

Oxidative damage also hinders cellular function by altering protein composition. Generation of ROS causes the development of carbonyl groups (C=O) on cellular proteins. These abnormal proteins are typically degraded by proteasomes whose function declines with age, leading to buildup of the altered and often nonfunctional proteins [10].

In order to counteract free radical accumulation, cells contain a variety of enzymatic antioxidant molecules, including glutathione peroxidases, catalases, and superoxide dismutases. Nonenzymatic protection against ROS in primarily mediated by antioxidants such as vitamin E and coenzyme Q10. Despite their existence and efficacy in youth, these antioxidant systems are far from perfect and tend to depreciate with age [11].

Another mechanism that contributes to intrinsic aging is cellular senescence. A senescent cell has an extremely limited ability to divide; it has critically short telomeres and is resistant to apoptosis and altered differentiation. In addition, cells in senescence overexpress genes that encode for proteins such as fibronectin and proteases that modulate the extracellular matrix and contribute to skin aging [12–14]. Finally, modification of amino acids within proteins is another mechanism that plays a role in intrinsic aging. Within proteins, D-amino acids undergo racemization to form L-amino acids; these changes can render whole proteins nonfunctional and resistant to degradation, which in turn leads to their intracellular accumulation and ultimately interference with cellular function [2].

Epidermis

The skin is composed of three distinct layers that are all affected by the aging process: the epidermis, dermis, and subcutaneous tissue. The epidermis is the outermost layer of the skin; it is a stratified squamous epithelium composed of keratinocytes, but also houses melanocytes, Langerhans cells, Merkel cells, and inflammatory cells. The innermost epidermal layer, the stratum basale, consists of fairly proliferating basal cells that attach to the underlying basement membrane and dermal connective tissue; cells of the basal layer differentiate to form the overlying spinous and granular cell layers [15]. The outermost epidermal layer consists of anucleate and terminally differentiated keratinocytes that form the basis of the stratum corneum, which serves as the main environmental barrier of the epidermis [15].

Within the epidermis, signs of aging are most pronounced and consistent in the DEJ. The most salient histologic change is a flattening of the DEJ, with effacement of the dermal papillae and epidermal rete pegs. The loss of the dramatic wave-like form of the epidermis results in less surface area contact between the epidermis and dermis [2]. In addition to a presumed decrease in intercommunication and nutrients, this loss of contact surface area most likely weakens the strength of epidermal attachment to the dermis and explains why the elderly are more prone to tears, abrasions, and blisters after minor trauma [16].

It is estimated that epidermal turnover rate declines between 30% and 50% between the third and eighth decades. The rate of stratum corneum replacement correspondingly increases. Not surprisingly, epidermal repair after injury slows down and growth rates for hair and nails decline as well [2].

In addition, the epidermis undergoes a thinning of 10%–50% between the ages of 30 and 80 years [17]. Not only does this thinning occur almost inevitably, but it also occurs unevenly throughout the skin resulting in variability in epidermal thickness. An increase in variability of keratinocyte size is also seen. Evidence exists that implicates aged keratinocytes as inherently predisposed to malignant transformation: these cells ultimately enter a senescent state, become resistant to apoptosis, and sometimes accumulate mutations that increase their risk for malignant transformation [2]. Studies have also shown a gradual decrease in stem cells in the epidermis with the passage of time [18]. Aged epidermal skin also displays disruptions in cohesion between keratinocytes and a decrease in adhesion of the basal layer to the underlying dermis [17].

Despite the eventual increase in variability in epidermal thickness of aged skin, the thickness of the stratum corneum seems to remain constant over the years, even though individual cell sizes within the stratum corneum increase [2]. Also age affects the transcutaneous delivery of certain medications across the stratum corneum. Hydrophilic compounds have been shown to be less well absorbed percutaneously in older skin than in younger skin while absorption of hydrophobic substances is not affected by skin aging [19]. Furthermore, as epidermal skin ages, stratum corneum lipid generation and activities of enzymes necessary for synthesis of these lipids decline. This is presumably caused by reduction in gene expression of these enzymes and/or aberrant autocrine/paracrine signaling within aging keratinocytes [20]. The decrease

in lipid composition of the stratum corneum is clinically significant because the slowed replacement of lipids in the cornified layer leads to a delay in repair and restoration of its integrity after any damaging insults [21].

Aging epidermal skin also undergoes a gradual decrease in filaggrin content. In elderly patients, this is most notable in the lower extremities where the skin tends to appear dry and scaly. In patients with ichthyosis vulgaris, similar histologic findings are noted, and the lack of filaggrin in both conditions is thought to cause the characteristic appearance of the skin [22]. In addition, the number of active melanocytes decreases by approximately 10%–20% per decade as the epidermis ages [2]. This in turn decreases melanin production and the protective barrier against ultraviolet radiation [2].

With increasing age, the immunologic barriers of the epidermis are also affected. Langerhans cells (LCs) are dendritic cells that are found in the epidermis, lymph nodes, and other organs. LCs process and present antigens to T-lymphocytes, resulting in modulation of immune responses. As the epidermis ages, the number of Langerhans cells decreases 20%–50% between early and late adulthood. The remaining LCs have been shown to demonstrate abnormal morphologies, such as fewer and shorter dendrites, as well as decreased antigen-presenting capability [23]. All of these changes in the cutaneous immune system contribute to age-associated decreases in skin immunity.

The skin's endocrine functions are also impaired as aging ensues, the most important of which is vitamin D production. Vitamin D production decreases with age [24]. Deficiency in vitamin D causes osteomalacia and has been associated with diabetes, hypertension, and malignancy [25]. Both the lack of dietary intake and insufficient sunlight exposure contribute to vitamin D deficiency. However, studies have shown that even provitamin D_3, the precursor to vitamin D_3, tends to decrease by about 75% in the skin between early and late adulthood [24]. This finding emphasizes the importance of dietary vitamin D intake [26].

Dermis

Beneath the epidermis lies the dermal layer. The dermis is connected to the epidermis through a number of specialized junctions that are responsible for mechanical integrity, cell–cell communication, and nutrient exchange between these two layers. The dermis is composed of a connective tissue milieu of collagen and ground substance, composed of glycosaminoglycans and proteoglycans. It also contains elastic fibers, cells of the immune system, fibroblasts, blood and lymphatic vessels, nerve fibers, hair follicles, and eccrine and apocrine glands. The dermis is generally divided into the superficial papillary dermis and the deeper reticular dermis. The papillary dermis houses smaller, finer, looser collagen fibrils whereas the reticular dermis is composed of larger, denser, interwoven collagen fibrils. The dermis provides the skin with its tensile strength, elasticity, and malleability—qualities that are modified in aging skin. It also holds sensory receptors, aids in thermal regulation, and protects the deeper structures from mechanical injury [15].

With aging, the dermis, which represents the thickest layer of the skin, gradually begins to lose volume. The dermal layer thins by about 20% as one approaches late adulthood, with the most significant thinning corresponding to the most sun-exposed areas [2]. Older skin demonstrates depletion of cellularity, reduction in vasculature, and an age-related loss of elastic fibers and dermal collagen [27].

In old age, the skin begins to lose its pliability resulting in an increase in rigidity that is due to biomedical changes in collagen, elastin, and the ground substance. It is estimated that collagen content decreases by 1% every year throughout adult life [28], and the remaining collagen loses its organization, becomes more compact and granular, and displays increased cross-linking [2]. The increase in cross-linking is thought to be due to a decrease in collagen synthesis, defects in collagen processing, and an increase in collagenases [17].

As early as young adulthood, elastic fibers begin to decrease in size and number. By late adulthood, as elastin is degraded, elastic fibers lose their structural integrity and become more fragmented, especially at the DEJ [29]. Similar to collagen, elastic fibers display more cross-linking and may become progressively calcified. Not only do elastic fibers undergo structural changes, but they also endure compositional changes, showing decreases in numerous components including elastin and fibrillin [2]. One of the earliest age-associated changes is a decrease in fibulin-5, an extracellular protein that provides a support base for elastic fibers. Studies have shown that decreases in fibulin-5 expression occur before other changes are observed in aging skin, suggesting that fibulin-5 might be a suitable early marker for skin aging [30].

The dermal ground substance is composed of glycosaminoglycans (GAGs), proteoglycans, and mucopolysaccharides. The content of these components, especially hyaluronic acid, decreases with age likely due to either decreased hyaluronic acid extractability or decreased hyaluronan secretion [2]. Proteoglycans bind about 1000 times their own weight in water and affect collagen deposition and size; thus, changes in the composition of these substances most likely adversely affect skin turgor and pliability [31].

The elderly exhibit decreased cutaneous inflammatory responses most likely due to decreased cytokine production and release, decreased inflammatory effectors, impaired endothelial response to inflammatory signals, and impaired endothelial capacity to induce leukocyte adhesion [2]. In the dermal vasculature of the middle-aged, blood vessel walls display mild thickening, especially in the lower extremities [32]. This is thought to be due to gravitational effects [32]. As aging progresses, vessel walls display thinning to less than one half of a young adult and this most probably results in vascular fragility. Elastin depletion and deterioration of elastic fibers in arteriole walls contribute to vascular rigidity in the skin [2]. The typical clinical appearance of elderly skin,

including pallor, decreased temperature, and decreased blood flow results from losses of vascular beds, especially in the dermal papillae and increases in distance between the existing vasculature and the epidermis [33].

Preservation of dermal vasculature is aided by epidermal VEGF that appears to induce anti-apoptotic proteins in endothelial cells; the age-associated decrease in VEGF most likely contributes to endothelial apoptosis and ongoing destruction of dermal vasculature [32]. In addition, angiogenic homeostasis is disturbed and compromised in older skin [34]. Aging gradually impairs the skin's ability to respond to heat or cold, by impairing the aged vessels' abilities to contract, dilate, or shunt [32]. The elderly are also predisposed to heat stroke and hypothermia. This may be due in part to impaired thermoregulation in addition to subcutaneous fat loss. The decrease in hair follicles and associated adnexal structures in the dermis may also be in part due to the loss of the vasculature supplying vital nutrients to these structures resulting in their subsequent degeneration and fibrosis [2].

Several observations have displayed that transdermal absorption of substances decreases with age [35], probably due to changes in both the underlying vasculature and the extracellular milieu [2]. Elderly skin has displayed prolonged time to producing a tense blister after exposure to ammonium hydroxide application, indicating a decrease in transudation rates due to injury. Several studies have also demonstrated impaired transfer of cells and solutes between the extravascular and intravascular dermal spaces [2]. Finally, dermal lymphatic vessels show age-associated gradual loss in density and size, increased rigidity, and impaired lymphatic drainage, partly due to loss of surrounding elastic fibers [32].

The biochemical changes in dermal cellularity, elastic composition and organization, ground substance composition, vasculature, and lymphatics all contribute to changes in the global mechanical functioning of skin as a whole. The skin gradually loses its elastic recovery, consistent with the deterioration of elastic network [2]. Observations using ultrasound have displayed differences in water distribution in the dermis between older and younger skin, which affects skin pliability, flexibility, and elasticity [36]. All the biochemical changes the dermis endures over time render it rigid, inflexible, and less capable or responding to stress or injury.

Hypodermis

The hypodermis, or subcutaneous tissue, is the layer below, and clearly demarcated histologically from, the dermis. The hypodermis is composed mainly of adipocytes, organized into lobules that are separated by fibrous septa. Vessels, lymphatics, and nerves run within the septa. The hypodermis provides insulation, cushioning, and protection of the underlying structures from trauma. It allows for the skin's unhindered mobility over the underlying structures and plays a major role in the cosmetic form of the face and body [17].

With the passage of time, there is a progressive atrophy and resulting redistribution of the subcutaneous fat within the hypodermis. Not only does this deterioration of adipocytes affect the skin's insulating capabilities, but its altered distribution throughout the body contributes significantly to the typical appearance and cosmesis of elderly skin [2]. Fat is depleted from certain facial areas such as the periorbital, forehead, and perioral regions, whereas there is a prominent increase in fatty tissue in other areas such as the jowls, the submental area, and the nasolabial folds. These changes in fat distribution of older skin along with gravitational effects contribute to sagging and drooping of older skin [37].

In addition to facial fat, the musculature of the face undergoes specific age-associated changes that contribute to the appearance of aged skin. Muscle cells gradually become damaged, as is signaled by the accumulation of lipofuscin, a pigment used as a marker for cellular damage. The progressive decrease in neuromuscular control, compounded with decrease in muscle cellularity, contributes to wrinkle formation [38]. Finally, facial skin appearance is also affected by bone resorption. Like the rest of the skeleton, facial bones constantly undergo remodeling, with a preponderance of resorption and bone mass loss occurring in later ages. Bone mass loss occurs primarily in the frontal, maxillary, and mandibular areas of the face. Loss of this bony scaffolding for the skin augments facial droopiness and contributes to the eradication of the distinct demarcation between the jawline and the neck that is so prevalent in younger individuals [39].

Glands and Nerves

The skin contains three types of glands. Eccrine glands are found on most of the body and produce sweat in response to acetylcholine-mediated stimuli, playing a major role in thermoregulation. Apocrine glands are also sweat-secreting glands that are located in the axillae, areolae of the nipples, and the genitoanal region and respond to adrenergic stimuli. Sebaceous glands are associated with hair follicles and produce oily sebum.

Total eccrine glands decrease by an average of 15% during adulthood in most areas of the body, and sweating is reduced by over 70% in older individuals when compared to younger subjects [2]. This is mainly caused by a decrease in sweat production per gland and contributes to the elderly predisposition to heatstroke. Apocrine glands also decrease in size and function with aging [2]. Observations have shown that sebaceous gland size and number do not seem to change with age; however, sebum production decreases significantly, possibly due to a decrease in circulating adrenal and gonadal hormones in older age [40].

Furthermore, the elderly experience significant decreases in sensory perception secondary to changes in the network of nerves contained within the skin. With age comes a decreased sensation to light touch, vibration, and corneal stimulation; special acuity; and ability to discriminate two points [41,42]. Pacinian and Meissner's corpuscles are the

end receptors responsible for pressure and light touch perception. They show greater size variability and structural abnormalities, and their density decreases to approximately one-third of their original density between the second and ninth decades of life [2].

Hair

Hair shows several changes with advancing age. By the beginning of around the age of 50, approximately half the population has at least 50% gray scalp hair, with almost every individual displaying some degree of graying; this change is due to the progressive loss of melanocytes in hair bulbs [43]. Melanocyte loss becomes evident more rapidly and dramatically in hair than in interfollicular epidermis due to the fact that melanocytes within the hair bulb proliferate and secrete melanin at maximal rates when compared to the relatively inactive epidermal melanocytes [2]. One study suggests that melanocyte loss in the epidermis might increase oxidative stress in the keratinocytes of the hair bulb, compromising their function and viability [44]. In addition, atrophy and fibrosis cause a significant decrease in hair follicles; remaining hairs are smaller in diameter, finer, and grow more slowly. Also, there is an increase in proportion of hair follicles in telogen or the resting phase [2].

Hair also exhibits changes in structure and distribution secondary to alterations in circulating hormones with advancing age. The process known as "balding" is primarily androgen dependent; thick and dark scalp hairs are gradually converted to lightly pigmented, fine, and short hairs [2]. This process tends to affect men more severely than women [2]. In women, menopause causes decreased estrogen levels and estrogen–androgen ratio, resulting in hair loss and mild facial hirsutism. Testosterone or progestin supplements that may be present in hormone replacement therapy may aggravate these changes [45].

Menopause and the Skin

Menopause is a pivotal change in a woman's life in which her development, physiology, and biological balance are altered. Estrogens play a chief role in female development and reproductive life and also impact hair and nails [2]. Menopause normally occurs in a woman's early 1950s, but may occur anytime after the age of 40 [46]. As life expectancy in the United States continues to approach 80 years [47], it is estimated that a woman will spend nearly one-third of her life in the postmenopausal state. Thus the dermatologic changes secondary to menopause deserve special mention.

In the premenopausal state, estradiol, the principal circulating estrogen, is produced by the ovaries and plays a critical role in female physiology. With the onset of menopause, estradiol levels decrease by more than 90% [48]. Progestin and androgen levels also decrease strikingly after menopause, and it is hypothesized that the decrease in estrogens and androgens and/or the decreased sensitivity of skin cells to these circulating hormones augments the age-associated changes seen in skin such as delayed wound healing, impaired barrier function, and altered immune-regulation [2].

Certain changes in the skin occur as a result of the onset of menopause rather than chronologic age alone [49]. Reduced levels of estrogens are associated with decreased skin elasticity, decreased collagen levels in the dermis, and increased skin extensibility. Also menopausal skin exhibits reduced water-holding capacity, reduced sebum levels, increased dryness, and increased fine wrinkling [2]. It is reported that menopausal women not receiving hormone replacement therapy experience more pronounced wrinkling than those receiving hormone treatment [2].

Normally, estrogen and progesterone play roles in cutaneous inflammation modulation. They also enhance proliferation of keratinocytes and collagen synthesis, decrease the activity of matrix metalloproteinases (MMPs), and increase the production of dermal ground substance [45]. Therefore, shifts in circulating levels of these hormones in menopause undoubtedly play a role in the loss of these critical components to skin's structure and function.

PHOTOAGING

As previously mentioned, skin aging is due in large part to the interaction of two processes: intrinsic skin aging and the photoaging. Photoaging is the result of chronic, lifelong exposure to ultraviolet (UV) radiation that superimposes on and compounds the effects of intrinsic aging, causing the typical physical appearance associated with old skin. Elastosis is a salient feature of photoaged skin: visible clinically as yellow, pebbly skin (Figure 76.1) and histologically as tangled deteriorated elastic fibers [2]. Even though



FIGURE 76.1 (See color insert.) Photoaging versus intrinsic aging. Consistently sun-exposed skin above the collar shows prominent wrinkling and laxity, in contrast to the sun-protected skin below the collar. (From Yaar, M. and Gilchrest, B.A., Aging of skin, in *Fitzpatrick's Dermatology in General Medicine*, 7th edn., K. Wolff et al., eds., McGraw-Hill Companies, Inc., New York, http://www.accessmedicine.com, 2008.)

fibrillin remains abundant in the elastotic substance in the deeper zones of the dermis, it becomes significantly reduced in the upper zone of the dermis, at the DEJ [50]. Also the amount of ground substance, composed of GAGs and proteoglycans, increases in photoaged skin as the amount of collagen decreases. Photodamaged skin, in contrast to sun-protected skin of the same chronologic age, exhibits a multiplication in the number of hyperplastic fibroblasts and inflammatory cells [2]. In addition, UV radiation seems to induce a pro-inflammatory state, manifested by recruitment of inflammatory cells including histiocytes, mast cells, and other mononuclear cells; in addition, sun-damaged skin observed in immunohistologic studies displays an increase in the number of dermal CD4+ T cells. This state of chronic mild inflammation may be referred to as dermatoheliosis [2]. Mild sun damage also tends to cause vascular wall thickening, whereas in significant sun-damaged skin, dermal vasculature displays vascular wall thinning and dilations (telangiectases) consistent with changes observed with skin aging [2]. Table 76.1 summarizes features of photoaged skin.

Sun damage can affect skin of all types, from fair-skinned individuals to individuals with darker skin with a history of significant sun exposure. The manifestation and severity of UV-induced skin changes vary from individual to individual, suggesting that photodamage depends on the susceptibility and repair capacity of each individual's skin [2]. Although UV damage tends to affect the same areas including the face, neck, and upper extremities, it tends to manifest differently in skin phototypes I and II than in darker skin types. Lighter skin tends to become more atrophic and dysplastic, exhibiting more actinic keratoses and epidermal malignancies, whereas darker skin tends to display hypertrophic changes that manifest as furrowing, lentigines, and coarseness (Figure 76.2) [2].

Photoaging affects skin of various ethnicities, including Caucasians, Asians, Hispanics, and Africans, but skin changes induced by photoaging are manifested differently between these ethnicities due to inherent differences in UV defense mechanisms [2]. In Asians, Hispanics, and Africans, melanin plays a critical role in UV protection, whereas in whites, stratum corneum thickening plays a more significant role in defense than melanin [52]. Epidermis with high melanin content provides a greater sun protection factor compared to epidermis with low melanin content. One study reported that epidermis from darker individuals transmitted to the dermis approximately 6% of UVB and 18% of UVA light, compared to epidermis from light individuals that transmitted approximately 30% of UVB and more than 55% of UVA light [53].

In Asian skin, photodamage manifests clinically as solar lentigines and mottled pigmentation. Melasma in Asians is considered a clinical sign of photoaging [54]. Similar to lighter skin patients, the aging Asians present clinically with moderate to severe wrinkling, but only in the sixth decade of life and only in individuals who spent significant time in the sun [55]. Finally, lighter-skinned Hispanics and Africans may show clinical signs of photodamage, including fine wrinkles and mottled pigmentation, earlier in life than darker-skinned individuals of the same ethnicity [54].

TABLE 76.1
Clinical and Histologic Traits of Photodamaged Skin

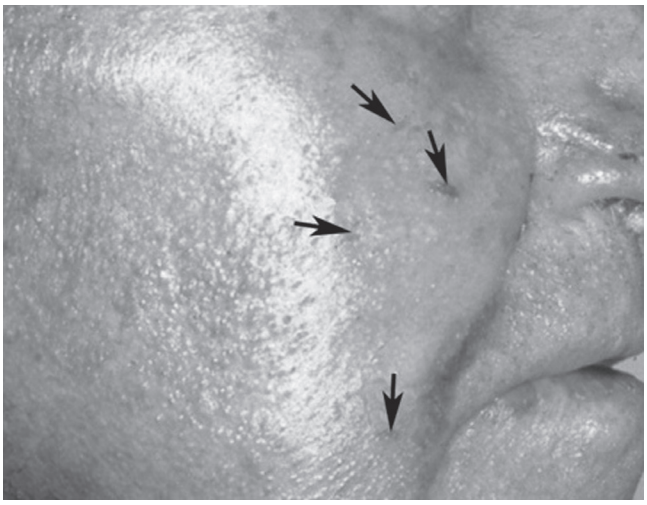
Clinical	Histologic Findings
Xerosis	Increased compaction of stratum corneum, increased thickness of granular cell layer, reduced epidermal thickness, reduced epidermal mucin content
Actinic keratoses	Partial thickness atypia, loss of orderly, progressive keratinocyte maturation; irregular epidermal hyperplasia and/or hypoplasia
Irregular pigmentation	
Solar lentigines	Elongation of epidermal rete ridges; increases in number and melanization of melanocytes
Idiopathic guttate hypomelanosis	Reduced number of melanocytes
Diffuse irreversible hyperpigmentation (bronzing)	Increased number of DOPA-positive melanocytes and increased melanin content per unit area and increased number of dermal melanophages
Wrinkling	
Fine surface lines	No histologic changes detected
Deep furrows	Contraction of septae in the subcutaneous fat
Stellate pseudoscars	Histologically same as a scar; absence of epidermal pigmentation, altered dermal collagen bundles
Solar elastosis	Nodular aggregations of fibrous to amorphous material in the papillary dermis
Telangiectasia	Ectatic dermal vessels often with atrophic walls
Venous lake	Single dilated vascular channel often with atrophic walls
Purpura	Extravasated erythrocytes and increased perivascular inflammation
Actinic comedones	Dilated pilosebaceous follicular orifice
Sebaceous hyperplasia	Hyperplasia of sebaceous glands

Source: Yaar, M. and Gilchrest, B.A., Aging of skin, in *Fitzpatrick's Dermatology in General Medicine*, 7th edn., K. Wolff, et al., eds., McGraw-Hill Companies, Inc., New York, http://www.accessmedicine.com, 2008.

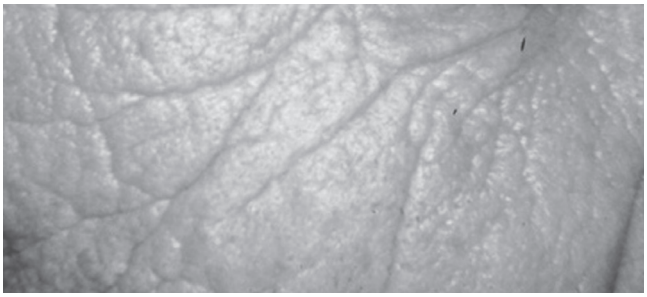
Mechanisms of Photoaging

Signaling

Photoaging employs distinct molecular mechanisms from those involved in intrinsic aging of the skin. One such mechanism involves the upregulation of membrane and nuclear



(A)



(B)

FIGURE 76.2 (See color insert.) (A) Photoaging. The skin of a lighter individual displays atrophic photoaging with relatively few wrinkles but with several actinic keratoses (arrows). (B) Photoaging. The skin of a darker individual displays hypertrophic aging with deep wrinkles, furrowing, and coarseness. (From Yaar, M., The chronic effects of ultraviolet radiation on the skin: Photoaging, in *Principles and Practice of Photodermatology*, H. Lim, ed., Taylor & Francis Group LLC, New York, p. 99, 2007.)

signaling. Under circumstances of oxidative stress, reactive oxygen species (ROS) inhibit phosphatases that normally retain cell surface receptors in an inactive state [56]. UV radiation, partly by generating these ROS, causes the activation of cell surface receptors that results in an intracellular signaling cascade culminating in the activation of the nuclear transcription complex AP-1 [57]. AP-1 activity serves to decrease collagen synthesis through a number of mechanisms. First, AP-1 inhibits transforming growth factor β (TGFβ), a cytokine whose function is to stimulate collagen gene expression. This inhibition of TGFβ impairs the production of dermal collagens I and III [57]. Next, AP-1 reduces the number of TGFβ receptors, thereby decreasing collagen synthesis even further [58]. AP-1 also reduces collagen synthesis by interfering with the retinoic acid functions in the skin [2]. Finally, AP-1 augments activity of enzymes that degrade extracellular matrix, including MMP-1 (collagenase), MMP-3 (stromelysin-1), and MMP-9 (92-kd gelatinase) [57]. UV light also induces the degradation of extracellular matrix by activating the nuclear factor kappa B (NFκB) transcription factor that among other actions increases the levels of MMP-1 and MMP-9, thereby increasing extracellular matrix degradation [59]. This process is further aggravated by the release of MMP-8 by neutrophils that infiltrate into UV-irradiated skin [60]. Notably, the activity of tissue inhibitors of metalloproteinases is increased concurrently; however, it is presumed that their upregulation is not sufficient to protect the skin from damage to collagen by UV light [61]. Interestingly, collagen degradation due to UV damage tends to be somewhat incomplete, yielding debris of partially degraded collagen fragments in the dermis [57]. It has been shown that the accumulation of partially degraded collagen fragments inhibits new collagen synthesis, exacerbating the generalized decrease in collagen synthesis seen in UV-irradiated skin [62].

Mitochondrial Damage

Mitochondria are the major energy-producing cellular organelles in eukaryotic cells. Mitochondria use oxygen to generate energy in the form of adenosine triphosphate (ATP). This function predisposes these organelles to constant oxidative stress through the production ROS. Despite the presence of antioxidant systems in mitochondria, oxidative damage is still a major cause of damage to mitochondrial DNA (mtDNA). Also, due to lack of repair capacity, mtDNA accumulates mutations at a significantly higher rate than nuclear DNA [2]. UV radiation seems to exacerbate mtDNA mutations, as photodamaged skin seems to show higher rates of mtDNA mutation than sun-protected skin [63–66]. Damage to mtDNA results in disruption of mitochondria, further ROS accumulation, and reduced ATP production in the cell. Impaired mitochondrial function, in turn, seems to correlate with increased MMP levels, further intensifying collagen breakdown and worsening skin aging [63–66].

Protein Oxidation (Smoking)

Smoking plays a major role in skin aging by directly affecting the cells of the dermis and epidermis and intensifying effects of UV-associated changes in the skin. There is a significant increase in wrinkling and discoloration of the skin due to smoking, with the severity of these changes correlating directly with the amount of cigarettes smoked [67,68]. In general, features of photoaged skin present more severely in smokers than in nonsmokers with comparable risk factors [69]. Smokers' skin displays histologic features similar to that of photoaged skin. Elastic fiber fragmentation seen in photodamaged dermis is found to penetrate deeper in the dermis of smokers [70]. Smoking induces a pro-inflammatory state, recruiting neutrophils with increased elastase activity that is presumed to contribute to the deep dermal elastosis in smokers' skin [71]. In addition, the elastosis is exacerbated by constant ischemia and oxidative stress caused by smoking [67,68]. Smoking also seems to decrease the water content and estrogen levels in the skin, possibly contributing to dryness and atrophy [68].

Additionally, smoking impairs wound healing and increases the risk of cutaneous neoplasia [72].

NEOPLASIA

With advancing age, the incidence of benign and malignant neoplasia increases in nearly every organ system, including the skin. Certain benign growths are characteristically present in nearly every adult over the age of 65, and these include acrochordons (skin tags), cherry angiomas, lentigines (sun spots), and seborrheic keratoses [2].

Seborrheic keratoses are benign lesions that may be considered biomarkers of intrinsic skin aging as their numbers increase with aging, regardless of sun exposure [73]. Their appearance varies greatly in size and color, but they often present as flat, warty lesions, appearing to be "stuck onto" the skin's surface. Seborrheic keratoses result from the proliferation of keratinocytes and are not considered premalignant lesions [74]. The pathogenesis of these benign growths is not completely understood.

As humans age, there is an exponential increase in the incidence of malignant cutaneous neoplasms, including melanomas [75]. Over a lifetime, human skin cells are repeatedly exposed to oxidative stress and carcinogens in addition to experiencing normal cell turnover and replication; these factors in combination predispose DNA to mutation [2]. It has been shown that with aging, there is a gradual decrease in cells' ability to repair mutated DNA [76] and a decrease in the immune system's capacity to detect and destroy neoplastic cells [77].

Sun exposure is the major factor in the pathogenesis of skin cancer. Cumulative exposure to UV radiation over a lifetime, especially in fair-skinned people, predisposes to the development of actinic keratosis squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Actinic keratoses are premalignant lesions that may go on to develop into SCC [78]. In addition, total cumulative sun exposure, as well as a history of sporadic, intense sunburns, increases the risk of development of malignant melanoma [79]. The etiology causing this difference in the pathogenesis of malignant melanoma when compared to non-melanoma skin cancer is not completely understood.

With increasing age, there is an increased incidence of all types of melanoma (Figure 76.3) [75]. The incidence of lentigo maligna melanoma is particularly increased in individuals 60 years or over [80]. As a whole, melanomas in the older population are usually thicker than those in younger adults. This is thought to be due to the lack of proper skin examinations, poor vision, and other medical problems, including those that can compromise the elderly individual's immunologic surveillance [2]. Also, men over the age of 50 have an increased risk of mortality from melanoma in comparison to women or younger men, likely due to late diagnosis [2]. Finally, there is an increased incidence of Merkel cell carcinoma, a rare tumor that develops from cells of neuroendocrine lineage [82,83]. Incidence of angiosarcoma, a rapidly growing vascular tumor, of the head and neck is also increased with age [84]. Angiosarcoma is an aggressive malignancy that metastasizes early, usually causing death within 2 years of diagnosis [85].

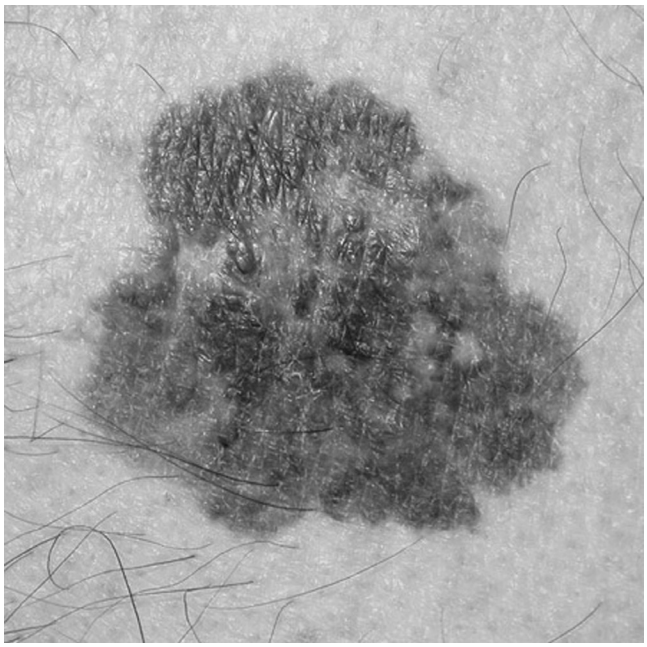


FIGURE 76.3 (See color insert.) Melanoma, with classic asymmetry, irregular borders, blotchy color, large diameter, and central elevation. (From Paek, S.C. et al., Cutaneous melanoma, in *Fitzpatrick's Dermatology in General Medicine*, 7th edn., K. Wolff, et al., eds., McGraw-Hill Companies, Inc., New York, http://www.accessmedicine.com, 2008.)

INFECTIONS

Skin infections caused by bacteria, viruses, or fungi can occur in any age group; however, special considerations must be acknowledged when dealing with the elderly population. Impetigo is most commonly associated with the pediatric age group; however, it must be noted that impetigo and follicultis do present in the elderly population. Impetigo is typically caused by *staphylococci* and should be cultured and treated with appropriate systemic antibiotics [86].

Cellulitis is an infection that involves the dermis and subcutaneous tissue and may be caused by *streptococci* or *staphylococci*. Traits that are more prevalent in the elderly population and predispose this age group to cellulitic infections include chronic lower extremity edema, poor circulation, chronic fungal infections of the feet (tinea pedis), surgical wounds, and diabetes mellitus [2].

Methicillin-resistant *Staphylococcus aureus* (MRSA) carriage is extremely prevalent in the age group of 80 or above [87], and infection by MRSA can present as impetigo or cellulitis [2]. Hence, practitioners should be aware of this

pathogen as a causative agent when dealing with skin and soft-tissue infections in this age group.

The major viral cutaneous infection that affects the elderly is caused by reactivation of the varicella-zoster virus, also known as shingles. The incidence of herpes zoster peaks at age 75 [2], and post-herpetic neuralgia is estimated to occur in 40% of adults aged from 60 to 69 years and in 50% of individuals over the age of 70 and can be debilitating [86]. The reason for the increased incidence of post-herpetic neauralgia is not entirely clear; however, impaired cellular immunity and wound healing might be implicated [2].

Recurrent or uncontrollable *Candida albicans* infections in the elderly population may represent a more serious underlying disease process such as a malignancy, poorly controlled diabetes, or severe immunosuppression [87]. Fungal nail infection (onychomycosis) is present in 40% of individuals greater than the age of 60, and tinea pedis is present in about 80%, sometimes so severe and ulcerated that it can predispose to more serious consequences like bacterial cellulitis [88].

CONCLUSION

Although much research is still needed to further understand the biological mechanisms involved in skin aging, large advances have been made in understanding this process. Skin aging is believed to be a result of two mechanisms: the presumably inevitable intrinsic aging and the superimposed effects of UV photoaging. As the proportion of aging population continues to increase, it is essential for practitioners to be able to understand and recognize the normal and expected changes of skin aging and, in doing so, be able to differentiate abnormal findings that may need further investigation.

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77 Sun and the Skin

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CONTENTS

Electromagnetic Radiation from the Sun 965
Physics of UV 965
Physiologic Reaction to UVR, VL, and IR Radiation 966
Inflammation 966
Skin Pigmentation 966
Immunosuppression 967
UV-Induced DNA Damage and Carcinogenesis 967
Photoaging 968
Vitamin D Synthesis 968
Pathologic Reaction to Light 969
Immunologically Mediated Photodermatoses 969
Inherited Photodermatoses 969
Phototoxicity and Photoallergy 969
Photoaggravated Dermatologic Conditions 969
Photoprotection 970
Indoor Tanning 972
Summary 972
References 973

Exposure to ultraviolet radiation (UVR) from the sun and artificial ultraviolet (UV) sources is now recognized to be associated with the development of premature skin aging and skin cancer [1,2]. Basal cell carcinoma (BCC) accounts for 75% of all non-melanoma skin cancer (NMSC) and is the most common malignant tumor in white populations [3]. Squamous cell carcinoma (SCC) comprises the majority of remaining cases. Although BCC is more prevalent, SCC has a higher mortality rate due to metastasis. It has been estimated that 84% of BCC and 74% of SCC are found at chronically sun-exposed sites [4]. Compared to the NMSC, melanoma is much less common, but it accounts for the vast majority of all skin cancer-related fatalities due to its metastatic rate and resistance to chemotherapy and radiation [5].

This chapter will provide an overview on the physics of UVR, followed by discussions of the physiologic and pathologic relationships between sunlight and skin. The pathologic reaction to UVR includes NMSC, melanoma, immunologically mediated photodermatoses, inherited photodermatoses, phototoxic and photoallergic reactions, as well as photoaggravated dermatologic conditions. Lastly, methods of effective photoprotection will be discussed.

ELECTROMAGNETIC RADIATION FROM THE SUN

Sunlight is a form of electromagnetic radiation; as it reaches the surface of the earth, it comprises the UV, visible light (VL), and infrared (IR) spectra, with UVR being approximately 6.8% of solar radiation [6]. UVR is further divided according to wavelength: UVC (200–290 nm), UVB (290–320 nm), UVA II (320–340 nm), and UVA I (340–400 nm). UVA accounts for 95%–98% of the UVR reaching the earth, while UVB accounts for the rest. UVC is largely absorbed by stratospheric ozone [7]. Depletion of the ozone layer has led to an increase in UV transmission to the earth's surface [8]. Other factors such as time, season, latitude, altitude, presence of fog, clouds, water, snow, sand, concrete, and even air pollution can influence one's exposure to UVR [9].

PHYSICS OF UV

Energy in UVR is packaged as photons. According to Planck's theory, the amount of energy in a photon is directly proportional to the frequency of the radiation and inversely proportional to the wavelength. As a result, radiation of shorter wavelength has

greater energy per photon. The depth of penetration, however, is proportional to the wavelength. Based on these principles, UVA has lower energy but is able to reach deeper into the skin when compared with UVB [10]. Although UVB is 1000 times more biologically active and has more energy compared with UVA, the biologic effect of UVA is significant for two reasons. First, the proportion of UVA to UVB in sunlight as it reaches the surface of the earth is approximately 20:1. Second, because UVA has greater ability to penetrate through cloud cover, it has a more constant presence throughout the daylight hours compared to UVB [11].

Biologic effects occur only when photons of UVR and VL are absorbed by skin chromophores, which are molecules that absorb electromagnetic radiation. Endogenous chromophores in the skin include water, hemoglobin, melanin, protein, pyrimidine and purine, urocanic acids, and 7-dehydrocholesterol [12]. Exogenous compounds can also serve as chromophores in the skin, producing phototoxic or photoallergic reactions. Absorption of photons by chromophores can induce biochemical responses involving signal transduction, ultimately altering levels of transcription factors, synthesis of proteins, and secretion of cytokines and inflammatory factors, all of which contribute to the physiologic and pathologic cutaneous changes associated with sun exposure [10].

TABLE 77.1
Major Properties and Physiologic Effects of UVR, VL, and IR

	Wavelength (nm)	% in Solar Radiation	Physiologic Effects
UVR[a]	200–400	6.8	Inflammation, immediate and PPD, delayed tanning, vitamin D synthesis, immunosuppression, DNA damage and repair, photoaging, photocarcinogenesis
VL	400–700	38.9	Immediate and PPD in darker skin color
IR	700–3000	54.3	Photoaging, photocarcinogenesis

[a] Further divided into UVC 200–290 nm, UVB 290–320 nm, UVA II 320–340 nm, UVA I 340–400 nm.

PHYSIOLOGIC REACTION TO UVR, VL, AND IR RADIATION

Physiologic reactions upon UVR exposure can be conveniently divided into acute and chronic effects, which represent a continuum. Acute effects include inflammation (sunburn), pigmentary changes, vitamin D synthesis, immunosuppression, and DNA damage and repair, while chronic changes include photoaging and photocarcinogenesis.

While the effects of UV have been extensively studied, recent data have shown that VL and IR also have biologic effects (Table 77.1). VL, used for general illumination purposes, has been demonstrated to induce pigmentation in dark-skinned, but not in light-skinned individuals [13]. IR, which is responsible for the warm sensation that one gets with sun exposure, is involved in carcinogenesis and can upregulate metalloproteinases responsible for skin aging [6].

Inflammation

Sunburn, an inflammatory reaction with increased vascular permeability and blood flow, is characterized by erythema (redness), warmth, pain, and swelling and is the most well-recognized acute cutaneous response to UVR; it peaks 24 h after sun exposure. UVB is the main contributor of sunburn, with a minor contribution from UVA II. Mast cells contain mediators such as histamine and tumor necrosis factor, which are important in the development of erythema [14]. Other pro-inflammatory cytokines, chemokines, complement, and adhesions molecules are also upregulated after UVR exposure [7]. Neutrophils and T lymphocytes appear as early as 3 h after UVB exposure, further contributing to the inflammatory reaction [15].

TABLE 77.2
Skin Types

Skin Types[a]	Skin Reaction after Sun Exposure/Skin Phenotypes
I	Always burn, never tan
II	Always burn, sometimes tan
III	Sometimes burn, always tan
IV	Never burn, always tan
V	Moderately pigmented skin
VI	Darkly pigmented skin

[a] Skin types I–IV determined by history. V and VI determined by exam.

The degree of inflammation and erythema produced is determined by the total dose of UVR energy received. Since UVR energy is inversely related to its wavelength, the erythemal effect of UVR rapidly decreases with increasing wavelength. This explains how the small amount of UVB reaching the earth's surface actually accounts for the majority of solar radiation erythemal effect [7]. An individual's ability to tan or burn constitutes his/her skin type (Table 77.2). Individuals with skin type I have a higher skin cancer risk than individuals with skin type VI.

Skin Pigmentation

Sun exposure induces pigmentary alterations, which include immediate pigment darkening (IPD), persistent pigment darkening (PPD), and delayed tanning. IPD is a grayish color induced by UVA and VL; it occurs immediately after exposure and resolves in 10–20 min. IPD blends into PPD, which is noticeable within 10–20 min of

exposure and lasts for 2 h. Both IPD and PPD are due to photooxidation of existing melanin and redistribution of existing melanosomes to more peripheral melanocyte dendrites; there is no new melanin synthesis. Delayed tanning, by contrast, occurs days after UV exposure. It is the result of new melanin production via enhanced activity in tyrosinase, the rate-limiting enzyme in melanogenesis, as well as an increase in the number and activity of melanocytes. There are also increases in the number and size of melanosomes. Neither IPD nor delayed tanning demonstrates effective photoprotection [7].

UVR also stimulates melanin-stimulating hormone (α-MSH) locally from keratinocytes and regulates the expression of its receptor, melanocortin 1 receptor (MC1R), on melanocytes. The binding of α-MSH and MC1R activates the cAMP pathway and regulates the synthesis of melanin [16]. Furthermore, the paracrine secretion of α-MSH plays a critical role in local inflammation and immunosuppression (see UV-induced DNA damage and carcinogenesis) [17]. Polymorphism of MC1R has been associated with the risk of NMSC and melanoma [18,19].

Immunosuppression

UVA and UVB both cause immunosuppression in humans. The relationship between immunosuppression and the development of skin cancer is further highlighted by the frequent development of NMSC and melanoma in organ transplant patients who are iatrogenically immunosuppressed [20–22].

UVR causes immunosuppression through downregulation of cell-mediated immunity. The balance between CD4+ Th1 and Th2 subtypes is regulated delicately by various cytokines. A vigorous Th1 response is required for destruction of tumor cells, while a Th2 response has been linked to tolerance. It has been shown that patients with progressive melanoma elicit a Th2 response, while those who respond to therapy show a Th1 immune response [23]. UVR also generates regulatory T cells that suppress the immune response in an antigen-specific manner [24].

Langerhans cells (LCs) are dendritic cells in the skin that play a critical role in the induction and maintenance of specific T-cell immunity. Alteration of the number and the function of LCs will therefore change host immune response. It has been shown that UVA irradiation reduced the ability of LCs to stimulate lymphocytes, and UVB irradiation, even at low doses, can deplete human epidermal LCs [11].

A further immunosuppressive effect of UVR is that of the isomerization of urocanic acid. Urocanic acid normally exists in its *trans* isoform in the stratum corneum. With UVB irradiation, it is transferred to its *cis* isomer, which has an immunosuppressive property [25]. The complex nature of UVR-induced immunosuppression is compounded by the ability of UVR to induce various growth factors and cytokines. For example, platelet-derived growth factor is thought to be pivotal in both UVB- and psoralen-UVA (PUVA)-induced immunosuppression [26].

UV-Induced DNA Damage and Carcinogenesis

The relationship between solar exposure and NMSC and to a lesser extent, melanoma, has long been established by extensive epidemiologic studies. There are considerable biologic differences between the two common types of NMSC, SCC and BCC. While SCC is clearly associated with cumulative sun exposure, the association between BCC and the amount or timing of personal sun exposure appears to be more complex. It has been shown that infrequent, intense, and intermittent sun exposure before the age of 20 years increases the risk of BCC more than if a similar dose was delivered more continuously over the same period [27,28].

The molecular events involving the progression from UVR-induced DNA damage to the development of NMSC and melanoma are complex. The details of such pathways are beyond the scope of the current discussion. Only important players will be discussed.

UVA radiation, while not a major contributor to sunburn, has now been demonstrated to play a role in the pathogenesis of skin cancer [29]. UVA is capable of exciting endogenous chromophores and generating reactive oxygen species (ROS), resulting in the formation of oxidative products. By producing singlet oxygen, UVA causes oxidative modifications at guanine bases, leading to generation of a premutagenic compound, 7, 8-dihydro-8-oxoguanine (8-oxoG) [30]. Analysis has shown that G → A and G → T are the major mutations induced by UVA [31].

DNA is believed to be a direct chromophore for UVB radiation [32]. UVR photons absorbed by DNA can produce excited electron states, leading to direct DNA damage, or they can generate toxic by-products, leading to indirect DNA damage. After DNA is exposed to UVB, a photochemical reaction occurs between pyrimidine dimers, leading to formation of two specific photoproducts. If a covalent binding between C5 and C6 carbon atoms is formed, cyclobutane pyrimidine dimers (CPDs) are produced. On the other hand, a pyrimidine 6–4 pyrimidone photoproduct is formed if the covalent binding occurs between C6 and C4 positions [33]. In a perfect world, the DNA repair machinery recognizes and corrects these UVB-induced photoproducts. However, DNA repair is not error proof. Incorrect repair of the damaged DNA leads to mutations in the epidermal cells, thus initiating the development of cancer. When UVB-induced CPDs and pyrimidine 6–4 pyrimidone photoproducts are incorrectly repaired, the signature mutations formed are C → T and CC → TT [30]. More recently, it was suggested that UVA may also trigger DNA damage via CPD formation similar to that induced by UVB [34]. As one ages, the skin also becomes less effective at removing CPDs [35].

UVB irradiation also induces early epidermal apoptosis in the form of highly characteristic sunburn cells (SBCs). These apoptotic SBCs are thought to represent a way to eliminate keratinocytes that have failed to adequately repair DNA.

The *p53* gene itself is also a direct target of UV radiation. It has been postulated that UVR-induced *p53* mutations result in a decreased number of SBCs, which gives rise to a

selection bias toward clonal expansion of *p53*-mutated cell lines, which then progress to various skin cancers [36]. Clones of mutant cells carrying *p53* mutations with UVR signature mutations have been found in chronically UVR-exposed skin, BCC, actinic keratosis (AK), SCC, and to a lesser degree in melanoma [36–38]. In the situation where DNA damage is sustained, *p53* triggers both intrinsic and extrinsic apoptotic pathways [39]. In addition to *p53* mutations, mutations in the *PTCH* gene have been found in 30%–40% of sporadic BCC.

While certain UV-induced mutations are shared between NMSC and melanoma, it is important to remember that melanocytes are fundamentally different from keratinocytes. When compared with keratinocytes, melanocytes are highly differentiated cells with poor proliferation ability; they live much longer and are more resistant to apoptosis [40]. The longevity of melanocytes increases their chance to acquire and accumulate mutations over time due to repetitive sun exposure. The presence of a few severe sunburns during childhood or early adolescence is thought to cause mutations that represent a first hit in melanocytes. With repetitive sun exposure, further hits accumulate and result in melanoma formation [41,42].

Although details of the response of melanocytes to UV radiation are far from being completely understood, it is now well accepted that this response is mediated to a large extent by a network of paracrine factors that is activated upon UV exposure [43]. While melanocytes provide photoprotection for keratinocytes by donating melanin-containing melanosomes, keratinocytes synthesize biochemical mediators that stimulate melanin synthesis and ensure the survival and genomic stability of melanocytes following UV exposure.

The search for common melanoma susceptibility genes is ongoing. One of the most susceptible genes for melanoma, especially familial melanoma, is *CDKN2A*, which encodes for two different but related proteins regulating cell cycle checkpoints [44].

Photoaging

Photoaging, defined as accelerated aging from UVR exposure, is distinct from intrinsic chronological aging. However, the two may share similar molecular events. UVA is a greater contributor to photoaging than UVB, because of its ability to penetrate deeper into the dermis and its greater abundance in sunlight [45]. Photoaging is clinically characterized by deeply wrinkled, inelastic, leathery skin with telangiectasias and irregular pigmentation [7].

UVR activates multiple signal transduction pathways, which converge to stimulate the transcription factor activator protein-1 (AP-1). Matrix metalloproteinase (MMP) and procollagen expressions are regulated by AP-1 [46]. MMPs are a family of zinc-dependent endopeptidases that degrade structural proteins such as collagen and elastin. UVR-induced production of MMPs thus participates in photoaging via matrix and basement membrane degradation [47,48]. UV-enhanced matrix degradation is also accompanied by decreased collagen production [46].

Vitamin D Synthesis

Not all UVR-induced molecular events are detrimental. One such beneficial effect of UV exposure is the synthesis of vitamin D, a fat-soluble vitamin. The most well-documented role of vitamin D in maintaining human health is its role in regulating calcium and bone homeostasis. More recently, low vitamin D has also been implicated, by epidemiologic studies, in unfavorable outcome in cardiovascular diseases, autoimmune diseases, neurological diseases, cancer, and overall mortality [49–54].

Vitamin D can be obtained through three sources: exogenous acquisition of vitamin D through dietary intake, ingestion of oral supplements, and endogenous vitamin D synthesis induced by UVR in the skin. Sources of dietary vitamin D include egg yolk, cod-liver oil, as well as oily saltwater fish such as salmon, sardines, tuna, and mackerel. Milk, yogurt, orange juice, and many other food products are also fortified with vitamin D in the United States and other countries [55].

The action spectrum of vitamin D synthesis in the skin falls in the UVB range. After UVB exposure of the skin, 7-dehydrocholesterol (provitamin D_3) is converted to previtamin D_3 at the basal and suprabasal layer of the epidermis [56]. Pre-vitamin D_3 then undergoes nonenzymatic isomerization to form vitamin D_3 (cholecalciferol). Vitamin D_3 enters the circulation and is carried by vitamin D-binding protein to the liver where it is hydroxylated by 25-hydroxylase to 25-hydroxyvitamin D [25(OH)D], which is the major measurable circulating form. 25(OH)D is transported to the kidney by vitamin D-binding protein, where it is further hydroxylated by 1α-hydroxylase to its active form, 1,25-dihydroxyvitamin D [1α, $25(OH)_2D$]. Conversion of 25(OH)D to 1α, $25(OH)_2D$ also occurs at other sites of the body, although these are not thought to contribute significantly [57]. Intrinsic skin factors also influence vitamin D synthesis: aged skin synthesizes vitamin D less efficiently than younger skin, and darker skin synthesizes less vitamin D than lighter skin due to the more abundant presence of UV-absorbing melanin [58,59].

The serum level of 25(OH)D is used to assess overall vitamin D status. In November 2010, the Institute of Medicine (IOM) of the U.S. Academies recommended a daily vitamin D intake of 400–800 IU, based on the age of the individual (Table 77.3; [60]). This recommendation was made according to data on skeletal health only, as the IOM judged

TABLE 77.3
Recommended Dietary Vitamin D Intake Based on Age

Age (Year)	Recommended Daily Vitamin D Intake (IU/Day)
0–1	400
1–70[a]	600
>71	800

[a] Including pregnant and lactating women.

that extra-skeletal data were inconsistent and insufficient for making recommendations, and was based on the assumption of minimal or no sun exposure. IOM further recommended that serum 25(OH)D levels of 20 ng/mL (50 nmol/L) be considered sufficient.

Recently, concerns regarding the effects of regular sunscreen use on decreased vitamin D levels have been raised. A 2009 literature review on all published evidence regarding this matter showed that while sunscreen use under strictly controlled conditions may reduce vitamin D production significantly, normal use of sunscreen does not result in vitamin D insufficiency [61]. This could be explained by the fact that in actual use, individuals apply sunscreens at concentrations lower than that used in SPF testing (2 mg/cm^2) (see the section on Photoprotection).

Because of the carcinogenic effect of UVR on skin, and the variability of UVR exposure with environmental and intrinsic skin factors, UVR exposure is an unreliable and risky method for obtaining vitamin D [62,63]. The readily available dietary sources and vitamin D supplements make oral intake a much safer and reliable method for obtaining a sufficient amount of vitamin D.

PATHOLOGIC REACTION TO LIGHT

In addition to the carcinogenesis discussed earlier, UVR also results in other pathologic conditions. These conditions can be divided into immunologically mediated photodermatoses, inherited photodermatoses, phototoxic reactions, photoallergic reactions, and photoaggravated dermatologic conditions. Correct diagnoses of these conditions require detailed history, physical examination, laboratory workup, phototesting, and possible photopatch testing. Referral to a dermatologist is often necessary for diagnosis and management. Details of the evaluation of a photosensitive patient are beyond the scope of the current discussion but are reviewed elsewhere [64]. Each of the pathologic reactions to light will be briefly discussed here. Photoprotection is important in all photosensitive patients.

Immunologically Mediated Photodermatoses

This group of diseases with wide clinical presentations is thought to be mediated by the immune system. However, the exact molecule responsible for initiation of the photochemical reactions has not been completely elucidated. These diseases, their frequency, age of onset, and action spectrum are summarized in Table 77.4.

TABLE 77.4
Immunologically Mediated Photodermatoses

Diseases	Frequency	Age Onset	Sex	Action Spectrum
Polymorphous light eruption (PMLE)	Most common	Adult	Female > male	UVA, UVB, rarely VL
Actinic prurigo	Common in Native American	Childhood	Female > male	UVA, UVB
Chronic actinic dermatitis	Uncommon	Adult	Male > female	UVA, UVB, rarely VL
Solar urticaria	Rare	Adult	Female > male	UVA, UVB, VL. May change as the disease progresses
Hydroa vacciniforme	Rare	Childhood	Male > female	UVA

Inherited Photodermatoses

Inherited photodermatoses usually have an early onset of photosensitivity due to defect in DNA repair mechanism or chromosomal abnormality. This group includes xeroderma pigmentosum, Cockayne syndrome, trichothiodystrophy, Bloom syndrome, and Rothmund–Thomson syndrome [64]. Kindler syndrome, a syndrome with combined features of photosensitivity and epidermolysis bullosa, shows distinct mutation in an actin cytoskeleton-associated protein. The photosensitivity in patients with Kindler syndrome tends to improve with age [65].

Phototoxicity and Photoallergy

Photosensitivities can be induced by endogenous or exogenous chemicals. Exogenous photosensitizers can be from agents either topically applied or systemically absorbed. PUVA therapy, which is used to treat various dermatoses, takes advantage of the phototoxicity of an exogenous agent, psoralen. Phototoxic reactions present as a sunburn-like reaction due to direct tissue injury caused by the phototoxic agent and radiation. This reaction can occur after the first exposure and often happens within minutes to hours after exposure. A photoallergic reaction, by contrast, represents an eczematous reaction that is mediated by type IV-delayed hypersensitivity reaction. It occurs only in previously sensitized individuals, hence does not happen after first exposure. Time from reexposure to onset of eruption ranges from 24 to 48 h [66]. Numerous topical and systemic agents can cause phototoxic and photoallergic reactions. A partial list includes diuretics (thiazides, furosemide), tetracyclines (especially doxycycline), NSAIDs, quinolones, and antiarrhythmics (amiodarone, quinidine). A comprehensive list can be found elsewhere [64,66]. Ironically, some sunscreen ingredients can elicit photoallergic responses (see the section on Photoprotection).

Photoaggravated Dermatologic Conditions

The heterogeneous group of disorders mentioned in this section shares one common feature: precipitation or exacerbation by exposure to UVR. These, however, are not true

photodermatoses as they do develop without exposure to UVR. Photoaggravated dermatoses include acne, atopic dermatitis, carcinoid syndrome, cutaneous T-cell lymphoma, dermatomyositis, disseminated superficial actinic porokeratosis, erythema multiforme, familial benign pemphigus, granuloma annulare, Darier disease, lichen planus, lupus erythematosus, pellagra, pemphigus foliaceus, pemphigus erythematosus, pityriasis rubra pilaris, psoriasis, reticulate erythematous mucinosis, rosacea, seborrheic dermatitis, Grover disease, and viral infection such as herpes simplex [64,67].

PHOTOPROTECTION

Because of the previously mentioned deleterious effects of UV exposure, it is crucial to modify one's behavior to minimize damage from UV radiation. This behavior modification can potentially have a tremendous impact on health care cost and morbidity and mortality relating to skin cancer.

One of the most popular methods of photoprotection when engaged in outdoor activities is sunscreen. Ideal sunscreens should not only provide protection from both UVA and UVB radiation but also maintain this protection during the entire period of exposure to the sun. In the United States, sunscreens are regulated by the Food and Drug Administration (FDA) as over-the-counter drugs. Sunscreen formulations in different countries vary due to regulations and approval of UV filters. In general, because of the availability of more UV filters, sunscreen manufacturers from Europe, Australia, and Japan have more options for UV filters compared with manufacturers in the United States. Only the commonly found FDA-approved sunscreen filters will be discussed.

Sunscreen filters can be divided into two groups: inorganic (physical) filters and organic (chemical) filters. Inorganic filters work by both scattering and absorbing UVR. There are two FDA-approved inorganic filters, titanium dioxide and zinc oxide. Inorganic filters offer several advantages. First, both are photostable, producing a predictable degree of photoprotection after UV exposure. Second, both have low allergic potential, therefore, low rates of sensitization. Furthermore, the newer technology of incorporating nanosized (<100 nm in diameter) particles has contributed tremendously to the cosmetic acceptability of these inorganic sunscreens compared with early-generation products [8]. While nanoparticle-contatining sunscreens are safe to use on normal skin, the significance of its absorption on inflamed skin remains unclear.

Organic filters work by absorbing UV radiation through their conjugated aromatic rings. Organic filters can be further divided into UVA and UVB filters (Table 77.5). Although widely found in sunscreens in the United States, oxybenzone has been implicated in many cases of contact and photoallergic dermatitis [68,69]. In addition, it is not photostable and can generate oxygen radicals upon UV exposure [70]. As a result, most European sunscreens have replaced oxybenzone in their formulations [8]. Avobenzone is the most efficient long-wave UVA organic filter available in the United States because its protection extends into UVA1 range. However, similar to oxybenzone, avobenzone is also intrinsically photolabile and significant degradation can occur after less than 1 h of UV exposure [71]. Photostabilizers such as octocrylene and diethylhexyl 2,6-napthhalate can be added to increase the stability of avobenzone upon UV exposure [8]. Avobenzone should not be combined with octinoxate, a widely used UVB filter. After absorbing UV radiation, the excited and unstable avobenzone can react with octinoxate to form a new compound, destroying the photoprotective property of both during the process [72,73]. In contrast to the photounstable oxybenzone and avobenzone, ecamsule is photostable. It is also water resistant and has low percutaneous absorption because of its high molecular weight [8].

TABLE 77.5
FDA-Approved UVA and UVB Organic Filters

UVA filter

Benzophenone:
- Oxybenzone (benzophenone 3)
- Sulisobenzone (benzophenone 4)
- Dioxybenzone (benzophenone 8)

Avobenzone (Parsol 1789, butyl methoxydibenzoylmethane)

Ecamsule (Mexoryl SX or terephthalylidene dicamphor sulfonic acid)[a]

Methyl anthralinate (Ensilizole, meradimate)

UVB filter

Aminobenzoates:
- Para-aminobenzoic acid (PABA)
- Octyl dimethyl *p*-aminobenzoic acid (padimate O)

Cinnamates:
- Octinoxate or octyl methoxycinnamate
- Cinoxate or ethoxy-ethyl-*p*-methoxycinnamate

Salicylates:
- Octisalate (octyl salicylate)
- Homosalate (homomethyl salicylate)
- Trolamine salicylate

Octocrylene (2-ethylhexyl-2-cyano-3,3-diphenylarylate)

Ensulizole (phenylbenzimidazole sulfonic acid)

[a] Approved as part of a New Drug Application process.

Currently there is no global consensus regarding the labeling and testing standards for measuring UVA protection. In the United States, the FDA has proposed using both *in vitro* and *in vivo* testing results for rating the overall UVA protection. The lowest category determined by either test will be used in product labeling. A five-category four-star system (i.e., no star to four stars) has been proposed to be assigned to products, with 4+ rated products offering the highest UVA protection [8]. However, this proposal has not been finalized by the FDA at the time of this writing.

There are five classes of FDA-approved UVB filters in the United States, aminobenzoates, cinnamates, salicylates, octocrylene, and ensulizole (Table 77.5). Para-aminobenzoic

acid (PABA), a compound in the aminobenzoates class, was the first UVB filter widely used in the United States [74]. However, because of the yellow discoloration that stains clothing and its potential for photoallergic reaction, PABA has largely fallen out of favor [8]. Padimate O is the most potent UVB absorber [75].

Within the class of cinnamates, two compounds are available, octinoxate and cinoxate. Octinoxate is the most potent UVB absorber used worldwide [8]. Its advantages include low skin irritancy and its water-resistant property [76]. The major drawback of octinoxate is its incompatibility with avobenzone as previously mentioned.

The third class of UVB filters available is salicylates. Currently, octisalate, homosalate, and trolamine salicylate are approved by the FDA. As a class, they have low sensitizing potential. Both octisalate and homosalate are water insoluble and retain their effectiveness after water exposure and perspiration [8]. Trolamine salicylate is water soluble and has been used in hair products. Salicylate compounds also play a minor role in stabilizing and preventing photodegradation of oxybenzone and avobenzone [77]. Octocrylene has an excellent safety profile with low irritation, low phototoxicity, and low photoallergic potential [76]. In addition, it is considered the best photostabilizer for avobenzone [8]. Ensulizole is water soluble and it is used in product formulated to feel lighter and less greasy [75].

In contrast to the different labeling systems for UVA protection from different countries, sun(burn) protection factor (SPF) has become the worldwide standard for labeling sunscreen regarding its protection from UVB. It is an in vivo test and is defined as the ratio of the least amount of UV dose required to produce a minimal erythema on sunscreen-protected skin, compared to the amount of dose required to produce the same erythema on unprotected skin, with the sunscreen applied at an even rate of 2 mg/cm^2. The 2 mg/cm^2 coverage translates to about 1 oz of sunscreen to cover the entire body. In the United States and Australia, water resistance of a sunscreen can be claimed only if the full SPF is retained after defined water immersion tests [78].

Recently, the SPF of available sunscreens has crept up to triple digits, which leads to tremendous confusion among consumers. The bottom line is that if adequately applied (2 mg/cm^2), sunscreens with sky-high SPFs offer slightly better protection against UV-induced erythema than SPF 30 sunscreens [78]. However, the increase in protection from an SPF 50 to an SPF 100 sunscreen is minimal; as such, SPF 50 sunscreens, if properly applied and reapplied, should be sufficient for the vast majority of individuals.

Unfortunately, in real life, most people do not apply the product evenly, leaving parts of the body uncovered. Furthermore, most individuals use only about 0.5–1 mg/cm^2 [79]. As a result, a consumer who uses an SPF 30 product may only receive an SPF of 15 or less. In a recent sunscreen knowledge assessment of the general public, only 18% of respondents knew the correct amount of sunscreen needed for each application [80].

In addition to applying a sufficient amount, another important issue regarding sun protection with sunscreen is applying it correctly. In order to achieve the desired protection level stated on the product label, sunscreen needs to be applied 30 min before going outdoors and reapplied every 2 h, especially when coming into contact with water or sweat. In a survey assessing sunscreen knowledge, only 32% of respondents reported the need to apply sunscreen 30 min before going outdoors and likewise, and only 30% reported the need to reapply them every 2 h [80]. It is also important to choose a sunscreen that offers both UVA and UVB protection; these products are now labeled as "broad-spectrum" sunscreens in the United States. Unfortunately, until the FDA makes a final decision on the proposed UVA labeling, consumers will not be able to differentiate different levels of UVA protection in a particular "broad-spectrum" product.

Behavior modifications, in addition to sunscreen application, are also important in UV protection. It has been found that when discussing photoprotection, many physicians recommend sunscreen use while omitting the message of shade seeking, use of sun-protective clothing and wide-brimmed hats, and wearing sunglasses [81,82]. One should seek shade from 10 AM to 4 PM when the UVR is most intense. It has been shown that shade reduces UV radiation from the sun by 50%–90%, with dense foliage providing superior UV reduction to a beach umbrella [83].

Wearing clothing and broad-brimmed hats has also been emphasized as an important means for photoprotection [84]. The wearing of protective garments offers several advantages. First, clothing and hats offer a balanced and uniform protection for both UVA and UVB. Second, they offer a more reliable protection as long as users wear them. Third, clothing and hats offer immediate and prolonged protection, as they avoid the needs of application prior to sun exposure and reapplication. Therefore, wearing sun-protective garments may have better compliance. Fourth, clothing and hats are less costly than sunscreens. Lastly, clothing and hats are devoid of any complications such as photoallergic contact dermatitis [8,84].

To accurately and quantitatively measure UV protection by garments, most regulatory agencies use UPF (UV protection factor) as a standard measurement. To obtain the UPF of any clothing item, the amount of UV transmission through the clothing is measured with a spectrophotometer. UPF is then calculated based on the amount of UV transmission at each wavelength and the erythema response from each spectra of the UVR [8]. Because erythema is the end point, UPF, similar to SPF, is a better reflection of UVB, rather than UVA, protection. As expected, the degree of UV protection offered by garments varies greatly depending on several factors. Fiber characteristics such as material, thickness, color, and the type of weave all influence the UPF of clothing (Table 77.6; [85–89]. When clothing is wet, the presence of water eliminates the scattering of UV light at the fabric–air interface. As a result, moisture and wetting can decrease UPF. This effect is especially important for

TABLE 77.6
Fiber Characteristics That Influence the UPF of Clothing

	Increased UPF	Decreased UPF
Fabric material	Polyester, wool	Cotton, linen, rayon
Fiber thickness	Thicker fiber	Thinner fiber
Fiber weave	Tightly woven	Loosely woven
Fiber color	Darker color	Lighter color

light-colored clothing, since scattering rather than absorption is the dominant protection mechanism [78,90].

Washing, especially after the first wash, makes certain fibers shrink, thereby decreasing the gaps between the individual fibers and making them thicker. As a result, a higher UPF is obtained [91]. The effect of washing on UPF is most pronounced on garments made from cotton, rayon, and flax materials [84]. Chemical treatment of garments with optical brightening agents, UV absorbers, and bleaching agents can also alter UPF measurements. Optical brighteners increase UPF values by absorbing UV energy and reemitting this energy in the form of VL. They are found in many household laundry detergents [84]. Similar to optical brighteners, UV absorbers such as Tinosorb FD also increase UPF via chemical binding to individual fibers with each wash [8]. It has been demonstrated that the UPF of cotton fabric can be increased by several 100-fold with the addition of UV absorbers [8]. Harsh treatment damages fabric materials and decreases UPF by either creating new or enlarging existing interstices, allowing more UV transmission [8]. Bleaching also reduces UPF [85].

Aside from its deleterious effect on the skin, UV exposure can also directly damage the cornea, conjunctiva, lens, and retina. Most ocular damage from UV radiation results from scattered and reflected light from the periphery [66]. Sunglasses can protect the eye from UV damage. However, while protecting the anterior and superior sides of the eyes, most sunglasses do not adequately shield the lateral and inferior portions. Although much less fashionable, an ideal pair of sunglasses should wrap closely to the eyes. Currently, in the United States, there is no mandatory standard to categorize the different types of sunglasses according to the degree of shading and UV absorption profile. A pair of sunglasses may offer shade without adequate UV protection. Price, brand, and polarizing lenses also do not ensure adequate UV protection [8].

Because most public education emphasizes avoidance of midday sun, one may generalize and assume that eye protection can be ignored during off-peak hours. However, in fact, most ocular damages occur during the morning and late afternoon hours when the incident rays are parallel to the pupil axis. During these times, the UV incident angle is low and the UV rays bypass the defense of the brow ridge and eyelid. In addition, squinting and papillary constriction mechanisms are not initiated due to lower light intensity, allowing more UV radiation to be transmitted. To ensure adequate protection of eyes from UV radiation, sunglasses need to be worn throughout the day [8]. The most effective photoprotection should employ combinations of shade seeking, sunscreens, sun-protective clothing, broad rim hats, as well as sunglasses.

INDOOR TANNING

In recent decades, indoor tanning booths have emerged as another significant source of UV radiation. The utilization of indoor tanning facilities continues to rise with the highest rates of reported use in young adult females [92,93]. Epidemiologic data have demonstrated a clear association between use of indoor tanning and melanoma as well as NMSC. In an analysis performed by the International Agency for Research on Cancer (IARC), the relative risk of melanoma among individuals who first used indoor tanning before 35 years of age was 1.75. The same study also found that ever-use of indoor tanning equipment was associated with a 2.25 relative risk of SCC [2]. Although the IARC analysis did not find sufficient evidence to support an association between indoor tanning and BCC, a population-based case–control study demonstrated an odds ratio of 1.5 for BCC with any use of tanning device. This study also confirmed the IARC finding of increased SCC in tanning bed users [95].

Behaviors that motivate indoor tanning are complex and involve both physiologic and psychologic responses. There is evidence suggesting the presence of an opiate-like addiction in tanning [94–97]. This could be explained by the fact that MSH production in tanning is accompanied by the release of β-endorphin, as both share a common precursor, proopiomelanocortin (POMC). Some advocate indoor tanning as a way to obtain vitamin D. However, this is erroneous, as the action spectrum for vitamin D synthesis is in the UVB range and most modern tanning equipment emits predominantly UVA. Of note, the FDA does not regulate the relative amounts of UVA and UVB in tanning devices [98]. Many countries have banned indoor tanning for individuals under the age of 18. Some states in America have also enacted restriction of access to tanning facilities for minors, but many states have not. Indoor tanning should be strongly discouraged across all age groups [99,100]. Furthermore, a tight regulation of the tanning industry is needed. Such regulation will have a profound impact on skin cancer prevention.

SUMMARY

NMSC and melanoma are unique in that few human cancers demonstrate such tightly linked associations to known and preventable environmental carcinogens. Primary care physicians are in a unique position in aiding dermatologists to provide patient education regarding the detrimental effects of excessive UVR and the importance of photoprotection.

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78 Exercise and the Skin

Brian B. Adams, MD, MPH

CONTENTS

Introduction 978
Traumatic Conditions 978
- Blisters 978
- Calluses 978
- Runner's Nipple 978
- Athlete's Nail 979
- Piezogenic Pedal Papules 980
- Talon Noire 980
- Athlete's Nodules 980
- Alopecia 980
- Acne Mechanica 980

Inflammatory Conditions 981
- Allergic Contact and Irritant Dermatitis 981
- Exercise-Induced Anaphylaxis 981
- Urticaria 981
- Cholinergic Urticaria 982
- Cold Urticaria 982
- Aquagenic Urticaria 982
- Solar Urticaria 982

Infections 982
- Bacterial 982
- Folliculitis 983
- Impetigo 983
- Furunculosis 983
- Pitted Keratolysis 984
- Fungal 984
  - Tinea Pedis 984
  - Onychomycosis 984
  - Tinea Corporis 985
  - Tinea Versicolor 985
- Viral 985
  - Herpes Simplex 985
  - Herpes Gladiatorum 986
  - Verruca 987
  - Molluscum Contagiosum 987

Environmental Conditions 988
- Organisms 988
  - Jellyfish Envenomations 988
- Cold 988
  - Frostbite 988
- Heat 988
  - Miliaria 988
  - Ultraviolet Radiation 988

Conclusion 988
References 989

INTRODUCTION

As individuals increase their participation in exercise, they also unfortunately experience untoward effects on their skin. Most of the skin-related conditions related to sports result in self-limited minor ailments, while some dermatoses result in significant morbidity, loss of practice time, and even infectious epidemics. This chapter reviews the traumatic, inflammatory, infectious, and environmental cutaneous ailments of sports participation. The early recognition and treatment of these dermatoses minimize exercise loss; this chapter also focuses on preventative approaches that should limit the interference of skin problems in one's dedication to exercise.

TRAUMATIC CONDITIONS

Blisters

Bulla, which represent one of the most common skin conditions related to exercise, result from repeated friction between athletes' skin and their equipment. Sporting implements cause friction bulla on the hands, whereas shoes and socks create blisters on the feet (Figure 78.1). Factors that increase the likelihood of friction bulla include moisture, frequency of the repeated rubbing, tightness of fit or coarseness of the implement or clothing material, and heat [1]. Frequently, athletes will acutely recognize a warm sensation that portends the development of a bulla. Rarely, some young athletes who often do not know that they have an unusual form of a genetic blistering condition called epidermolysis bullosa simplex (Weber–Cockayne variant) will present with severe blisters [1].

Proper treatment of bulla allows continued participation in sports activity. The bulla should be punctured with a sterile needle at one focal point so that the blister roof remains intact and can act as a biologic dressing [2]. As fluid recurs in the blister space, the athlete should repeat the lancing procedure.

Prevention remains the key for athlete's blisters. Sports participants must wear non-coarse, moisture-wicking clothing; cotton retains moisture and increases the probability of blister formation. Synthetic moisture-wicking socks, shirts, shorts, and undergarments, readily available in many retail establishments, keep the skin relatively dry and minimize friction. Furthermore, athletes can apply petroleum jelly at maximal friction points. Athletes who continue to develop blisters, despite employing these techniques, can also wear two layers of synthetic moisture-wicking socks with petroleum jelly applied to the socks corresponding to the areas most at risk for blisters. In all instances, athletes need properly fitted footwear though lacing techniques can mitigate the effects of poorly fitted footwear [1] (Figure 78.2).



FIGURE 78.1 **(See color insert.)** Friction bullae result from chronic friction on athletes' skin.

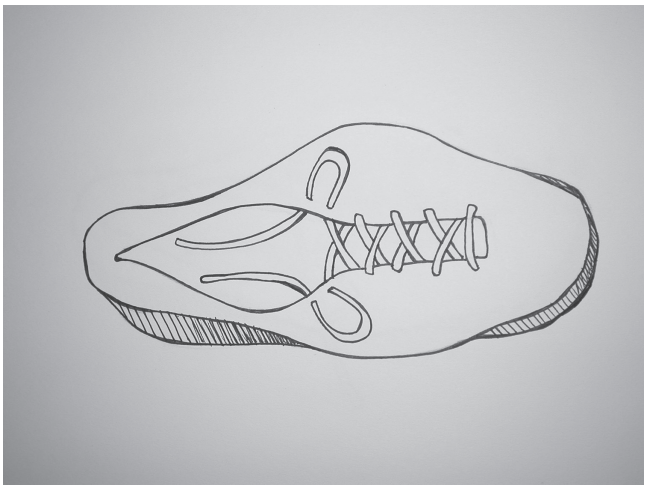
Calluses

Areas that chronically develop blisters often become callused. Occasionally, clinicians will confuse calluses for verruca or corns or vice versa. Clinicians must pare all apparent calluses in athletes. Calluses retain the typical skin markings upon paring, whereas corns will demonstrate a central core and verruca will display pericapillary hemorrhages (Figure 78.3). Occasionally, athletes also develop verruca within preexisting calluses.

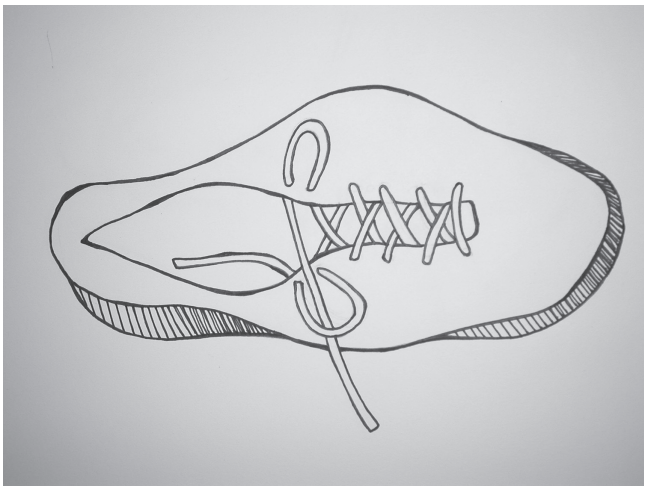
While these calluses protect the athlete from repeated blisters, some enthusiasts will desire therapy. An optimal approach to callus therapy includes soaking the affected area for 10 min in lukewarm water, thereafter rubbing the area with an abrasive element, such as a pumice stone, applying urea cream, and finally covering with an occlusive dressing such as plastic wrap or duct tape [1]. The preventative techniques employed for bulla also work well for calluses.

Runner's Nipple

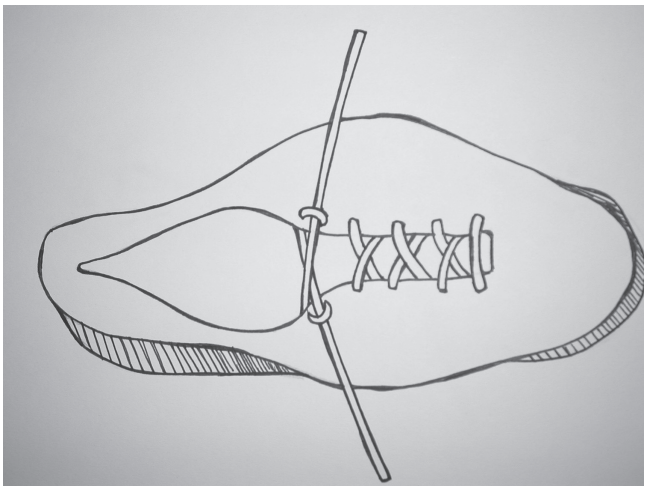
Friction between an athlete's nipple and clothing causes an erosive skin condition termed runner's nipple [3]. While the cutaneous signs often appear subtle, the athlete frequently experiences intense sensitivity and pain. Occasionally, bleeding from the lesions results in two parallel, linear, red streaks on a long-distance runner's pale colored shirt. Several factors increase the likelihood of developing runner's nipples including increased moisture, coarse fiber shirts (i.e., cotton), and increased frequency and intensity of friction between the nipple and the clothing [4]. Ointment-based products such as petroleum jelly, polysporin, and aquaphor not only minimize the discomfort and accelerate the healing but also prevent runner's nipples. Athletes should wear synthetic moisture-wicking clothing; cotton clothing conversely retains moisture and heat that promotes the development of runner's nipples [4]. Commercially available waterproof pads also exist that cover and protect the nipple.



(a)



(b)



(c)

FIGURE 78.2 (a–c) Special lacing techniques minimize the movement of the foot in athletic shoes. (Reprinted with kind permission from Springer Science + Business Media: *Sports Dermatology*, Adams, B.B., Chapter 12, Figure 5, © 2006.)



FIGURE 78.3 **(See color insert.)** Paring of this callous-like lesion ultimately reveals a central core characteristic of a corn.

Athlete's Nail

Sports enthusiasts endure many different types of nail changes that vary with the type of athletic activity. Nail changes result from constant slamming of the most distal toes into the toe box such as those that occur with long-distance running [5] from abrupt forces into the toe box, which occur in sports with quick starts and stops such as basketball or tennis; or from singular, strong, explosive forces experienced while kicking a ball in sports such as soccer and football [1]. The range of nail changes includes discolored nail plate, onycholysis, ridging, periungual callosities, and onychomadesis (Figure 78.4). Athletes must ensure that the toe box has adequate room by wearing properly sized footwear and should cut their nails straight across without curving the edges. A curve nail plate experiences greater force when it slams into the toe box. Unique lacing techniques, which also minimize friction bulla, help prevent athlete's nail [4].



FIGURE 78.4 **(See color insert.)** This dystrophic nail demonstrates discoloration and transverse ridging typical of athlete's toenail.

Piezogenic Pedal Papules

Pressure on the posterior–medial aspect of the heel may induce piezogenic pedal papules in susceptible athletes. It appears that athletes more often experience pain with these lesions that represent protrusions of subcutaneous fat into the dermis. The pain theoretically results from impingement of either the vasculature or nerves as the fat protrudes into the upper layers of the skin [1]. The lesions, often demonstrable only upon standing on one foot, exhibit well-defined, skin-colored to yellow papules. Multiple therapies for piezogenic pedal papules exist and include intralesional steroid injections [48], compression therapy [6], and acupuncture [7]. The use of heel cups can also provide pain relief.

Talon Noire

Talon noire, also known as black heel or calcaneal petechiae, represents asymptomatic, minute bleeding into the epidermis [8]. Constant sheering forces on the heel create these many, small, closely set, punctate, and black macules that mimic verruca (Figure 78.5). Many different types of athletes experience this skin condition including runners and tennis, lacrosse, and basketball players [1]. Clinicians may confuse talon noire not only for verruca but also for acral melanoma; a biopsy confirms the later diagnosis. Heel cups may help prevent talon noire, but affected athletes do not require therapy [4].

Athlete's Nodules

Some athletes develop nodules at pressure points between their skin and their sports equipment. Surfers may acquire these nodules, also known as surfer's nodules or surfer's knots, on their knees and lower legs [9]. Some of these nodules result from a foreign body reaction to sand and wax (used to minimize slippage while surfing) that get embedded in the athlete's skin. As surfers kneel on the board while paddling out to catch waves, they apply a great deal of pressure on their knees that causes the sand and wax on the board to become embedded. Conversely, other athletes such as runners, figure skaters, and hockey players develop athlete's nodules at sites corresponding to areas of constant tight rubbing with equipment (most often footwear) [10]. The biopsy of these athlete's nodules reveals a collagenoma. Clinically, athlete's nodules appear as well-defined thick, often erythematous, scaling nodules at sites of pressure (Figure 78.6).

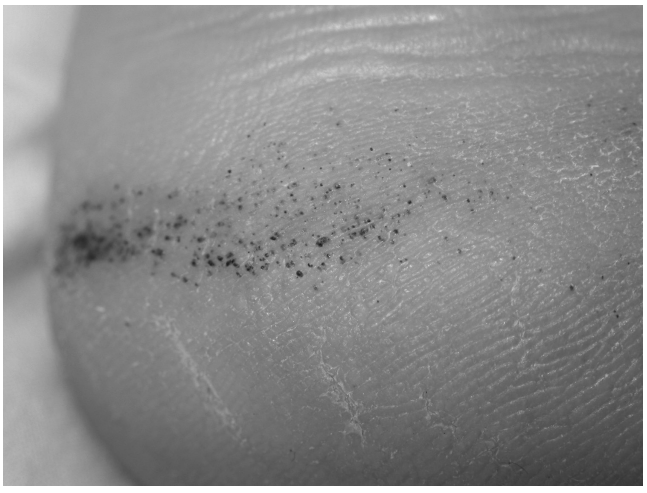


FIGURE 78.5 **(See color insert.)** Clinicians may confuse these black dots of talon noire with the pericapillary hemorrhages of verruca.

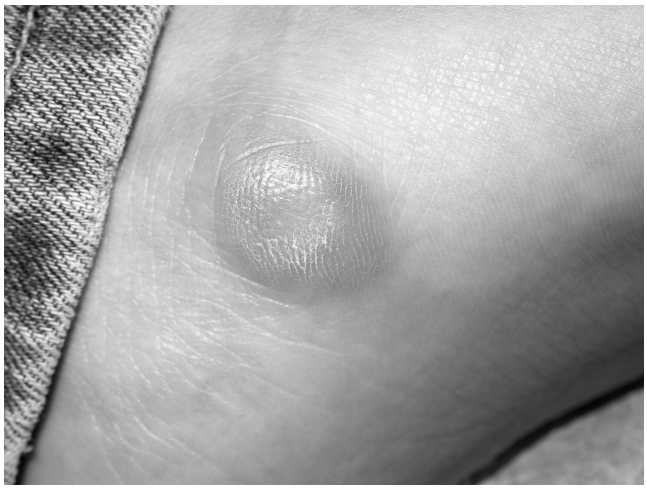


FIGURE 78.6 **(See color insert.)** This figure skater's foot developed an athlete's nodule while wearing markedly too small skates.

Either type of athlete's nodule clears with surgical excision or intralesional triamcinolone injections. Occasionally, these nodules resolve without therapy when the athletes discontinue their sporting activity. At-risk athletes should ensure that their sports footwear fits properly; extra padding also decreases the friction and pressure experienced by the skin [10].

Alopecia

Some athletes acquire alopecia from constant friction between their hair and the sporting environment. Gymnasts risk alopecia from traction applied to their scalp hair while on the beam, while some water slide enthusiasts may develop round, symmetrical, alopecic patches on the posterolateral aspects of their legs while they speed down the slide [11]. Discontinuation of the activity allows the hair to regrow.

Acne Mechanica

While most of the traumatic cutaneous ailments of athletes relate to one specific type of force, acne mechanica results from a compilation of friction, heat, pressure, and moisture. This type of acne can occur in athletes with or without a prior history of acne vulgaris and affects athletes with occlusive



FIGURE 78.7 (See color insert.) The chin of this football player displays the papules and pustules of acne mechanica that occur beneath chin straps.

equipment such as helmets and protective pads [1,12]. The distribution of the erythematous papules and pustules, typical of acne mechanica, corresponds to the occlusive equipment worn [13]. For example, football and hockey players acquire lesions on the chin and posterior scalp and shoulders corresponding to their helmets and shoulder pads, respectively (Figure 78.7). Wrestlers and volleyball players frequently develop acne mechanica on their knees that relate to their use of kneepads.

Clinicians may confuse acne mechanica with infectious folliculitis especially due to its atypical distribution. Acne mechanica does not respond as well to typical therapy for acne vulgaris; topical tazarotene, benzoyl peroxide, and clindamycin as well as oral antibiotics help assuage lesions. To prevent acne mechanica, athletes should place synthetic moisture-wicking material between their skin and the equipment and shower immediately after practice or competition.

INFLAMMATORY CONDITIONS

Allergic Contact and Irritant Dermatitis

Athletes develop allergic and irritant contact dermatitis from items that they encounter in the practice of their sport (Table 78.1) [14]. Allergic contact dermatitis represents a type IV delayed hypersensitivity reaction to an allergen, while irritant contact dermatitis does not require any immunologic sensitization. Both conditions cause well-defined (often uniquely patterned), erythematous, vesicular papules and plaques. In the subacute form, both types of dermatitis will lack vesicles, exhibit less intense erythema, and possess more scaling than the acute variety.

Affected athletes should use topical steroids to clear the eruption. The choice of strength of the topical steroid depends on the anatomical location of the dermatitis. The face (especially the eyelids), groin, and axilla require less potent topical steroids to avoid adverse events associated with their use. The choice of vehicle within which the active steroid ingredient resides depends on athlete preference and the presence of hair in the affected location. Occasionally, in severe reactions, clinicians may need to use systemic steroids. Many equipment alternatives exist for sensitized athletes (Table 78.1).

TABLE 78.1
Contact Dermatitis in Athletes

Equipment	Rash Location	Allergen	Alternate Equipment
Helmets	Forehead, scalp	Epoxy resins	Silicone
Tape	Focal	Formaldehyde resins	Acrylate tape
Sailing wishbone	Hands	Thiorams	Aluminum
Analgesic cream	Focal	Eucalyptus	Hot/cold packs
Shin pads	Shins	Urea formaldehyde	Barrier between guard and skin
Maggots	Hands of fishers	Dyes	Non-dyed

Exercise-Induced Anaphylaxis

Epidemiologic research reveals that runners appear particularly prone to develop exercise-induced anaphylaxis, although the mechanism by which exercise causes the condition remains unclear [15]. Most athletes with exercise-induced anaphylaxis do not experience pulmonary or vascular collapse but nearly universally complain of pruritus [16] (Table 78.2).

Affected athletes should take oral antihistamines and epinephrine if they experience respiratory or circulatory collapse. Exercising in extreme temperatures (either cold or hot) or after eating places athletes at increased risk to develop exercise-induced anaphylaxis; athletes who avoid these triggers can avert outbreaks 50% and 33% of the time, respectively [1,15].

Urticaria

In part related to increased core body temperature and the environments wherein practice and competition occurs,

TABLE 78.2
Prevalence of Various Symptoms in Exercise-Induced Anaphylaxis

Symptom	Prevalence (%)
Pruritus	92
Urticaria	86
Angioedema (palms and soles)	72
Dyspnea	50
Chest tightness	33
Nausea or diarrhea	25

athletes experience various types of urticaria including cholinergic, cold, aquagenic, and solar.

Cholinergic Urticaria

Cholinergic urticaria represents the most common type of urticaria among athletes. Runners appear particularly susceptible, but any athlete can develop cholinergic urticaria as a result of increased core body temperature. Affected athletes demonstrate small edematous and erythematous wheals that resolve spontaneously within minutes to hours. Lesions that persist greater than 24 h should prompt investigation of urticarial vasculitis. Oral antihistamines can both treat and prevent outbreaks of cholinergic urticaria in susceptible athletes.

Cold Urticaria

Athletes who compete in outdoor winter or cold water sports risk developing cold urticaria, which presents as urticarial plaques on exposed skin. To confirm the diagnosis, clinicians should perform an ice cube test. A positive test reveals a wheal as the skin rewarms after an ice cube is removed from the forearm and helps the clinician differentiate this type of urticaria from the cholinergic and aquagenic varieties. Cyproheptadine effectively prevents cold urticaria; additionally, winter athletes should minimize exposed skin while they practice their sport [1].

Aquagenic Urticaria

While exceedingly rare, aquagenic urticaria affects water sport athletes. Contact with water, regardless of temperature, causes urticarial plaques and has resulted in some cases of anaphylaxis. A positive test reveals an urticarial plaque on the forearm after the clinician applies room temperature water. To prevent this condition, susceptible athletes should apply inert oils on the exposed skin and take oral antihistamines; these athletes should never swim alone [1].

Solar Urticaria

Athletes occasionally also develop wheals from ultraviolet (UV) light within minutes of exposure, but resolve within hours. Phototesting confirms the diagnosis, and broad-spectrum sunscreen helps prevent solar urticaria [1].

INFECTIONS

Athletes acquire skin infections more commonly than nonathletes for a variety of reasons. First, many sports involve intense skin-to-skin contact that promotes the spread of infection among athletes. Second, sweating, inherent to athletic activity, macerates the epidermis and allows for easier penetration of the microorganisms into the skin. Third, trauma related to sports competition further facilitates the entry of microorganisms. Last, athletes routinely share equipment on and off the field. This frequent sharing often results in epidemics [1,17].

Prevention remains paramount as it relates to athletes who acquire skin infections from repeated skin-to-skin contact. Athletes must minimize the amount of exposed skin during practices; loose fitting, synthetic, moisture-wicking clothing keeps the skin relatively dry and cool, while it covers and protects the athlete's cutaneous barrier. Athletes also should not share personal items (such as towels and soap), equipment (such as helmets, gloves, clothing, and pads), or clothing (such as spandex). Athletic trainers and other medical professionals should carefully cleanse their hands between caring for athletes. These same medical professionals should perform careful skin examinations of their athletes, bandage infected skin during practices, and encourage daily laundering of athletic equipment and clothing. Athletic facilities require proper cleansing to eliminate bacterial contamination of common areas [1,17].

Bacterial

The majority of bacterial infections in athletes are caused by the methicillin-sensitive variety of *Staphylococcus aureus* (MSSA); however, increasing numbers of bacterial infections result from methicillin-resistant strains [18]. In addition, occasionally *streptococcal* species cause these bacterial infections. The majority of these infections result from skin-to-skin contact. As such, the at-risk sports include basketball, football, hockey, rugby, soccer, and wrestling [18]. Some sports without intense skin-to-skin contact, however, also have documented epidemics; fomite transmission likely causes these outbreaks in sports such as cross-country, fencing, gymnastics, and weight lifting.

Recent research has documented a high prevalence of methicillin-resistant *S. aureus* (MRSA) on the surfaces of the athlete's environment [19]. All studied high school athletic facilities had positive MRSA cultures. Ninety percent of mats, 78% of benches, and 20% of the doorknobs to athletic training rooms possessed MRSA. Additionally, a longitudinal, 1-year study of one division I college's women's lacrosse and men's football teams revealed a prevalence of MRSA in the nares ranging from 4% to 24% [20]. Because MRSA infects athletes at epidemic levels, clinicians should consider performing nares cultures on all infected athletes to determine carrier status. While no studies confirm the effectiveness of controlling epidemics by clearing nasal carriage, mupirocin twice daily to the nares clears MRSA/MSSA carriage for 4–5 months. Many epidemics of MSSA and MRSA in athletes appear in the literature, and several epidemiologic investigations note many risk factors [21–23] (Table 78.3).

Clinically, MSSA- and MRSA-related skin infections appear quite differently based on the specific location of infection within the different portions of the skin. Superficial infection of hair follicles results in folliculitis,

TABLE 78.3
Football Risk Factors for the Development of Staphylococcal Skin Infections

Risk Factor	Relative Risk of Infection
Adjacent locker	60
Shared towels	47
Cornerbacks	17.5
Shared soap	15
Wide receivers	11.7
Turf burns	7.2
Body shaving	6.1

while superficial infection of the epidermis creates impetigo. Furunculosis occurs when *S. aureus* infects deeper portions of the follicle.

For these bacterial infections, athletes should apply warm water soaks to affected areas three times daily for 5–10 min. Studies confirm that athletes treated empirically with antibiotics risk reoccurrence 33 times more likely than athletes for whom clinicians prescribe antibiotics based on the results of culture sensitivity testing [24]. Oral dicloxacillin and cephalexin effectively clear athletes' skin infections related to MSSA. Trimethoprim–sulfamethoxazole and the tetracycline family of antibiotics most often clear MRSA [1,18]. Even though resistance has increased in prevalence, most MRSA still responds to topical mupirocin. To prevent transmission and thwart epidemics of folliculitis, impetigo, and furunculosis, athletes should receive 72 h of antibiotics before returning to practice or competition [1]. Athletes may return to practice, during therapy, as long as the trainer can safely cover the infected skin site with a bandage that won't dislodge. Without an adequate duration of oral antibiotics, wrestlers cannot compete with bandages.

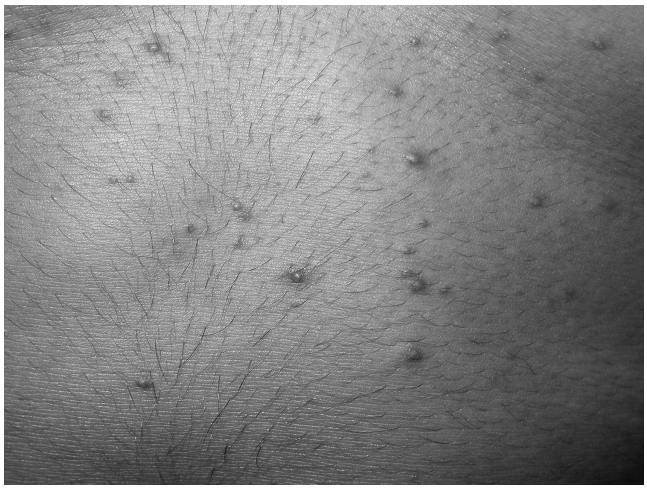


FIGURE 78.8 **(See color insert.)** Pustular eruption on the chest of a collegiate football player typifies folliculitis.



FIGURE 78.9 **(See color insert.)** A wrestler who has acquired impetigo contagiosum.

Folliculitis

Folliculitis, caused by both MSSA and MRSA, appear as follicular pustules and occur primarily at sites of skin-to-skin contact. Clinicians can easily confuse MRSA or MSSA folliculitis with other types of folliculitis such as *Pityrosporum*, *Pseudomonal*, acneiform, steroid, and eosinophilic (Figure 78.8). Usually a combination of biopsy, cultures, and history taking help differentiate among these conditions [25].

Impetigo

Athletes infected with impetigo present with honey-colored crusted papules and plaques on exposed skin (Figure 78.9). While most mature lesions of impetigo do not pose diagnostic difficulty, a typical lesion early in the course of the disease exhibits a nonspecific, erythematous papule. As such, impetigo early in the course of disease appears similar to early lesions of tinea corporis gladiatorum, herpes gladiatorum, dermatitis, acne, and lupus erythematous [17,25]. Performing cultures and taking a careful history confirms the diagnosis. Only rarely do clinicians need to perform biopsies.

Furunculosis

Furunculosis presents as tender, erythematous nodules on exposed skin surfaces. The differential diagnosis includes other infections (deep fungal infections, cutaneous myiasis), inflammatory conditions (inflamed cyst, arthropod bite reaction), and neoplasms (amelanotic melanoma, squamous cell carcinoma (SCC) cutaneous lymphoma) [17,25]. In addition to using the treatments that exist for folliculitis or impetigo, clinicians should also perform incision and drainage on all furuncles.



FIGURE 78.10 (See color insert.) Craterlike pits on the sole characterize pitted keratolysis.



FIGURE 78.11 (See color insert.) This scaling, mildly erythematous eruption on the lower sides of the foot, illustrates the moccasin variant of tinea pedis.

Pitted Keratolysis

Caused by gram-positive organisms (*Corynebacteria* or *Micrococcus*), pitted keratolysis occurs in athletes more commonly than nonathletes secondary to exertional hyperhidrosis and occlusive footwear [26]. Affected athletes have small, round, craterlike pits on the soles, particularly the weight-bearing aspects (Figure 78.10). Often, clinicians mistake pitted keratolysis for tinea pedis. Topical clindamycin and topical benzoyl peroxide clear the eruption. Benzoyl peroxide not only acts as an antibacterial agent but also dries the sole, making it a less hospitable environment for the bacteria. Athletes can prevent pitted keratolysis by wearing synthetic, moisture-wicking socks and by applying aluminum chloride solution to the sole before athletic activity [1,25].

Fungal

Tinea Pedis

Tinea pedis, otherwise known as athlete's feet, occurs far more frequently in athletes compared to nonathletes [27–31] (Table 78.4). This increased risk results from the warm, moist, and dark environment of the athletic footwear as well as exposure to shower and locker room floors colonized by fungal organisms. The three clinical types of tinea pedis include interdigital, moccasin-like, and inflammatory. The interdigital and moccasin variants, most often caused by *Trichophyton rubrum*, present with asymptomatic scaling plaques in the interdigital spaces and the soles, respectively (Figure 78.11). The inflammatory (or vesicular) type, which results most often from *Trichophyton mentagrophytes* infection, presents with pruritic vesicles and scaling plaques on the soles (particularly the instep) [1,25].

Clinicians often mistake the scaling variants of tinea pedis for xerosis and the vesicular variants for dermatitis. Athletes may develop allergic or irritant dermatitis from contact with compounds found in their athletic footwear, clothing, or other protective equipment. A potassium hydroxide examination of the scale reveals hyphal structures and confirms the diagnosis of tinea pedis; rarely must the clinician perform cultures. Depending on the severity of the eruption, clinicians may prescribe topical allylamines (such as ciclopirox or terbinafine) with or without oral antifungal agents (such as terbinafine or griseofulvin). To prevent tinea pedis, all athletes must wear synthetic moisture-wicking socks and don sandals in the locker room, showers, or pool decks. Antifungal powders shaken into the footwear can also not only decrease moisture that facilitates fungal growth but also destroy any present fungal elements [1].

TABLE 78.4
Prevalence of Tinea Pedis among Sports

Sport	Prevalence
Basketball players	39% (24/61) [28]
Runners	45% (66/147) [30]
	55% (20/36) [28]
Soccer	12.5% (7/56) [29]
	44% (35/79) [28]
	69% (22/32) [31]
Swimming	22% (22/150) [27]
	55% (17/31) [28]

Onychomycosis

In addition to acquiring tinea pedis, athletes also frequently develop fungal infection of their nails. Affected nails demonstrate nail plate thickening, discoloration (most often yellow), onycholysis, and subungual debris. Clinicians can confuse onychomycosis with athlete's toenail [25]. Permanent clearance presents challenges as oral therapies only clear toenails in a minority of the cases. As such, athletes and their medical staff should pay careful attention to prevention using the same techniques discussed for tinea pedis.

Tinea Corporis

Epidemics of tinea corporis, termed tinea corporis gladiatorum (also known as ringworm) in wrestlers, have occurred for decades. The prevalence ranges from 24% to 77% and varies based on study methodology [25,32–35]. In the study with the lowest prevalence, the investigators examined a wrestling team without a known epidemic and found that nearly one-quarter of the wrestlers had tinea corporis gladiatorum [35]. While *T. rubrum* remains the most likely causative organism of tinea corporis in non-athletes, *Trichophyton tonsurans* (typically cultured from tinea capitis) causes tinea corporis gladiatorum [25,35]. These interesting epidemiologic facts suggest that wrestlers ultimately acquire their ringworm from other wrestlers' tinea capitis. One study cultured fungus in 29% of wrestlers' scalps even though the athletes had no symptoms of infection [36]. This asymptomatic spread could, in part, account for the epidemics noticed in wrestlers.

Infected athletes often do not possess the prototypical annular morphology expected with ringworm; rather, lesions appear as red, round minimally scaling papules and plaques (Figure 78.12). The differential diagnosis includes early lesions of acne, dermatitis, lupus erythematous, impetigo, and herpes gladiatorum. Potassium hydroxide examination confirms the diagnosis [25]. An optimal therapeutic approach includes both oral and topical therapies, but controversy exists surrounding the optimal duration of administration.

Two trials support the use of oral prophylactic therapy (weekly fluconazole [100 mg] [34] and every other week itraconazole [400 mg] [33]) to further prevent tinea corporis gladiatorum. To further prevent epidemics and expedite a player's return to play, infected athletes should apply topical fungicidal cream, wash with selenium sulfide or ketoconazole shampoo, and cover their lesion with a biodressing or tape. After 72 h from the start of topical fungicidal creams, athletes can return to competition with minimal risk to other competitors [1].



FIGURE 78.12 (See color insert.) This wrestler's back and neck demonstrate the annular and round, red, scaling lesions of tinea corporis gladiatorum.

Tinea Versicolor

In hot and humid conditions, *Malassezia globosa* and *Malassezia furfur* may cause tinea versicolor in susceptible athletes. Clinically, such athletes develop round and oval, variably sized, hyperpigmented or hypopigmented, scaling macules and patches on the trunk and proximal upper extremities, predominantly (Figure 78.13). Occasionally, the scale from these lesions becomes obvious only after scraping the lesions. Unlike the potassium hydroxide examination of tinea pedis or tinea corporis, the hyphae from tinea versicolor scrapings appear short and occur along with small spheres that represent spores. Occasionally, tinea versicolor mimics the pattern and hyperpigmentation of confluent and reticulated papillomatosis of Gougerot and Carteaud (Figure 78.14) or the pattern and hypopigmentation of progressive macular hypomelanosis (Figure 78.15) [25]. Confluent and reticulated papillomatosis of Gougerot and Carteaud clears quickly upon institution of daily minocycline, while the therapy of progressive macular hypomelanosis remains more elusive. Phototherapy and topical antibiotics purportedly improve this condition [1].

Myriad regimens exist to clear tinea versicolor, but athletes need to understand that the discoloration may take months to recover its natural shade. Selenium sulfide 2.5% lotion or shampoo applied to the affected areas, left on for 15 min, and then rinsed off once per day for 7–10 days clears tinea versicolor. Ingestion of 400 mg of ketoconazole once, followed by another dose 1 week later, also effectively clears this fungal eruption. Weekly application of sulfide 2.5% lotion or shampoo may prevent future tinea versicolor outbreaks [1].

Viral

Herpes Simplex

Athletes develop herpes simplex virus-1 (HSV-1) infection as a result of reactivation of prior disease or due to transmission



FIGURE 78.13 (See color insert.) This athlete has the hyperpigmented variety of tinea versicolor on his trunk and upper arms.



FIGURE 78.14 (See color insert.) This football player's reticulated red-brown diffuse eruption represents confluent and reticulated papillomatosis of Gougerot and Carteaud.



FIGURE 78.15 (See color insert.) Progressive macular hypomelanosis frequently occurs on the lower aspect of the trunk.

from infected athletes. Outdoor athletes, with extensive UV exposure, risk reactivation of herpes labialis. Skiers and other winter athletes experience even greater UV exposure for two main reasons [37]. First, skiers participate at high altitudes on the mountain where less atmosphere exists to filter out harmful UV radiation [38]. Second, snow reflects nearly 100% of all solar radiation; as such, if athletes protect themselves even with broad-brimmed hats, the reflected sun from the ground still affects the athlete's skin and can reactivate herpes labialis.

Athletes will notice a burning or stinging sensation before the typical erythema or vesicle develops. Taking valacyclovir orally during this prodrome, athletes significantly decrease the duration of the eruption and can even, in many cases, abort the development of herpes labialis altogether. Studies on prophylactic use of sunscreen [39] or oral acyclovir [40] by skiers reveal a significant decrease in reactivation of herpes labialis.

Herpes Gladiatorum

Athletes can also acquire HSV-1 from skin-to-skin contact with other competitors; most of the research regarding sports-related herpes simplex virus infection in wrestlers. Herpes gladiatorum refers to herpes virus infection wrestlers while herpes rugbeiorum or "scrum pox" refers to herpes simplex virus infection among rugby players who also experience an extensive amount of skin-to-skin contact. Many reports document epidemics with a range of 7.6%–37% of the team infected [41]; the first reported epidemic of herpes gladiatorum occurred in 1964 when 5 of 30 (17%) wrestlers developed lesions [42]. Fomites do not appear to play as large a role in transmission as does skin-to-skin transmission. One study noted that wrestlers who sparred with an infected athlete contracted herpes gladiatorum 33% of the time [43].

Infected wrestlers will often experience a prodrome characterized by burning or stinging preceding the presence of an obvious skin lesion. Classic, mature lesions of herpes gladiatorum appear as grouped vesicles on an erythematous base located on the head, neck, and upper extremities (Figure 78.16). Nonspecific erythematous papules represent very early lesions of herpes gladiatorum, whereas crusted plaques may typify later-stage lesions; recognizing the impact of age on clinical morphology assists the clinician in making an accurate diagnosis. The differential diagnosis of



FIGURE 78.16 (See color insert.) Grouped vesicles upon an erythematous base typify herpes gladiatorum.

early lesions includes tinea corporis gladiatorum, impetigo, acne, and dermatitis [1,17]. Tzanck smear or culture confirms the diagnosis; however, cultures can take several days to produce results.

Herpes gladiatorum becomes noninfectious after 5 days of oral valacyclovir (2 g daily) therapy, and athletes at that time can safely return to competition [44]. Some special groups of athletes, especially highly competitive athletes preparing for championships and those athletes with frequently recurrent lesions, should take daily suppressive doses (1 g) of valacyclovir to prevent outbreaks.

Verruca

Human papilloma virus causes verruca (warts) in athletes as it does in nonathletes. Athletes, however, acquire these warts more frequently due to their exposure to areas that harbor the virus such as pool decks and weight rooms [25]. Additionally, calluses, inherent to many sporting activities, may help harbor warts. These verrucae appear frequently on the hands and feet and may hinder athletic activity. The thick and rough nature of the wart presents a distraction to the athlete by causing pain and by catching on equipment. Occasionally, warts may mimic calluses or corns; paring the hyperkeratotic portion of the lesion ultimately reveals the tiny, round, black dots characteristic of pericapillary hemorrhages in the case of verruca (Figure 78.17). The presence of normal skin markings or a central core confirms the diagnosis of callus or corn, respectively [1,25].

While destructive methods such as liquid nitrogen, topical cantharidin, and laser often work well to clear verruca, these surgical approaches frequently cause significant discomfort that may prevent athletic activity for several days. To minimize the disruption of an athlete's routine during their season, clinicians should attempt more conservative measures. Athletes can soak their verruca in water for 10 min and subsequently rub or pare the affected area with a pumice stone or sharp instrument (such as a #15 blade), respectively. Thereafter, they can apply topical salicylic acid and cover the wart with duct tape. Repeated nightly, this procedure will slowly decrease the size of the verruca and may eradicate the verruca altogether. Instead of salicylic acid, athletes may also try off-label prescription topical options such as imiquimod and 5-fluorouracil [1,25]. Athletes should always wear footwear in the showers, locker rooms, and pool decks. While using the weight room, athletes should use gloves to minimize cutaneous exposure to fomites. Meanwhile, athletes should clean or discard protective pads, helmets, and clothing.

Molluscum Contagiosum

Molluscum contagiosum, caused by the Pox virus, affects athletes who experience intense skin-to-skin contact and who contact certain environments, such as pool decks. As such, swimmers, wrestlers, and hockey, basketball, and rugby players most often contract molluscum contagiosum [1,25]. One study showed that swimmers experienced a relative risk of two to develop molluscum contagiosum [45].

Mature lesions of molluscum contagiosum appear as discrete, most often small (2–4 mm), white papules with a central umbilication (Figure 78.18). Very early and tiny lesions may not acquire this central indentation, and clinicians can easily confuse these papules for folliculitis. Clinicians rarely must perform biopsies to confirm this viral infection except in these aforementioned instances.

Surgical methods to rid the athlete of this virus include curettage and liquid nitrogen. Off-label use of topical tretinoin or imiquimod daily for 4–6 weeks often clears the lesions as well. The surgical methods cure the lesions instantaneously, while the topical agents take much longer to work. Occasionally, athletes will have all visible lesions treated and return to competition only to discover that extremely tiny, previously subclinical, lesions have enlarged. Athletes must minimize all exposed skin and wear footwear on the pool decks and locker room floors [1,25].

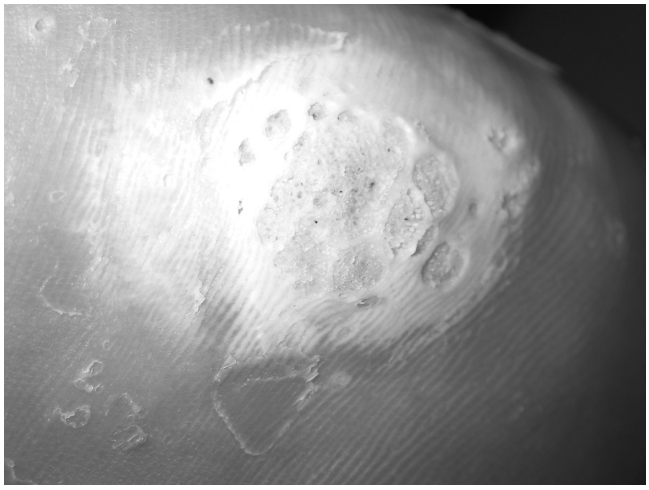


FIGURE 78.17 (See color insert.) This large plantar verruca caused significant pain for an elite marathoner.



FIGURE 78.18 (See color insert.) A moderate, endogenous, eczematous reaction surrounds the white lesions of molluscum contagiosum.

ENVIRONMENTAL CONDITIONS

Organisms

Jellyfish Envenomations

Water sport enthusiasts occasionally encounter various types of *Cnidaria* in their athletic pursuits. Like other classes within the *Cnidaria* phylum, the true jellyfish possesses nematocysts that sting athletes. The characteristic linear pattern of erythema and vesicles corresponds to the dangling threads of tentacles (Figure 78.19). The symptoms often include pruritus and pain, but rarely, depending on the type of jellyfish involved, severe systemic reactions occur. Treatments include vinegar solution applied to the attached tentacles and physical removal of the tentacles [1]. Athletes should avoid applying fresh water to the tentacles as this substance may activate nematocysts. Swimmers should avoid areas infested with jellyfish or wear wet suits to cover all submerged surfaces.

Cold

Frostbite

Numerous reports exist of frostbite in athletes who compete in cold weather such as long-distance runners and athletes who compete on the snow and ice [46]. After the initial exposure to cold, athletes develop pain and erythema; continued exposure can lead to blisters and eventual necrosis. Rapid rewarming in 40°C–42°C water bath remains the treatment of choice for affected athletes [1,46]. Athletes should never rewarm the frostbitten area until they can ensure no future exposure to freezing. To prevent frostbite, athletes should minimize any exposed skin. Especially for high-risk areas such as acral areas, layered clothing traps warm air. In addition, commercially available chemical packets activated and placed in gloves or socks keep the skin warm [1,46].



FIGURE 78.19 (See color insert.) While playing in extremely hot and humid conditions, this tennis player developed the extremely fragile blisters of miliaria crystallina.



FIGURE 78.20 (See color insert.) Jellyfish stings created linearly arranged erythematous papules on this swimmer's lower legs.

Heat

Miliaria

Miliaria crystallina occurs occasionally in outdoor athletes who compete and practice in extremely hot and humid environments. The eccrine duct, very superficially, becomes obstructed and quite fragile vesicles form on the trunk (Figure 78.20). Acclimating to the environment and wearing clothes that keep one cool (i.e., synthetic, moisture-wicking, light-colored clothing [with added UPF]) help prevent future outbreaks.

Ultraviolet Radiation

Athletes experience greater exposure to UV radiation for several reasons. First, athletes practice and compete for innumerable hours in the sun. Second, during these activities, athletes expose their skin to harmful UV rays during the peak hours of UV radiation (10 a.m. to 4 p.m.). Third, sweating decreases the efficacy of sunblock, and athletes do not adequately reapply their sunscreen. Fourth, athletes' sweat actually increases the risk for sunburn. Studies have shown that the minimal erythematous dose decreases markedly (more than 40%) after the athlete sweats [47].

To prevent the acute and chronic damage of UV radiation, athletes need to apply waterproof and sweatproof sunscreen 30 min before athletic activity. Broad-brimmed hats also provide sun protection; dark-colored, tightly woven clothing blocks more UV radiation than loosely woven, light-colored clothing. New synthetic sports clothing wicks away moisture to keep the athlete cool even though dark fabric generally absorbs infrared radiation and can cause athletes to overheat [1].

CONCLUSION

Athletes represent a unique group of patients who acquire some skin lesions, for a variety of reasons, more frequently than nonathletes and rarely also develop particular cutaneous ailments. Clinicians must recognize the impact of a patient's participation in sporting activities to ensure precise diagnosis, minimize infectious epidemics, and optimize therapeutic and prevention plans.

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79 Skin Care

Zoe Diana Draelos, MD

CONTENTS

Introduction 991
Cleansers and Skin Cleansing 992
Soap 992
Lipid-Free Cleansers 992
Cleansing Cream 992
Abrasive Scrub 993
Woven Mesh Cleansing Implements 993
Facial Cleansing Wipes 993
Summary 993
Moisturizers 994
Dry Skin 994
Skin Moisturization 994
Occlusive Moisturizing Ingredients 994
Humectant Moisturizing Ingredients 995
Hydrophilic Matrix Moisturizing Ingredients 995
Moisturizers and Skin Emollients 995
Moisturizer Formulation 995
Moisturizer Ingredients 996
Petrolatum 996
Dimethicone 996
Glycerin 997
Summary 997
Antiperspirants and Deodorants 997
Antiperspirants versus Deodorants 997
Perspiration Reduction 998
Antiperspirant Efficacy 998
Antiperspirant and Axillary Odor 998
Mechanism for Sweat Control 998
Clinical Strength Antiperspirants 999
Improving Sweat Control 999
Summary 999
Sunless Tanning Products 999
Sunless Tanning Cream Formulation 1000
Sunless Tanning Safety 1000
Summary 1000
Summary 1001
References 1001

INTRODUCTION

Skin care is an important element in total body health. Once the skin disease has been treated, skin care products are necessary for the maintenance of healthy skin. However, skin care products, if improperly chosen or improperly used, can also cause skin disease. For example, the overuse of cleansers can cause eczema, more readily experienced in those with dry skin. This necessitates proper cleanser selection as part of the skin treatment algorithm. However, patients with dry skin also need to supplement their inadequate or ineffective sebum production with a moisturizer. Many moisturizers are on the market, yet the patient must pick the proper product for optimal results. Not only should cleanser and moisturizer selection be customized for dry, normal, and oily skin, but it must also be customized based on sex, age, and ethnicity. Skin care product selection is not as simple as it might seem.

This chapter delves into the basics of skin care, to include cleansing and moisturizing, but also discusses some of the other important skin care categories such as antiperspirants/deodorants and sunless tanning products. It is hoped that the reader will have a greater appreciation for skin care and its nuisances after reading.

CLEANSERS AND SKIN CLEANSING

What is the perfect cleanser? What is the perfect method for cleansing the face and body? These are simple, yet complicated questions that cannot be easily answered. Just walk down the isle of any mass merchandiser and count the number of cleansing products for purpose. There are bars, liquids, creams, scrubs, meshes, and wipes all trying to achieve the optimal clean. There are foaming and nonfoaming cleansers customized to every body area. There are scented and unscented cleansers with some labeled as appropriate for sensitive skin. There are cleansers for women and separate formulations for men. Finally, there are treatment cleansers for acne and eczema. However, in reality, there are only several basic categories of cleansers upon which many variations have been manufactured.

Soap

Soap is a common term used by many as synonymous with cleanser. However, soap is a specific cleanser with a definite chemical composition. Soap is defined as a chemical reaction between a fat and an alkali resulting in a fatty acid salt with detergent properties.[1] The simplest soaps are manufactured in bar form. There are currently three different types of bar cleansers on the market all called "soap" by consumers, but with very different skin effects. There are the true soaps, which are composed of long-chain fatty acid alkali salts, with a pH between 9 and 10.[2] This is the original soap formulation developed that revolutionized health care in the United States. Perhaps soap, more than any other invention, has improved the quality of human life by preventing the spread of disease. This is the type of soap that grandma cooked in her backyard from ash and animal fat. The high pH of these cleansers is excellent at thoroughly removing sebum, but can also damage the intercellular lipids in diseased or sensitive skin. This formulation also experiences difficulty when used with hard water. The alkali chemically combines with calcium and other minerals in the water to form what is commonly termed "soap scum." Soap scum decreases the ability of the soap to rinse cleanly from the skin, causing irritant contact dermatitis in susceptible individuals. The only major brand of true soap left on the market today is Ivory soap manufactured by Procter & Gamble, Cincinnati, Ohio.

Following the development of true soaps came the invention of synthetic detergents. Synthetic detergents are known as syndets and contain less than 10% real "soap." Rather than possessing a highly alkaline pH, these products can be made with a pH adjusted to 5.5–7. This more neutral pH is similar to the normal acid mantle pH of the skin, causing less irritation. The tightness that is experienced following cleansing is actually the perception of altered skin pH. This is not a problem in normal-complected individuals, but can be a source of concern in persons with eczema or atopic dermatitis. Unfortunately, many associate the tight feeling with cleanliness, and it can be a challenge to convince a patient that the tight feeling is possibly an indicator of impending skin disease. Most syndet cleansers leave the skin with a smooth, sometimes slimy, feel that indicates that the intercellular lipids have not been removed and the skin barrier is intact. Syndet cleansers, sometimes known as beauty bars, are the most popular cleansers in use today. They offer milder, yet thorough, cleansing of all body areas.

The third form of cleanser is known as a combar, an abbreviation for combination bar. Combars combine true alkaline soaps with syndets to create a bar with greater cleansing abilities, but less intercellular lipid damage.[3] The majority of the bars in this category are also known as deodorant bars. They contain triclosan, a commonly used topical antibacterial, to decrease body odor caused by bacteria especially in the armpits and groin.

Selecting the proper type of "soap" may be tricky for the physician, but once the three categories of cleansers are identified, the task becomes much easier. In general, all beauty bars, mild cleansing bars, and sensitive skin bars are of the syndet variety (Oil of Olay, Dove, Cetaphil). Most deodorant bars or highly fragranced bars are of the combar variety (Dial, Coast, Irish Spring), and very few true soaps are currently on the market (Ivory).

Lipid-Free Cleansers

There are cleansers manufactured for each skin type based on the need to remove sebum balanced by preservation of the skin barrier. For persons with little sebum production, but the need to obtain adequate hygiene, lipid-free cleansers have been developed. Lipid-free cleansers are liquid products that clean without fats, which distinguishes them from the soap-type cleansers previously discussed. They are applied to dry or moistened skin, rubbed to produce minimal lather, and rinsed or wiped away (Cetaphil cleanser, Aquanil).

Lipid-free cleansers, also known as low-foaming cleansers because of their inability to foam copiously, may contain water, glycerin, cetyl alcohol, stearyl alcohol, sodium laurel sulfate, and occasionally propylene glycol. They leave behind a thin moisturizing film and can be used effectively in persons with excessively dry, sensitive, or dermatitic skin. They do not have strong antibacterial properties, however, and may not remove odor from the armpit or groin. They also are not good at removing excessive environmental dirt or sebum. Lipid-free cleansers are best used where minimal cleansing is desired, but can be used remove cosmetics of the face and eyes in persons with sensitive skin.

Cleansing Cream

Another variant of a mild cleanser is the cleansing cream, perhaps the first beauty cleanser invented. Cleansing creams

are popular among mature women who grew up in an era where cleansing cream offered the only alternative to the harsh alkaline soaps of the past. Cleansing creams are composed of water, mineral oil, petrolatum, and waxes.[4] The most common variant of cleansing cream, known as cold cream, is created by adding borax to mineral oil and beeswax (Pond's Cold Cream).[5] Cleansing creams can remove cosmetics and provide cleansing for patients with dry skin in one step. They are rubbed over a dry or wet face and then wiped away with a cloth. A residue is left behind on the skin. These products are making a comeback as eye cosmetic removal products for waterproof eyeliner and mascara in persons with sensitive eyes.

Abrasive Scrub

Other forms of cleansing combine removal of sebum from the skin surface with exfoliation, the removal of the desquamating corneocytes. With advancing age, the ability of the corneocytes to slough is decreased. The retained corneocytes give the skin a rough texture and yellowish appearance. Exfoliation removes the corneocytes, smoothes the skin surface, and restores a pinker skin color. Many antiaging cleansers are abrasive scrubs because the exfoliated skin may have a younger appearance. However, aggressive frequent use of an abrasive scrub can remove too much stratum corneum resulting in sensitive skin and can even provoke eczema.

Abrasive scrubs use a particulate material rubbed over the skin surface with the hands to mechanically remove the corneocytes. Abrasive scrubs incorporate polyethylene beads, aluminum oxide, ground fruit pits, or sodium tetraborate decahydrate granules to induce various degrees of exfoliation.[6] The most abrasive scrub is produced by aluminum oxide particles and ground fruit pits. In general, products containing these rough-edged particulates are not appropriate for sensitive skin patients. More mild facial scrubbing is produced by polyethylene beads, which are smooth and round (Clinique 7th Day Scrub). The least aggressive abrasion of the skin is found in products that contain sodium tetraborate decahydrate granules, which soften and dissolve during use. The main problem with abrasive scrub products for exfoliation is the tendency for overuse by the patient.

Woven Mesh Cleansing Implements

Cleansers have also been combined with implements to aid in applying the cleanser to the face and body or to offer an added benefit. The first cleansing implement introduced for facial cleansing was a woven mesh, also designed to deliver exfoliation benefits. The first product to enter the marketplace was composed of a nonwoven polyester fiber web sponge (Buf-Puf).[7] Originally, this product was designed to remove open comedones, but was ineffective due to the stiffness of the mesh. More modern softer versions have been introduced that are impregnated with a cleanser appropriate for various skin types. The mesh is more aggressive than an exfoliating scrub in removing corneocytes and must be used with care. More recently, the woven sponge technology has given way to the facial cleansing wipe.

Facial Cleansing Wipes

The desire for thorough, but less abrasive, cleansing led to the development of the disposable cleansing cloth, also known as the facial wipe. These wipes are composed of a combination of polyester, rayon, cotton, and cellulose fibers held together via heat through a technique known as thermobonding. Additional strength is imparted to the wipe by hydroentangling the fibers. This is achieved by entwining the individual rayon, polyester, and wood pulp fibers with high-pressure jets of water, which eliminates the need for adhesive binders, thereby creating a soft, strong cloth. Adhesives stiffen the cloth making it more injurious to the skin. The soft cloths also are more likely to traverse the skin dermatoglyphics providing better cleansing of the skin around the pores.

These cloths are packaged dry and wet. The dry cloths are impregnated with a cleanser that foams modestly when the cloth is moistened. A variety of cleansers can be used to create products for normal to dry and normal to oily skin. The cleanser can be placed on the cloth with other skin-conditioning ingredients. For example, the cleanser can be placed on one side of the cloth for washing and the cloth can be turned over during the rinse phase to leave behind skin-conditioning humectants and emollients. The antiaging cloths may also contain vitamins, such as vitamin E and vitamin B_5 (panthenol), to provide cosmeceutical benefits. Humectants and emollients can also be added to the cloth to decrease barrier damage with cleansing or to smooth the skin scale present in xerosis. In general, the cloths that are packaged dry and wetted prior to use are more gentle than those that come premoistened.

In addition to the cleansing and skin-conditioning ingredients applied during cloth manufacture, the weave of the cloth will also determine its cutaneous effect. There are two types of fiber weaves used in facial products: open weave and closed weave. Open weave cloths are so named because of the 2–3 mm windows in the cloth between the adjacent fiber bundles. These cloths are used in persons with dry and/or sensitive skin to increase the softness of the cloth and decrease the surface area contact between the cloth and the skin yielding a milder exfoliant effect. Closed weave cloths, on the hand, are designed with a much tighter weave and provide a more aggressive exfoliation. Ultimately, the degree of exfoliation achieved is dependent on the cloth weave, the pressure with which the cloth is stroked over the skin surface, and the length of time the cloth is applied. Cleansing cloths offer a versatile hygienic method for skin hygiene.

Summary

Cleansing of the face, hands, and body is probably the single most important event in maintaining hygiene and preventing the spread of disease. It is interesting to note that soap is the only substance that is not regulated by any type of

governmental document in the United States. This is because the government recognized the importance of soap to public health and felt that regulation would increase the cost of soap and make people less likely to use it. There can be no doubt that cleansing must be customized to the needs of the individual and used to maintain skin health.

MOISTURIZERS

Moisturizers have a significant impact on skin health. They can become indispensable in the treatment of xerotic skin conditions. Further, moisturizers form the vehicle for many skin preparations including topical corticosteroids, facial foundations, and antiaging creams. Perhaps 80% of skin care products, both prescription and over-the-counter (OTC), have a moisturizer as a vehicle. Moisturizers are based on occlusive substances, such as petrolatum and dimethicone, and humectant substances, such as glycerin, with a variety of sunscreens and botanicals for added functionality and marketing impact.[8] This section discusses dry skin, moisturization, and the key ingredients in moisturizer formulations.[9]

Dry Skin

Dry skin, medically known as xerosis, results from a decrease in the water content of the skin. The water is lost to the environment due to a damaged barrier that is no longer waterproof. The skin barrier is contained in the stratum corneum, which resembles a brick wall. The bricks are the corneocytes and the mortar is the intercellular lipids. If the stratum corneum is aggressively exfoliated, the corneocytes are prematurely removed and xerosis results. Alternatively, if aggressive cleansers are used, as described earlier in this chapter, the intercellular lipids are removed and xerosis also occurs. Cleansers cannot distinguish between the sebum lipids on the skin surface and the intercellular lipids between the corneocytes. Probably the most common cause of dry skin in the United States is overbathing, especially among mature individuals whose sebum production is limited.

For the skin to appear and feel normal, the water content of must be above 10%.[10] Some sources believe that the normal water content of the dermis should be around 30%, but this depends upon where and how the measurement is made.[11] Water is constantly lost to the environment through evaporation and must be replenished by water from the lower epidermal and dermal layers.[12] More water is lost under low-humidity conditions and less under high-humidity conditions. For equilibrium to occur between the skin and the environment, the ambient humidity must be at least 70%. Most conditioned living spaces control the humidity below 30% meaning that water is lost from the body through the skin on a regular basis. This water loss is known as transepidermal water loss (TEWL) and can be measured with a noninvasive equipment, such as an evaporimeter.

A healthy stratum corneum must have the ability to maintain hydration or the skin will feel rough, scaly, and dry. Dehydrated skin also tends to fissure and crack, as can be observed in calluses over the heel and ball of the foot. The dehydrated skin cracks because it becomes a brittle material in the absence of water, which functions as a plasticizer of the skin. Thus, it is the role of the intercellular lipids, composed of sphingolipids, free sterols, and free fatty acids,[13] to inhibit excessive water loss. The major lipid by weight found in the stratum corneum is ceramide, which becomes sphingolipid if glycosylated via the primary alcohol of sphingosine.[14] Ceramides possess the majority of the long-chain fatty acids and linoleic acid in the skin. Some moisturizers contain ingredients, such as ceramides, found in the intercellular lipids to stimulate barrier repair, but the signal for barrier repair is TEWL.[15,16]

Following barrier damage, the skin must be remoisturized in four steps: initiation of barrier repair, alteration of surface cutaneous moisture partition coefficient, onset of dermal–epidermal moisture diffusion, and synthesis of intercellular lipids.[17] Other disease states, such as psoriasis and atopic dermatitis, also demonstrate abnormal barrier function due to ceramide distribution.[18,19] Interestingly enough, xerosis tends to increase with age due to a lower inherent water content of the stratum corneum,[20] but this does not account for the scaliness of mature skin; probably an abnormal desquamatory process is also present.[21] The main treatment for dry skin in persons of all skin types, colors, and ages is the use of moisturizers.

Skin Moisturization

Three major mechanisms exist for rehydrating xerotic skin. Well-formulated moisturizers combine ingredients functioning in each category: occlusives, humectants, and hydrophilic matrices.[22] Occlusives are oily substances that retard TEWL, much like an oil slick placed on an open-air water reservoir to prevent evaporation. Basically, the skin is hydrated from within, not from the outside or from the environment. Placing water on the skin actually increases water loss rather than rehydrating the skin. The second method for rehydration is the use of humectants. These are substances that function like sponges to hold water in the skin. They draw water from the lower epidermis and dermis to the dehydrated outer skin, which is then trapped in place by occlusive ingredients. All good moisturizers must contain both types of ingredients. Finally, hydrophilic matrices are large-molecular-weight substances that further inhibit water loss.

Occlusive Moisturizing Ingredients

There are many different oily substances that are suitable for topical application to retard TEWL and function as occlusives. Occlusives can be divided into 20 different chemical classes with each ingredient imparting a different feel and thickness to the moisturizer (Table 79.1).[23] The first occlusives used in skin care products were hydrocarbon oils and waxes, such as petrolatum and mineral oil. Petrolatum remains one of the most popular occlusive moisturizers because it more closely resembles the natural intercellular lipids than any other substance. Petrolatum reduces TEWL by 99%, yet the 1% water loss is sufficient to allow repair to occur.[24]

TABLE 79.1
Families of Occlusive Moisturizing Ingredients

1. Hydrocarbon oils and waxes: petrolatum, mineral oil, paraffin, squalene
2. Silicone oils
3. Vegetable and animal fats
4. Fatty acids: lanolin acid, stearic acid
5. Fatty alcohol: lanolin alcohol, cetyl alcohol
6. Polyhydric alcohols: propylene glycol
7. Wax esters: lanolin, beeswax, stearyl stearate
8. Vegetable waxes: carnauba, candelilla
9. Phospholipids: lecithin
10. Sterols: cholesterol

Humectant Moisturizing Ingredients

Another concept in rehydrating the stratum corneum is the use of humectants. Humectants have been used in cosmetics for many years to increase shelf life by preventing product evaporation and subsequent thickening due to variations in temperature and humidity. For example, humectants are a necessary part of all oil-in-water creams to maintain their required water content. Substances that function as humectants are glycerin, honey, sodium lactate, urea, propylene glycol, sorbitol, pyrrolidone carboxylic acid, gelatin, hyaluronic acid, vitamins and some proteins.[23,25] Hyaluronic acid is one of the most popular humectants found in some moisturizers. It is used in facial fillers in an injectable form to absorb water and fill facial wrinkles, but can also be applied topical to draw water to the skin surface that is then trapped by an occlusive moisturizing ingredient.

Cosmetic chemists have theorized that humectants could be used to draw water from the environment, under conditions where the ambient humidity exceeds 70%, and more commonly from the deeper epidermal and dermal tissues to rehydrate the stratum corneum. Water that is applied to the skin in the absence of a humectant is rapidly lost to the atmosphere.[26] Humectants may also allow the skin to feel smoother by filling holes in the stratum corneum through swelling.[27] However, under low-humidity conditions, humectants, such as glycerin, will actually draw moisture from the skin and increase TEWL.[28] Therefore, a good moisturizer should combine both occlusive and humectant properties.

Hydrophilic Matrix Moisturizing Ingredients

Hydrophilic matrices are large-molecular-weight substances that physically impede water loss from the skin surface. They are similar to occlusives in their mechanism of action, except that they are not necessarily oily substances. One of the oldest and still medically applicable hydrophilic matrices is colloidal oatmeal, which is available in a variety of particle sizes. Large-particle-size colloidal oatmeal is used as a powder placed in the bath to prevent water loss from the skin across an osmotic gradient in bath water. Colloidal oatmeal baths have been used by dermatologists for years in persons with eczema and atopic dermatitis. Fine-particle colloidal oatmeal is used in powders and oatmeal-based moisturizers similarly to retard water evaporation.

Moisturizers and Skin Emollients

Moisturization is the most medically important aspect of lotion and cream application to the body, but consumer product preference is based more on a concept known as emolliency. Emolliency is the ability of a lotion or cream to make the skin feel smooth and soft. Emollients provide this positive sensory experience by filling the spaces between the desquamating skin scale with oil droplets,[29] but their effect is only temporary. Most moisturizers are emollients, but not all emollients are good moisturizers. Most consumers base their opinion of how well a moisturizer works on skin feel, while it is more medically relevant to base the value of a moisturizer on how well it hydrates the skin. Thus, a popular moisturizer must both rehydrate and improve skin feel to succeed in the marketplace.

Moisturizer Formulation

The ideal moisturizer has yet to be invented, accounting for the myriad of products available for purchase. It is surprising to note, however, that the biggest difference among moisturizer formulations has more to do with the aesthetic than the medical aspects of the product. Fragrance, color, and packaging are the most distinguishing characteristics of modern moisturizers, which are only of importance for consumer appeal. The basic moisturizer formulation consists of water, lipids, emulsifiers, preservatives, fragrance, color, and specialty additives. Interestingly enough, water accounts for 60%–80% of any moisturizer; however, externally applied water does not remoisturize the skin. In fact, the rate of water passage through the skin increases with increased hydration.[30] The water functions as a diluent and evaporates leaving the active agents behind.

The most popular moisturizer formulations are oil-in-water emulsions where water is the primary phase into which oil droplets are introduced as the secondary phase. Oil-in-water emulsions are popular because the water evaporates leaving a minimally greasy film behind. Water-in-oil emulsions, where oil is the primary phase, are heavier and have a greasy feeling on the skin with poor consumer-accepted aesthetics, even though they are generally superior moisturizers. Of all the ingredients in the moisturizer formulation, emulsifiers are the most problematic. They are amphiphilic materials that are detergents emulsifying the oil within the water in concentrations of 0.5% or less. Emulsifiers can cause skin problems as they can also emulsify the sebum on the skin surface.

Finally, the other important ingredient in all skin care products is the preservatives. Preservatives are necessary to prevent the oil in the moisturizer from going rancid and to protect from microbe contamination. There has been a movement lately to manufacture preservative-free skin care products. This has been driven by some popular press

indicating that preservatives can cause cancer. These studies showing preservative-induced cancer were conducted in rodents that were fed the preservative in doses difficult for humans to consume. Indeed, preservatives for skin care products should not be eaten. The most commonly used preservatives in skin care products are from the paraben family.[17] Parabens are minimally allergenic and provide excellent protection against both gram-positive and gram-negative organisms. Formulations that claim to be preservative-free usually contain a preservative that is not labeled as such on the packaging. For example, phenoxyethanol is a frequently used preservative, but it smells like roses. It may be listed as a fragrance, but it is really a preservative. Similarly, clove and turmeric extracts may be used as fragrance ingredients, but they too are fragrances. Clove and turmeric are spices used in cooking. Most spices are flavorings but also preservatives and can be used multifunctionally in skin care preparations, as well.

A successful moisturizer formulation must meet three consumer-driven criteria: it must increase the water content of the skin (moisturization), it must make the skin feel smooth and soft (emolliency), and it must protect injured or exposed skin from harmful or annoying stimuli such as itching, stinging, and burning (skin protectant). If a moisturizer can produce these skin benefits, it will be useful to the consumer and medically relevant.

Moisturizer Ingredients

Most moisturizers use the same basic ingredients as the backbone of the formulation to achieve efficacy. While a review of all the ingredients in a moisturizer is beyond the scope of this chapter, the most beneficial and popular ingredients are reviewed to include petrolatum, dimethicone, and glycerin.

Petrolatum

The most commonly used active agent in skin care products, after water, is petrolatum.

Petrolatum is a semisolid mixture of hydrocarbons obtained through the dewaxing of heavy mineral oils. Pure cosmetic-grade petrolatum is practically odorless and tasteless appearing in the U.S. Pharmacopeia in 1880. *It is interesting that it has never been duplicated synthetically.*

Petrolatum is the most effective moisturizing ingredient on the market today, reducing TEWL by 99%.[31] It functions as an occlusive to create an oily barrier through which water cannot pass. Thus, it maintains cutaneous water content until barrier repair can occur. Petrolatum is able to penetrate into the upper layers of the stratum corneum and aid in the restoration of the barrier, which is initiated through the production of intercellular lipids, such as sphingolipids, free sterols, and free fatty acids.[32] Products containing petrolatum increase the rapidity with which these lipids are synthesized.

Petrolatum impacts all phases of skin remoisturization, the first step toward barrier repair and wound healing. Petrolatum allows the water content of the skin to rise by decreasing evaporative losses, which creates the moist environment necessary for fibroblast migration leading to wound healing and eventual barrier restoration. Furthermore, it is hypoallergenic, noncomedogenic, and nonacnegenic.

Petrolatum also decreases the appearance of fine lines on the face and body due to dehydration. It functions to reduce itching and mild pain by creating a protective film over exposed lower epidermal and dermal nerve endings. It acts as an emollient by entering the space between the rough edges of desquamating corneocytes, restoring a smooth skin surface. It can also function as an exfoliant by loosening desquamating corneocytes, which are physically removed as the petrolatum is rubbed into the skin. Petrolatum is also an important component of many other cosmeceutical formulations that contain additional actives.

Dimethicone

The major drawback to pure petrolatum as a moisturizer is its greasiness, which most patients find unaesthetic. This can be minimized by lowering the petrolatum concentration and adding dimethicone, known as an astringent moisturizer, to improve product aesthetics. Dimethicone is the second most common active agent in moisturizers today because it too is hypoallergenic, noncomedogenic, and nonacnegenic.[33] Dimethicone is one of a family of silicones that form the basis of all oil-free moisturizers and facial foundations.

Silicone originates from silica, which is found in sand, quartz, and granite. It derives its properties from the alternating silica and oxygen bonds, known as siloxane bonds, which are exceedingly strong. These strong bonds account for the tremendous thermal and oxidizing stability of silicone. Silicone is resistant to decomposition from ultraviolet radiation, acids, alkalis, ozone, and electrical discharges. The silicone used in topical preparations is an odorless, colorless, nontoxic liquid. It is soluble in aromatic and halocarbon solvents, but poorly soluble in polar and aliphatic solutes. Because silicone is immiscible and insoluble in water, it is used as an active agent in products designed to be water resistant. To date, there is no report of toxicity from the use of topical silicone.

Dimethicone cannot replace petrolatum, however, as a moisturizer for decreasing fine facial lines of dehydration or for creating an environment optimal for healing skin.[34] While dimethicone is insoluble in water, it is permeable to water vapor. Thus, if the skin barrier is wounded, dimethicone will not reduce TEWL. However, this water vapor permeability is important in the manufacture of facial foundations and sunscreens, since perspiration must evaporate or the product will contribute to miliaria and leave the skin feeling warm and heavy.

Dimethicone can provide many other skin benefits as an active agent besides moisturization. It can function as an emollient, making the skin smooth and soft to the touch by filling in spaces between the desquamating corneocytes. It can also smooth skin scale from the use of drying acne medications, such as benzoyl peroxide or tretinoin, without creating a greasy shine undesirable in oily complected patients. Dimethicone also does not easily mix with facial sebum,

allowing other ingredients in the formulation to remain in place on the face. This is valuable in sunscreens and facial cosmetics.

Glycerin

Glycerin is a commonly used humectant in skin moisturizers. Humectants are substances that attract water from the dermis and viable epidermis into the dehydrated stratum corneum.[26] However, if the skin barrier is damaged, the water will immediately evaporate into the lower-humidity environment. For this reason, humectants are always combined with occlusive moisturizers that retard water loss, such as the previously discussed petrolatum and dimethicone. Glycerin, petrolatum, and dimethicone form the backbone of most skin care products to which other novel agents are added.

Glycerin offers some unique skin benefits. It is one of the few moisturizers, in addition to petrolatum, that is able to form a reservoir effect on the skin. In other words, the effect of glycerin appears to persist long after the glycerin is no longer present. Previously, this effect was thought to be due to glycerin affecting the intercellular lipids. It is now recognized that glycerin is capable of modulating water channels in the skin, known as aquaporins.

Aquaporins are highly conserved water channels present in plants, bacteria, and human skin composed of integral membrane proteins from a larger family of major intrinsic proteins.[35] The 2003 Nobel Prize in Chemistry was awarded to Peter Agre and Roderick MacKinnon for work on aquaporins and ion channels. These channels conduct water in and out of the cell while preventing the passage of ions and some solutes. They are composed of a six-transmembrane alpha helical structure arranged in a right-handed bundle. Aquaporins form tetramers in the cell membrane and control the transport of water, but also glycerin, carbon dioxide, ammonia, and urea. Different aquaporins contain different peptide sequences controlling the size of the molecules that are able to pass; however, aquaporins are impermeable to charged molecules, such as protons. Typically, molecules can only pass single file through the channel.

The primary aquaporin in the epidermis is aquaporin-3. It is found in the basal and suprabasal layers of the epidermis, but not in the stratum corneum. Aquaporin-3 expression is also increased in human skin diseases with elevated TEWL. Thus, glycerin is being rediscovered as a moisturizing ingredient with potential to dramatically affect skin water balance. Since facial lines of dehydration are the easiest sign of aging to rapidly correct, skin care products based on glycerin, petrolatum, and dimethicone are commonly used to rapidly hydrate the skin and improve appearance. However, petrolatum, dimethicone, and glycerin are also present in the vehicle of most facial skin care creams and lotions. The vehicle is responsible for improving skin condition, but also delivers other active agents to the skin surface.

Summary

Moisturization of the skin occurs through the use of ingredients that function as occlusives, humectants, and hydrophilic matrices. Proper cleanser selection is the best way to avoid the need for moisturization, but the habit of daily bathing is hard to break in many patients. Thus, there is a need to synthetically replace skin lipids and maintain the barrier. Moisturizers attempt to create an environment for repairing the damage done by skin cleansing. The challenge is to find the balance that results in superior skin health and ultimately beautiful skin.

ANTIPERSPIRANTS AND DEODORANTS

Antiperspirants and deodorants are important skin care products different than any we have previously discussed because they fall into the OTC drug category. Antiperspirants contain active agents that are disclosed on product packaging. Whenever an active ingredient disclosure is made, the product is considered an OTC drug. This means that the ingredients and concentration of ingredients in the formulation are controlled by a government monograph. This places restrictions on the product different from cosmetics. Yet controlling axillary perspiration is important both to the patient and to the physician.

Antiperspirants are available in a variety of formulations from stick to cream to gel to aerosol spray, but the active ingredient in all is an aluminum-containing compound. The health safety of antiperspirants has been debated for years. Most recently, antiperspirants have been linked to breast cancer in the media, but no medical relationship has been established. While no antiperspirants are to be worn during breast mammography examinations, this is not related to breast cancer. The FDA did express some concern in 1978 regarding the long-term inhalation risk of aerosol antiperspirants; however, these preparations remain on the market.

The first antiperspirant was introduced in 1916, which was composed of a 25% solution of aluminum chloride hexahydrate in distilled water. This highly effective formulation only required every other day application but was extremely irritating and the low pH damaged clothing. The need to develop an antiperspirant that controls sweat yet is skin compatible has led to all of the products that are currently marketed. This discussion focuses on the important issues of sweat control.

Antiperspirants versus Deodorants

The words antiperspirant and deodorant are sometimes used interchangeably in the common vernacular, but to the cosmetic chemist, these are two very different personal care products. Antiperspirants contain ingredients to decrease sweating, while deodorants are used solely to manage axillary odor. For this reason, all antiperspirants can be considered deodorants, but not all deodorants are antiperspirants. Table 79.2 lists the mechanisms for axillary odor control. Most products in the current marketplace are both antiperspirants and deodorants. The rest of our discussion will focus on antiperspirants.

TABLE 79.2
Mechanisms for Axillary Odor Reduction

1. Reduce apocrine gland secretions
2. Reduce eccrine gland secretions
3. Remove apocrine and eccrine gland secretions from the axilla
4. Decrease axillary bacterial colonization

Perspiration Reduction

Sweat can be divided into apocrine and eccrine perspiration. Eccrine sweat is a clear, odorless fluid of pH 4–6.8 composed of 98%–99% water, sodium chloride, lower fatty acids, lactic acid, citric acid, ascorbic acid, urea, and uric acid. Apocrine sweat is a turbid, viscous, odorless fluid of pH 6–7.5 that has high content water, in addition to protein, carbohydrate waste materials, and sodium chloride. The amount of eccrine perspiration is much greater than the amount of apocrine perspiration. An effective antiperspirant must reduce both types of perspiration.

The reduction of apocrine and eccrine perspiration on the body is a daunting task, and the mechanisms for sweat control are summarized in Table 79.2. In the axilla, there are some 25,000 eccrine glands capable of producing large quantities of perspiration in response to heat and emotional stimuli. Antiperspirants work by coagulating the protein in the sweat duct. They contain metal salts that combine with intraductal keratin fibrils to cause eccrine duct closure and formation of a horny plug to obstruct sweat flow to the skin surface.[36]

The only two metal salts that are presently used in antiperspirants are aluminum and zirconium.[37] The original antiperspirant formulation was a 25% solution of aluminum chloride hexahydrate in distilled water, but it was extremely irritating.[38] More modern antiperspirant formulations contain aluminum chloride, aluminum chlorohydrate, aluminum zirconium chlorohydrate, and buffered aluminum sulfate.[39] These metals provide a better balance between efficacy and skin irritation.

Antiperspirant Efficacy

The FDA has established that an antiperspirant must reduce sweat by at least 20% to be marketed in the United States as an effective product. Antiperspirants that are labeled as highly effective must reduce sweat by at least 30%. Table 79.3 lists the efficacy of a variety of currently marketed formulations. Notice that the efficacy range is broad, but overall aerosols are the least effective and roll-ons are the most effective. This is due to the ability of the product to contact all of the sweat ducts in the axilla and deliver an optimal dose. For most patients, this amount of sweat reduction would be considered woefully inadequate. This is the main reason that not all antiperspirants provide sweat reduction in individuals with abundant perspiration. The ingredients were designed to perform at a 20%–30% reduction level.

TABLE 79.3
Antiperspirant Efficacy

Formulation	Percent Sweat Reduction
Aerosols	20–33
Creams	35–47
Roll-ons	14–70
Lotions	28–62
Liquids	15–54
Sticks	35–40

Efficacy is defined as the percentage reduction in the rate of sweating achieved after application of the antiperspirant product. The percentage sweating reduction can be determined gravimetrically.[40] This involves weighing an absorbent pad and then placing the pad in the armpit while the subject is induced to sweat in a hot room. The pad is then reweighed after a specified time in the hot room, and the increase in weight per time is converted into a sweating rate. The rate can be compared before and after the application of an antiperspirant.

Antiperspirant and Axillary Odor

Perspiration is the perfect medium for bacterial growth accounting for the odor associated with sweaty armpits. Axillary odor is caused by the action of bacteria on sterile eccrine and apocrine sweat. The apocrine sweat is responsible for a large part of the odor as it is rich in organic materials. Eccrine sweat, on the other hand, is more dilute and does not provide a high concentration of bacterial nutrients. However, eccrine sweat indirectly promotes odor by dispersing the apocrine sweat over a larger area and providing the moisture necessary for bacterial growth. Axillary hair also contributes to odor by acting as a collecting site for apocrine secretions and increasing the surface area suitable for bacterial proliferation.

Deodorants function either by masking the axillary odor with a perfume or by decreasing axillary bacteria. Therefore, many deodorants contain antibacterials, such as quaternary ammonium compounds (benzethonium chloride) and cationic compounds (chlorhexidine, triclosan).

Mechanism for Sweat Control

Antiperspirants reduce axillary moisture by employing aluminum salts to create a plug within the acrosyringium to occlude eccrine and apocrine ducts. Sometimes the aluminum is combined with zirconium to enhance efficacy. It takes about 10 days to create the plug, which physically blocks the transport of sweat from the gland on to the skin surface. Conversely, it takes 14 days for the plug to dissolve. It is for this reason that best results with antiperspirants are achieved with daily use to maintain the plug.

In order for the antiperspirant to work, it must physically contact every sweat duct. Even and thorough application to

entire axillary vault is necessary for optimal results. Some antiperspirants have a grid to encourage even application and metered dosing administered through turning a knob at the bottom of the stick container. Using the amount of antiperspirant recommended on the packaging is important.

Clinical Strength Antiperspirants

A new category of antiperspirants that have been introduced are labeled as "clinical strength" products. These products have a slightly higher concentration of active ingredients that must reduce sweat by 30% to substantiate the highly effective claim on package labeling, but are also recommended for twice-daily use. The twice-daily use is actually the key to their enhanced efficacy. The antiperspirant must remain in the axillary vault long enough to form or maintain the plug in the acrosyringium. If heavy sweating is occurring during application, the antiperspirant is washed away and ineffective. Since the armpit is generally at rest at night, bedtime application of antiperspirants allows the ingredients to contact the skin longer and create a better plug that translates into enhanced efficacy. Increased efficacy can be achieved with any antiperspirant that is used morning and evening.

The most effective antiperspirants create a deep plug in the acrosyringium. The more superficial the plug, the less sweat control obtained. Unfortunately, there is a direct connection between skin irritation and acrosyringial plug depth. Efficacious formulations must address both issues to create a skin-friendly product. Some manufacturers are including skin protectant ingredients, such as dimethicone, in antiperspirant formulations to increase efficacy while counteracting the inherent possibility of irritant contact dermatitis.

Improving Sweat Control

An effective antiperspirant must create a long-lasting plug in the sweat duct ostia quickly. This is best accomplished by evenly spreading the antiperspirant in the axillary vault. If the antiperspirant does not touch the sweat duct, it will not work. This is similar to botulinum toxin, which will work for sweat reduction only if it is injected over the entire area of moisture production. The ability to evenly distribute the antiperspirant accounts for the decreased efficacy of aerosol spray formulations that may easily miss sweat gland-containing areas.

The most effective antiperspirants are the sticks and lotions. These are vigorously rubbed in the axilla to remove the product from the specially designed applicator to distribute the chemical throughout the armpit. The active agent in the newer antiperspirants is aluminum–zirconium tetrachlorohydrex-gly complex. This complex can reduce axillary perspiration by 40%–60%. These aluminum salts have an acidic pH of 3.0–4.2.[41] Irritation is reduced by incorporating skin-conditioning agents, such as dimethicone or cyclomethicone, into the formulation. The silicone imparts skin soothing properties to the skin irritated by the antiperspirant ingredients.

The next most common reason for antiperspirant failure is the inability to get an even film that covers the entire armpit. The antiperspirant must be in contact with each and every eccrine and apocrine duct in the armpit to work. Thus, the applicator should be domed to fit into the axilla and dispense a thick even film of product. The film must be somewhat water resistant or it will be rinsed away by perspiration before the plug can be formed in the ducts. For this reason, the armpit should be dry when the product is applied. Many dermatologists recommend that patients apply an OTC or prescription antiperspirant and then occlude the armpit with plastic wrap. If the patient sweats profusely under the occlusion, the perspiration may wash away the active ingredients before a plug can be formed. Thus, the occlusion may decrease the efficacy of the antiperspirant rather than increase efficacy due to enhanced penetration.

Another possible cause for antiperspirant failure is inconsistent application. Compliance is important to achieve optimal results. It takes about 10 days of antiperspirant application for the complete plug to be formed in the sweat duct. If the patient decides after 3 days of application that the antiperspirant has not worked sufficiently, they have not given the product an adequate trial. Furthermore, the plug is completely gone 14 days after the last application. Continuous daily application is necessary to achieve and maintain the sweat reduction effect.

Another consideration is the depth of the plug within the sweat duct. Plugs that are more deeply placed in the sweat gland will provide better sweat reduction than those that are superficially situated. If the plug is very close to the surface, it is possible that it can be removed by the rubbing of clothing or shaving. Patients who complain that antiperspirants do not work may wish to wear loose fitting clothing around the armpits and use only light razor pressure when shaving the armpits. The deepest plugs are created by prescription aluminum chloride solutions, but these formulations must be used carefully as they can irritate skin and ruin natural fabrics, such as rayon, cotton, and silk. More superficial plugs are created by OTC antiperspirants containing aluminum chlorohydrate. Intermediate-depth plugs are created by OTC antiperspirants containing aluminum zirconium chlorohydrate.

Summary

Antiperspirants are a commonly used OTC drug. The creation of a deep plug within the sweat duct ostia is the key to excellent efficacy. This plug is best created by morning and nightly application of an even thin film of antiperspirant to the entire dry armpit. These simple tips may be helpful to the patient who is requiring treatment for hyperhidrosis.

SUNLESS TANNING PRODUCTS

Skin color has always been a source of preoccupation for the human race. There are reports of ancient man using burnt ashes to blacken the skin, Egyptians applying burnt ocher and beetle shells to adorn the face, and American Indians

decorating their bodies with vivid pigments. This concept of self-adornment still persists in the form of recreational tanning. The desirability of a tan was popularized by Coco Chanel, who was famous for her couture fashions. She conceived the idea of using tanned women in advertisements designed to promote her clothing and perfume. Prior to this time, women had shunned the sun, since tanned skin indicated that a woman performed manual labor outdoors. Society women, who dwelled indoors, used their fair skin color as a sign of class status. With the industrial revolution, more and more women were leaving their jobs in the fields to live in the city and work indoors in factories. These women had little time for recreational sunning. Thus, skin tanning became popular as a sign that northerners were able to vacation in a sunny locale.

Despite the known risks of premature aging and skin cancer associated with tanning, this remains a popular practice. Tanning from natural sun exposure or from artificial tanning booth light poses a health risk that is ignored by many. Since the societal desirability of tanned skin among Caucasians has not decreased, skin care manufacturers have searched for ways of achieving tanned skin without photodamage. Products designed to simulate a tan without sun exposure are known as sunless tanning creams or sunless tanning creams.

Sunless tanning creams utilize dihydroxyacetone (DHA) as the active agent.[42] This chemical was originally discovered in the 1920s as a possible substitute for sweetener in diabetic diets by Procter & Gamble, Cincinnati, OH. When the DHA was chewed in concentrated form as a candy, it was noted that the saliva turned the skin brown without staining clothing or the mouth. This side effect made the substance unsuitable as a glucose substitute, and DHA was not marketed until the 1950s when the first sunless tanning cream was introduced into the marketplace.

Sunless Tanning Cream Formulation

DHA is a three-carbon sugar that is manufactured as a white, crystalline hygroscopic powder. It interacts with amino acids, peptides, and proteins to form chromophobes known as melanoidins.[43] Melanoidins structurally have some similarities to skin melanin.[44] The browning reaction that occurs when DHA is exposed to keratin protein is known as the Maillard reaction.[45] DHA is technically categorized as a colorant or colorless dye.

DHA is usually added to a creamy base in concentrations of 3%–5%.[46] Lower concentrations of DHA produce mild tanning while higher concentrations produce greater darkening.[47] This allows sunless tanning creams to be formulated in light, medium, and dark shades. The depth of color produced by sunless tanning creams can be enhanced by increasing the protein content of the stratum corneum. This is accomplished by applying a sulfur-containing amino acid, such as methionine sulfoxide, to the skin just before applying the DHA.

As might be expected, skin areas with more protein stain a darker color. For example, keratotic growths such as seborrheic keratoses or actinic keratoses will hyperpigment. Protein-rich areas of the skin, such as the elbows, knees, palms, and soles, also stain more deeply. For this reason, it is advisable to remove all dead skin through exfoliation prior to sunless tanning cream application. DHA does not stain the mucous membranes, but will stain the hair and nails.

The chemical reaction is usually visible within 1 h after DHA application, but maximal darkening may take 8–24 h.[48] Many sunless tanning preparations contain a temporary dye to allow the user to note the sites of application and to promote even application, but this immediate color should not be confused with the Maillard reaction.

Sunless tanning creams have enjoyed a renewed popularity since their original introduction in the 1950s. The original self-tanners produced a somewhat unnatural orange skin color. This problem has been corrected through the use of more purified sources of DHA that yield a more natural golden color. Yet for persons with pink skin tones, the sunless tanning creams may still appear unnatural.

Sunless Tanning Safety

DHA is a nontoxic ingredient both for ingestion and for topical application. It has a proven safety record with only a few reported cases of allergic contact dermatitis.[49] Unfortunately, the browning reaction does not produce adequate photoprotection. At most, sunless tanning preparations may impart an SPF of 3–4 to the skin for up to 1 h after application.[50] The photoprotection does not last as long as the artificial tan. The brown color imparts limited photoprotection at the low end of the visible spectrum with overlap into the UVA portion of the spectrum.[51] DHA used to be approved as a sun-protective agent in combination with lawsone; however, the new sunscreen monograph has removed this ingredient largely due to its lack of popularity.

The staining reaction that occurs with DHA is limited strictly to the stratum corneum and can be readily removed with tape stripping and exfoliation. Thus, the product must be reapplied daily to maintain the optimal skin darkening. There are no known side effects, except for possible irritation, from frequent application. The DHA does have a distinct odor, which is difficult to mask with fragrances.

Summary

Sunless tanning creams are a safe, cost-effective, efficient manner to obtain temporary skin darkening. They should not be used in place of a sunscreen, however. A natural simulated tan can be achieved by applying the sunless tanning cream evenly to the desired areas. Care should be taken to apply less product to easily stained areas, such as the ankles, knees, elbows, and toes. The hands should be washed immediately following application to prevent unnatural staining of this skin surface. The product should not be applied to the hair or nails. Many times a more even application can be obtained by exfoliating large areas, such as the arms and legs, prior to application with a puff or scrubbing cream. Any loose skin scale will pigment more deeply than the surrounding skin.

Since a tan remains fashionable in our modern millennium society, sunless tanning creams should be used to stain the skin rather than risking sun exposure, which will ultimately result in premature skin aging and skin cancer.

SUMMARY

This chapter has summarized the major issues in skin care to include cleansers, moisturizers, antiperspirants/deodorants, and sunless tanning creams. These are all products that dramatically affect skin health, but are necessary for modern hygiene. An understanding of these products is important to the physician as patients frequently request advice on product use and selection. Further, some dermatologic problems may be related to improper product use. It is hoped that this chapter has provided a brief overview of skin care.

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Part XV

Cardiovascular Rehabilitation and Secondary Prevention

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80 Stress Testing for the Coronary Patient
Beyond ST Segment Depression

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CONTENTS

Exercise Stress Testing 1005
Protocols 1005
Nomograms 1006
Peak Heart Rate Nomograms 1006
Functional Capacity Nomograms 1007
Prognostic Significance of Exercise Stress Testing 1007
Cardiopulmonary Exercise Stress Testing 1009
ACC/AHA Guidelines for CPET 1010
ACC/AHA Guidelines for Orthotopic Heart Transplantation (OHT) 1012
Pharmacologic Stress Testing with Imaging 1013
Conclusion 1013
References 1013

ST segment changes remain an essential tool to detect myocardial ischemia, but so much more clinical information can be derived from a stress test. Other components of the electrocardiogram (ECG) are just as useful, as well as an assessment of symptoms, hemodynamics, and exercise capacity. In this chapter, we discuss the importance of stress testing beyond the interpretation of the ST segment. We will review exercise protocols, nomograms, Bayes's theorem, diagnostic and prognostic considerations of stress testing, utility of cardiopulmonary stress testing, and pharmacologic stress testing with cardiac imaging for non-ambulatory patients. When relevant, we also denote gender differences.

EXERCISE STRESS TESTING

Exercise stress testing has traditionally been conducted as a diagnostic tool focused on ST depression and/or onset of angina symptoms as indications of underlying obstructive coronary artery disease (CAD). The stress test can be performed using a treadmill (common in the United States) or a cycle ergometer (common in Europe). From a diagnostic standpoint, greater exercise-induced ST depression and anginal symptoms have been reported for treadmill exercise versus cycle ergometer testing. Comparison of treadmill and cycle ergometry also reveals maximal oxygen uptake 10%–20% higher for the treadmill and maximal heart rate (HR) 5%–20% lower for the cycle ergometer.[1,2]

Many exercise laboratories in the United States have both the treadmill and cycle ergometer available, but the treadmill is the preferred modality for exercise testing in the United States. For motor-driven treadmills, the patient must work at the set speed and grade based on a chosen exercise protocol. Several treadmill exercise protocols exist, and no one protocol is optimal for all subjects. The patient's reported exercise tolerance and specific limitations to activity should be considered when selecting the appropriate protocol.

PROTOCOLS

The use of exercise to elicit anginal symptoms, associated ST depression, or both was documented as early as 1928.[3] However, it was not until the middle of the century that exercise protocols were standardized. The Bruce treadmill protocol was one of the first attempts to standardize progressive exercise testing to evaluate cardiac function. It is arguably the most commonly used exercise test protocol in medicine despite its significant limitations in a clinical population. The staged protocol starts at approximately five metabolic equivalents (METs) and progresses in two to three MET increments every 3 min. Although it is used extensively in clinical populations, the Bruce protocol is best suited for healthy, younger subjects since it starts at an intensity beyond the exercise capacity of many patients with cardiovascular disease and progresses in large work increments between stages. Consequently, patients often fail to attain a leveling off or plateauing of physiologic responses, and delineation of the precise MET level at the ischemic or anginal threshold is therefore difficult.

Several protocols have since been developed that have lower initial metabolic demands and stages that progress in constant, gradual, one to two MET increments. No one protocol is best for all subjects. The patient's reported exercise tolerance and specific limitations to activity (cardiac, orthopedic,

TABLE 80.1
Comparison of Functional Class, VO_2 Cost, and METs for Select Treadmill and Cycle Ergometer Protocols

Function Class	Clinical Status	O_2 Cost mL/kg/min	METs	Bicycle Ergometer 1 W = 6 kpds	Treadmill Protocols: Sheffield[a] 3 min Stages		Naughton 2 min Stages		Cornell 2 min Stages		CAEP[b] 2 min Stages		METs
											mph	%g	
		66.5	19		5.5	20					7.0	15	19
		63.0	18	For 70 kg body weight									18
		59.5	17						Mph	%g			17
Normal and		56.0	16		5.0	18			5.0	18.0			
	Healthy, dependent on age, activity	52.5	15										15
	Sedentary, healthy	49.0	14	kpds					4.6	17.0	6.0	10	14
	Limited	45.5	13	1500	4.2	16			4.2	16.0			13
	Symptomatic	42 .0	12	1350							5.0	10	12
I		38.5	11	1200					3.8	15.0			11
		35.0	10	1050	3.4	14	Mph	%g	3.4	14.0	4.0	10	10
		31.5	9	900			2.0	21.0	3.0	13.0			9
		28.0	8	750	2.5	12	2.0	17.5	2.0		3.5	8	8
		24.5	7	600			2.0	14.0	2.5	12.0			7
		21.0	6	450	1.7	10	2.0	10.5	2.1	11.0	3.0	6	6
		17.5	5	300	1.7	5	2.0	7.0	1.7	10.0	2.5	5	5
II		14.0	4	150	1.7	0	2.0	3.5	1.7	5.0	2.0	4	4
III		10.5	3				2.0	0.0			1.5	3	3
IV		7.0	2	150			1.0	0.0	1.7	0.0	1.0	2	2
		3.5	1									1	

Source: Adapted from Pashkow, F.J. and Dafoe, W., *Clinical Cardiac Rehabilitation: A Cardiologist's Guide*, Lippincott Williams & Wilkins, Baltimore, MD, 1999.

[a] This is the Bruce protocol with two additional stages of 1.7/0 and 1.7/5.

[b] Cleveland Clinic Chronotropic Assessment Exercise Protocol.

pulmonary, neuromuscular, as well as patient preference) should be considered when selecting the appropriate protocol. Protocols that are too aggressive provide limited data and may grossly overestimate functional capacity. In general, protocols that reach termination criteria between 8 and 12 min provide adequate and reliable data. See Table 80.1 for a comparison of common protocols for treadmill testing.

NOMOGRAMS

The clinical value of any test is dependent on the standardized application of test procedures, appropriately calibrated equipment, and objective interpretation of test data. For maximal/symptom-limited stress testing, the patient is a critical variable that modulates test results. If a test is prematurely terminated, key information may be missed and the predictive/prognostic value of the study will be negatively impacted.

Peak Heart Rate Nomograms

Nomograms that predict maximal HR are one tool that clinicians use to assess the quality of effort put forth by the patient. Maximal HR nomograms are also used to determine chronotropic incompetence and HR recovery abnormalities, both of which have significant prognostic significance with respect to mortality and morbidity.

The most common nomogram to determine peak HR has been the following equation:

$$\textit{Age-predicted Max Heart Rate} = 220 - \textit{Age in years}$$

Although widely accepted and applied, a review of the origins of this formula found no published scientific research supporting its development. The large standard deviation of this equation (approximately ±11 bpm) and the lack of documentation regarding its validity and reliability bring its utility into question.[4]

A meta-analysis of maximal HRs from 351 studies including 18,712 subjects was conducted to develop an age-predicted HR max equation. The equation was then cross validated in 514 healthy subjects. This robust study yielded the following equation[5]:

$$\textit{Age-predicted Max Heart Rate} = 208 - 0.7\,(\textit{age in years})$$

Despite the large sample size of the meta-analysis, the applicability to women remained a concern, since the majority of the subjects were men. A female-specific prediction equation was later developed using data from 5437 asymptomatic women who underwent symptom-limited exercise testing in the St. James Women Take Heart Project. When predicting maximal HR for women, the authors recommend use of the following equation[6]:

$$\textit{Age-predicted Maximal Heart Rate} = 206 - 0.88\ (\textit{age in years})\ (SD = 11.8)$$

Although greater attention has been paid to the validity and accuracy of maximal HR prediction equations, there is no one ideal equation. To best predict maximal HRs, the population-derived equation that best fits the individual being tested should be utilized.

It is also important to emphasize that the equations referenced earlier are based on generally healthy populations, free of medications and clinical conditions that could reduce the maximal HR. Application to clinical populations is limited. For all these reasons, termination of exercise testing at a set percentage of age-predicted maximal HR is inappropriate when attempting to assess functional capacity, chronotropic response, HR recovery, or even ST depression.

Functional Capacity Nomograms

Functional capacity is a powerful prognostic variable for all-cause and cardiovascular mortality.[7] Several equations to predict functional capacity, based on age, gender, and activity status, have been published.[8] Nomograms based on maximal exercise tests of healthy active as well as sedentary men have also been developed. These nomograms can be used to express a patient's exercise capacity as a percent of his expected age- and activity-matched group.[9]

One of the largest samples of normative data for maximal oxygen consumption (VO_2 max), a measurement of functional capacity, comes from the Cooper Institute with data from exercise tests on over 44,000 men and nearly 15,000 women. The data are presented in percentile by age and gender. A VO_2 max lower than the 20th percentile has been associated with a 3.44-fold increased risk of mortality in men and a 4.65-fold increased risk in women[10] (see Table 80.2).

PROGNOSTIC SIGNIFICANCE OF EXERCISE STRESS TESTING

Stress testing is widely used for the detection of CAD. Exercise electrocardiography is reported to have a sensitivity of 60%–75% and specificity of approximately 80%–85% using the criterion of ≥1 mm ST segment depression at 80 ms beyond the J point. However, the interpretation of these results is highly dependent on the prevalence of the disease in the population being evaluated.

Bayes's theorem: Bayes's theorem relates the probability of disease after the results of a test are known (posttest likelihood) to the pretest likelihood of disease as well as the characteristics of the test itself (sensitivity and specificity).[11] Thus a patient with a low likelihood of disease (5% pretest likelihood) who has an abnormal exercise test response has only a 17% likelihood of disease if a sensitivity of 60% and specificity of 85% are used in Bayes's analysis. Therefore, most positive tests in a low-risk population will be "false-positive" results. The power of an exercise test to detect underlying CAD is greatest when the pretest probability for CAD is moderate (i.e., 40%–60%).

Exercise capacity: In most epidemiologic studies that have employed exercise stress testing, functional capacity, expressed as mL/kg/min or METs, is a very strong predictor of subsequent cardiovascular mortality. In a study of 3400 consecutive adults referred for single-photon emission computed tomography (SPECT) testing, patients with fair or poor functional capacity had markedly higher all-cause mortality at 2 years of follow-up with 81% of deaths occurring in this group.[12] In another study involving 6213 men, exercise capacity was the strongest predictor of the risk of death after adjustment for age. For each one-MET increase in exercise capacity, there was a 12% improvement of survival.[7] Similarly, in a cohort of 5700 asymptomatic women who underwent peak or symptom-limited stress testing, there was a 17% decrease in mortality (after adjusting for age and Framingham Risk Score) for each one-MET increase in exercise capacity.[13] In general, subjects with an exercise capacity less than six METs had a poor prognosis in each of these studies.

Exercise-induced angina: Angina pectoris is a common symptom elicited during exercise stress testing among patients with significant CAD. The Duke group reported that either non-limiting or exercise-limiting angina was an important prognostic variable in their database of over 2000 patients (both inpatient and outpatient).[14] However, subsequent analyses of other databases have not shown an independent predictive value of exercise-induced angina. In the Coronary Artery Surgery Study, exercise-induced angina was not predictive of survival when catheterization variables, exercise time, and ST depression were included in the survival model.[15] Similarly, in a study involving elderly patients, exercise-induced angina was not predictive of survival (workload was the only variable predictive of death).[16]

Exercise-induced arrhythmias: A number of investigators have reported the prognostic significance of premature ventricular contractions (PVCs) during exercise. Jouven et al. postulated that PVCs would have no effect on long-term prognosis if PVCs during exercise were a "normal finding." They recorded ECGs during each stage of exercise and during recovery. Patients were defined as having frequent ectopy if they had greater than 10% PVCs at any recording. They followed 6101 men for a mean duration of 23 years. A small but significant number (2.3%) had frequent PVCs during exercise. This group had an increased risk of death during

TABLE 80.2
Percentile of Maximal Aerobic Capacity by Age and Gender (VO_2 Expressed in mL/kg/min and METs)

	Males: Max VO_2 (mL/kg/min)							Female: Max VO_2 (mL/kg/min)						
Percentile	Age 20–29	Age 30–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79	Functional Rating[a]	Age 20–29	Age 30–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79	Functional Rating
99	61.2	58.3	57.0	54.3	51.1	49.7	S	55.0	52.5	51.1	45.3	42.4	42.4	S
90	54.0	52.5	51.1	46.8	43.2	39.5		47.5	44.7	42.4	38.1	34.6	33.5	
80	51.1	47.5	46.8	43.3	38.5	36.0	E	44.0	41.0	38.9	35.2	32.3	30.2	E
70	48.2	46.8	44.2	41.0	36.7	33.0		41.1	38.8	36.7	32.9	30.2	28.4	
60	45.7	44.4	42.4	38.3	35.0	30.9	G	39.5	36.7	35.1	31.4	29.1	26.6	G
50	43.9	42.4	40.4	36.7	33.1	29.4		37.4	35.2	33.3	30.2	27.5	25.1	
40	42.2	41.0	38.4	35.2	31.4	28.0	F	35.5	33.8	31.6	28.7	26.6	23.8	F
30	40.3	38.5	36.7	33.2	29.4	26.0		33.3	32.3	29.7	27.3	24.9	22.2	
20	38.1	36.6	34.6	31.1	27.4	23.7	P	31.6	29.9	28.0	25.5	23.7	21.2	P
10	35.2	33.8	31.8	28.4	24.1	20.8	VP	29.4	27.4	25.6	23.7	21.7	19.3	VP
	Males: Max VO_2 (METS)							Female: Max VO_2 (METS)						
Percentile	Age 20–29	Age 30–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79	Functional Rating[a]	Age 20–29	Age 30–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79	Functional Rating
99	17.5	16.7	16.3	15.5	14.6	14.2	S	15.7	15.0	14.6	12.9	12.1	12.1	S
90	15.4	15.0	14.6	13.4	12.3	11.3		13.6	12.8	12.1	10.9	9.9	9.6	
80	14.6	13.6	13.4	12.4	11.0	10.3	E	12.6	11.7	11.1	10.1	9.2	8.6	E
70	13.8	13.4	12.6	11.7	10.5	9.4		11.7	11.1	10.5	9.4	8.6	8.1	
60	13.1	12.7	12.1	10.9	10.0	8.8	G	11.3	10.5	10.0	9.0	8.3	7.6	G
50	12.5	12.1	11.5	10.5	9.5	8.4		10.7	10.1	9.5	8.6	7.9	7.2	
40	12.1	11.7	11.0	10.1	9.0	8.0	F	10.1	9.7	9.0	8.2	7.6	6.8	F
30	11.5	11.0	10.5	9.5	8.4	7.4		9.7	9.2	8.5	7.8	7.1	6.3	
20	10.9	10.5	9.9	8.9	7.8	6.8	P	9.0	8.5	8.0	7.3	6.8	6.1	P
10	10.1	9.7	9.1	8.1	6.9	5.9	VP	8.4	7.8	7.3	6.8	6.2	5.5	VP

Source: Adapted from Thompson, W. et al., *ACSM's Guidelines for Exercise Testing and Prescription*, 8th edn., Lippincott Williams & Wilkins, Philadelphia, PA, 2010.

[a] S, superior; E, excellent; G, good; F, fair; P, poor; VP, very poor.

follow-up (41.3% vs. 26.3% in the group with no PVCs).[17] Frolkis et al. used the criteria of greater than seven PVCs per minute to categorize frequent ectopy. Though exercise-induced ectopy was associated with increased all-cause mortality in the 29,000 patients in their cohort, increased PVCs during recovery were a better predictor of death (adjusted hazard ratio of 1.5, CI 1.1–1.9).[18]

Chronotropic incompetence: The HR increase during exercise is a result of withdrawal of parasympathetic inhibition (particularly in early exercise) and an increase in sympathetic tone. The inability to increase the HR adequately has been termed chronotropic incompetence. In one study, men whose resting HR did not increase as expected during daily activity or who had low peak HR response to exercise had a higher rate of sudden death than expected.[19] In another study involving heart failure patients, reduced peak HR was related to decreased sensitivity of the sinoatrial node to sympathetic stimulation.[20]

A number of approaches have been used to characterize the increase in HR with exercise. The classic method is using the regression formula of 220 minus age in years as the predicted maximum HR. The actual measured HR from the exercise test is reported as the percentage of the age-predicted maximum. This simple method unfortunately can be affected by testing modality, test termination criteria, medications, fitness level, and resting HR.

Chronotropic reserve has been used to overcome the problems with the percentage of age-related maximum. Chronotropic reserve is defined as the percentage of HR used (peak HR achieved on the exercise test – rest HR)/(220-age – rest HR) × 100. Using this definition, chronotropic incompetence has been defined as a value less than 80%. In one study involving 1877 men and 1076 women not taking β-blockers who were referred for treadmill thallium testing, a low chronotropic index was associated with an increased risk of death over a 2-year period after adjusting for age, sex, and thallium perfusion defects (adjusted risk 2.19; 95% CI 1.43–3.44).[21] In another study involving 2956 patients, a low percent HR reserve was a better predictor of cardiac death and all-cause mortality than failure to achieve 85% of the age-predicted maximal HR.[22]

Heart rate recovery: During the first few minutes after exercise, there is a significant decrease in HR, which is related to parasympathetic reactivation. Due to the known relationship of HR variability and cardiovascular mortality thought to be related to autonomic function (particularly parasympathetic function), it was hypothesized that a decrease in HR recovery would be related to cardiovascular mortality in a patient population referred for stress testing. In one study involving 2428 patients referred for a treadmill SPECT test, an abnormal value for 1 min HR recovery (less than 12 bpm drop) was strongly predictive of death, even after adjusting for confounding variables like age, sex, medications, thallium myocardial perfusion defects, known cardiac risk factors, resting HR, change in HR during exercise, and workload achieved (adjusted risk 2.0; CI 1.5 – 2.7).[23] In another study involving 5713 asymptomatic working men (ages 42–53) who underwent cycle ergometer exercise testing, there was an increased risk of sudden cardiac death in men who had a resting HR >75 bpm (relative risk 3.92), those who failed to increase their HR to 89 bpm (relative risk 6.18), and those who failed to decrease their HR by 25 bpm at 1 min postexercise (relative risk 2.20). This study emphasizes the differences of HR response to exercise and recovery during the cooldown period depending on the protocol used.[24]

Duke treadmill score: A number of studies have tried to incorporate many of the variables described earlier into a single risk score. The most widely accepted prognostic score is the Duke Treadmill Score, which incorporates exercise time (minutes), using the conventional Bruce Protocol, the magnitude of ST segment depression (mm), and anginal symptoms (0, none; 1, mild pain during test; 2, moderate-to-severe pain, which is the reason for termination of the test).

The Duke Treadmill Score = exercise time – (5 × ST displacement) – (4 × angina index). Investigators divided the patient cohort into three classes low risk (>5), moderate risk (–10 to +4), and high risk (–11 or lower). The score was derived on a population of 2842 consecutive inpatients who underwent an exercise stress test and cardiac catheterization and subsequently validated in outpatients. The high-risk group had a markedly worse 4-year survival (79% vs. 99% in low-risk group).[14] This score seems to be applicable to multiple populations; however, a subsequent study questioned its validity in the elderly (>75 years).[25]

CARDIOPULMONARY EXERCISE STRESS TESTING

Cardiopulmonary exercise stress testing (CPET) is the most objective and accurate way to assess exercise capacity while also distinguishing between cardiac and noncardiac causes of exercise intolerance or suboptimal effort. During CPET, progressive staged exercise is performed while analyzing breath-by-breath gas exchange using a mouthpiece or face mask connected to a non-rebreather valve to prevent mixing of inspired and expired air. Respiratory rate, tidal volume, and concentrations for expired oxygen and carbon dioxide are measured to determine oxygen uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) at rest and during exercise to assess exercise capacity. The oxygen and carbon dioxide gas analyzers are usually incorporated into a metabolic cart. The exercise protocols can be either with a cycle ergometer (more typical in Europe) or with a treadmill (more typical in the United States).[26–28] Exercise is ideally symptom limited but should be terminated if the patient develops significant ischemic ECG changes (>2 mm ST depression), hemodynamically unstable arrhythmias, second- or third-degree AV block, decline in systolic blood pressure >20 mmHg from the highest value, systolic blood pressure >250 mmHg or diastolic

blood pressure >120 mmHg, severe oxygen desaturation ≤80%, respiratory failure, or sudden pallor.[27]

Indications: CPET has been used to determine the cause of exertional shortness of breath, functional capacity, and candidacy for heart transplantation. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for CPET are outlined below in the following.[29]

ACC/AHA GUIDELINES FOR CPET[29]

Class	Indication
Class I	1. Evaluation of exercise capacity and response to treatment in patients with heart failure who are being considered for heart transplantation 2. Assistance in the differentiation of cardiac versus pulmonary limitations as a cause of exercise-induced dyspnea or impaired exercise capacity when the cause is uncertain
Class IIa	Evaluation of exercise capacity when indicated for medical reasons in patients for whom the estimates of exercise capacity from exercise test time or work rate are unreliable
Class IIb	1. Evaluation of the patient's response to specific therapeutic interventions in which improvement of exercise tolerance is an important goal or endpoint 2. Determination of the intensity for exercise training as part of comprehensive cardiac rehabilitation
Class III	Routine use to evaluate exercise capacity

Measurement of exercise capacity: Exercise capacity (also called functional capacity) is defined as the maximum ability of the cardiovascular system to deliver oxygen to skeletal muscle and for the skeletal muscle during maximum exercise to extract oxygen from the blood.[28] During exercise stress testing, we can approximate work performed (functional capacity) by estimating the peak MET with regression formulas based on the workload attained, as well as the duration of exercise:

$$1\ \text{MET} = 3.5\ \text{mL/kg/min of oxygen consumed}^{26}$$

However, the usage of MET to approximate work may be inaccurate when exercise duration is impacted by inappropriate protocol selection, nonstandardized testing procedure (i.e., handrail holding), abnormal gait/balance, suboptimal effort, cardiovascular disease, as well as noncardiac factors such as lung disease. Therefore, methods that directly measure oxygen consumption are preferred. Exercise effort during CPET can also be established with the measures of carbon dioxide production (VCO_2) and VE, which can be used to determine relative effort (respiratory exchange quotient) and the anaerobic threshold.[27] These important cardiopulmonary measurements in addition to oxygen consumption are further defined in the following text:

Maximum oxygen consumption (*max* VO_2): In normal healthy people, oxygen consumption increases with exercise intensity/workload and then reaches a plateau despite increasing workload. This plateau in oxygen consumption is referred to as the maximum oxygen consumption. It represents the aerobic capacity and is further related to hemodynamics by the Fick equation:

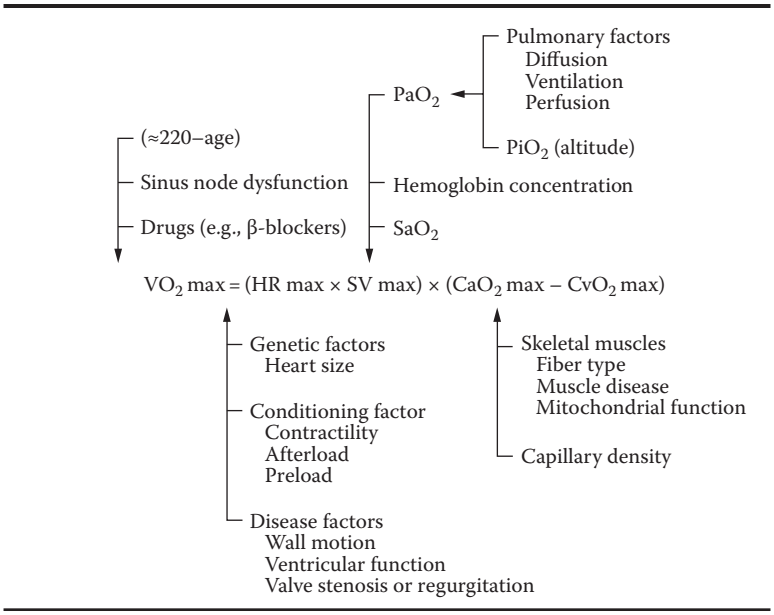
$$VO_2\ \text{max} = (\text{SV max} \times \text{HR max}) \times (CaO_2\ \text{max} - CvO_2\ \text{max})$$

where
- max is maximum
- SV is stroke volume
- HR is heart rate
- SV × HR is cardiac output
- CaO_2 is arterial oxygen content
- CvO_2 is mixed venous oxygen content

Therefore, maximum oxygen consumption is achieved when further increments in work produce no additional increases in stroke volume, HR, or tissue O_2 extraction[27,28] (see Figure 80.1).

Peak oxygen consumption (*peak* VO_2): Peak oxygen consumption is the highest oxygen consumption achieved by an individual during progressive exercise to volitional fatigue or adverse signs/symptoms. It can be equal to the maximum oxygen consumption; however, this is rarely the case.[28] The main determinants of peak VO_2 are genetic factors, muscle mass, gender, age, habitual physical activity, and body size. Exercise training can further increase a patient's peak VO_2, and poor motivation during exercise testing can cause an "abnormally low" peak VO_2.[27]

Ventilatory threshold: It was previously referred to as anaerobic threshold. CO_2 levels drive ventilation. As exercise intensity increases, the metabolic demands reach a point where the demand exceeds the ability of the body to meet this predominately via aerobic metabolism and an increased reliance on anaerobic metabolism occurs. It is the point at which a nonlinear relationship between VE and VO_2 or VCO_2 and VO_2 is noted, secondary to the increased CO_2 production that buffers lactic acid produced by anaerobic metabolism. It is an indicator of submaximal exercise tolerance and, in general, occurs at 45%–65% of VO_2 max. The VT can be identified invasively or noninvasively. Invasively, the anaerobic threshold can be identified using serial blood samples with the rise in lactic acid or via the decline in bicarbonate levels. Noninvasively, which is the more common method, it is usually identified by two methods: (1) ventilatory equivalents method and (2) V-slope method using regression analysis (see Figure 80.2).[27,28] During progressive exercise, VE increases linearly with CO_2 production due to detection by chemoreceptors in the carotid body. In the early phase of exercise, the CO_2 production is aerobic and plasma lactic acid levels are low. In the later phase of exercise, the oxygen demand by



VO_2, oxygen (O_2) uptake; SV, stroke volume; HR, heart rate; PiO_2, partial pressure inspired; O_2, FiO_2 × Patmospheric; CaO_2, arterial oxygen content; CvO_2, mixed venous oxygen content.

FIGURE 80.1 Determinants of VO_2 max in the Fick Equation. (From UpToDate: Functional exercise testing: Ventilatory gas analysis, available at http://www.Uptodate.Com/contents/functional-exercise-testing-ventilatory-gas-analysis?Source=search_result&search=functional+exercise+testing&selectedtitle=1%7e33, last accessed on January 27, 2012. With permission.)

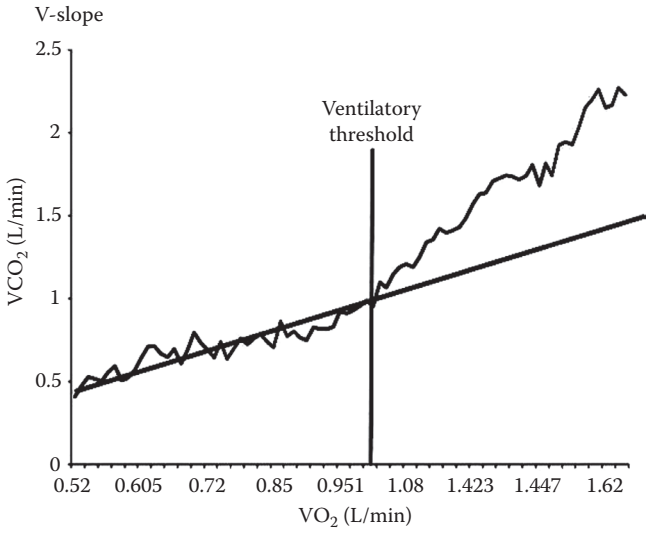


FIGURE 80.2 Determination of the ventilatory anaerobic threshold. (From Franco, V., *Curr. Heart. Fail. Rep.*, 8, 45, 2011. With permission.)

the muscle exceeds the metabolic supply and increasing reliance on anaerobic metabolism occurs, with the production of lactic acid. The lactic acid is buffered by sodium bicarbonate based on the carbonic anhydrase reaction:

$$HLa + NaHCO_3 \rightarrow NaLa + H_2CO_3 \rightarrow CO_2 + H_2O$$

The CO_2 produced during anaerobic metabolism is added to the aerobically produced CO_2 leading to disproportionate rise in VCO_2 and VE compared with VO_2.[26]

Respiratory exchange ratio: Respiratory exchange ratio (RER) is determined by the ratio of carbon dioxide production/oxygen uptake (VCO_2/VO_2). During rest and early exercise, VCO_2 production is slightly below oxygen consumption due to the reliance on aerobic metabolism and free fatty acids as the primary fuel source. As exercise intensity increases, there is a greater reliance on glucose as a fuel source and an increase in anaerobic metabolism for ATP production. Once the VT is reached, non-metabolic carbon dioxide is produced resulting in a disproportionate rise of VCO_2 relative to VO_2. RER values <1.0 reflect poor effort assuming that the patient is not limited by respiratory conditions, peripheral or myocardial ischemia, or neuromuscular disease. A RER between 1.0 and 1.1 indicates fair effort, 1.1–1.2 good effort, and >1.2 excellent effort, providing subsidiary evidence that a "true" max VO_2 has been attained.[26]

Differentiation of cardiac versus pulmonary symptoms: ACC/AHA guidelines recommend CPET to help evaluate shortness of breath and impaired exercise capacity when the cause remains unclear by history, physical examination, and laboratory tests.[29] CPET provides the unique opportunity to simultaneously assess physical effort, oxygen utilization, and exercise capacity. Impaired breathing reserve (BR) (<30%)

and desaturation during exercise suggest a pulmonary cause for symptoms.[30] BR is calculated by the following formula:

$$BR = 1 - \text{Peak minute ventilation following CPET/Maximum voluntary ventilation}$$

Maximum voluntary ventilation (MVV) is the maximum volume of air that can be inhaled and exhaled in 1 min.[31] MVV can be directly measured (ideal, especially if pulmonary limitation is suspected) or estimated using force expiratory volume in 1 s (FEV_1) × 40.[28] Arterial oxygen desaturation during peak exercise usually reflects underlying pulmonary disease or pulmonary hypertension but can also occur with congenital heart disease.[32]

Cardiac causes limiting exercise usually result in a low peak VO_2.[28] If the peak RER is adequate and VT and BR are normal, the cause is likely due to CAD or deconditioning. Heart failure often is identified by low peak VO_2, low absolute (high relative) VT, and normal BR (see Figure 80.3). However, these responses must be distinguished from poor effort, which will also be signified by a low RER. Low peak VO_2 and anaerobic threshold with low RER and low BR may also be seen with pulmonary disease, which may also represent a cause of exercise limitations.[28] Many patients are limited by both cardiac and pulmonary diseases, and a CPET algorithm can be used to help clarify the underlying causes (see Figure 80.3).

Prognostic significance in heart failure patients: ACC/AHA guidelines recommend CPET to determine optimal timing for heart transplantation in ambulatory patients with heart failure.[29] One of the most important predictors of mortality used to determine the need for transplantation is peak VO_2. According to ACC/AHA 2009 updated guidelines for management of heart failure, heart transplantation is indicated for the following:

ACC/AHA GUIDELINES FOR ORTHOTOPIC HEART TRANSPLANTATION (OHT)

Absolute OHT indication: Peak VO_2 < 10 mL/kg/min with achievement of anaerobic metabolism

Relative OHT indication: Peak VO_2 11–14 mL/kg/min (or <55% predicted) and major limitations in the performance of daily activities

Although these guidelines are not gender specific,[33] studies have shown that women often have a better prognosis than men for any given peak VO_2[34,35] (see Figure 80.4). Sex differences have also been noted in treadmill exercise time using a modified Naughton protocol, and the prognostic significance of treadmill exercise time may be similar to peak VO_2 based on one large single-center study.[36] Another important prognostic variable is the peak VE to carbon dioxide production slope (VE/VCO_2). In one study involving 470 heart failure patients, $VE/VCO_2 > 44.7$ was the strongest predictor of death and more important in predicting 18 month survival than a peak VO_2 < 14 mL/kg/min.[37] Others have reported poor outcomes with lower VE/VCO_2 slope including one study noting poor prognosis for heart failure patients with a VE/VCO_2 slope > 34.[38] Most of these studies have included heart failure patients with impaired systolic function; however, in a cohort of heart failure patients with both preserved and impaired systolic function, both peak VO_2 and VE/VCO_2 were powerful predictors of mortality.[39]

In summary, CPET is useful to determine the cause of exercise limitations and shortness of breath. Many variables measured during CPET have prognostic significance,

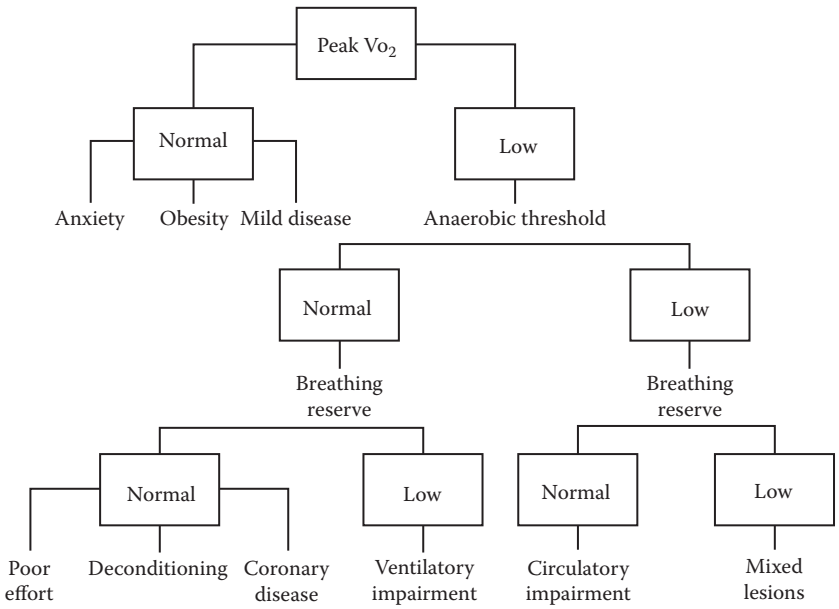


FIGURE 80.3 Evaluation of shortness of breath and fatigue with cardiopulmonary stress testing. (From Neuberg, G.W. et al., *Arch. Intern. Med*., 148, 2221, 1998. With permission.)

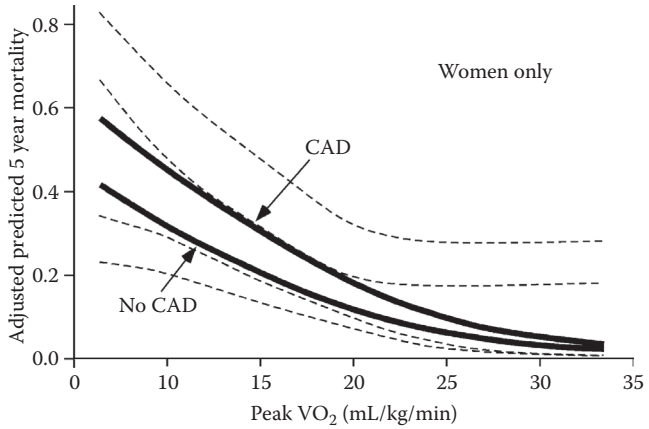


FIGURE 80.4 Adjusted predicted mortality in women with heart failure and impaired systolic function based on peak VO_2 and the presence or absence of CAD. (Adapted from Hsich, E. et al., *Am. J. Cardiol*., 100, 291, 2007. With permission.)

especially in heart failure patients. CPET is also useful in prescribing the intensity for exercise training as part of comprehensive cardiac rehabilitation.

PHARMACOLOGIC STRESS TESTING WITH IMAGING

The development of pharmacologic stress testing provides a noninvasive methodology to assess myocardial ischemia among patients who have contraindications or limitations in performing incremental exercise. The pharmacologic agents used are either vasodilators (dipyridamole, adenosine, regadenoson) or inotropes (dobutamine), and stress testing is usually performed with cardiac imaging (nuclear perfusion imaging or by echocardiography). Often the pharmacologic stress agent chosen is based on information regarding the patient, caffeine intake, concomitant medical therapy, and experience of the medical facility.

Vasodilators: Vasodilators used as pharmacologic agents for stress testing are drugs that cause coronary vasodilation mediated by A2A adenosine receptor stimulation. Relative differences in blood flow between stenotic versus normal coronary vessels during vasodilation help identify cardiac ischemia during stress testing. Vasodilator agents are often preferred for patients with left bundle branch block, hypertension, or aortic aneurysms. The drugs are contraindicated in patients with hypotension, high-degree AV block, sick sinus syndrome without a pacemaker present, dipyridamole usage, and significant reactive airway disease. Nonselective stimulation of adenosine receptors with these agents (more common with adenosine and dipyridamole) can lead to bronchospasm, which can be reversed with aminophylline. Caffeine and theophylline are adenosine receptor antagonists and should be discontinued 24 h prior to pharmacologic stress testing with these vasodilators. Nitrates are vasodilators that should also be discontinued prior to testing since they can alter the extent and the severity of perfusion defects.[40,41]

Dobutamine: Dobutamine is an inotrope used in pharmacologic stress testing for patients who are not candidates for vasodilators. The drug is given intravenously in increments to increase the HR to 85% of age- and gender-predicted maximum (starting with dobutamine 5 mcg/kg/min and increasing to a maximum of 40 mcg/kg/min). Atropine may be administered if goal HR is not achieved. Since dobutamine is a β-receptor agonist, it is less effective in patients who are using β-blockers. Side effects of dobutamine include arrhythmias, left ventricular cavity obliteration, and hypertension.[40,41]

Comparison of pharmacologic agents: A meta-analysis was performed involving 82 studies and over 10,000 patients to determine which pharmacologic agent best predicted significant CAD. The investigators compared adenosine, dipyridamole, and dobutamine stress testing, and all patients underwent cardiac catheterization. Adenosine and dipyridamole had similar sensitivities and specificities. Echocardiography increased the specificity of dipyridamole stress testing when compared with dipyridamole SPECT imaging but had a lower sensitivity. Dobutamine was the preferred agent in this meta-analysis with the highest sensitivity and specificity when combined with echocardiography (80% sensitivity, 84% specificity).[42] Although this analysis preceded the era of regadenoson, usage of this drug would be considered similar to the other vasodilators. Often, the decision to perform a given test is dependent on the experience of the center and additional factors regarding the patient.

CONCLUSION

This chapter reviewed the methodology and interpretation of stress testing beyond ST segment depression. The preferred stress test for most patients is an exercise stress test since this method can simultaneously assess functional capacity, concomitant ECG changes, symptoms, and hemodynamics during progressive activity. Cardiopulmonary stress testing is often utilized to help clarify the etiology of shortness of breath (cardiac vs. pulmonary) and, for heart failure patients, to aid in the optimal timing for cardiac transplantation. Pharmacologic stress testing should be reserved for patients who cannot achieve an adequate level of exercise stress or have ECG changes (e.g., left bundle branch block) that may limit the interpretation of results.

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81 Exercise Prescription for the Coronary Artery Disease Patient

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CONTENTS

Introduction 1017
Inpatient Cardiac Rehabilitation 1018
Outpatient Cardiac Rehabilitation 1018
Cardiorespiratory Exercise Training 1019
Mode of Cardiorespiratory Exercise 1019
Intensity of Cardiorespiratory Exercise 1019
Prescribing Exercise Intensity without Exercise Test Data 1020
Duration of Cardiorespiratory Exercise 1021
Frequency of Cardiorespiratory Exercise 1021
Progression of Cardiorespiratory Exercise 1021
Prescribing Exercise Based on Total Energy Expenditure 1021
Prescribing Exercise for Weight Management in Cardiac Rehabilitation 1022
Resistance Exercise Training 1023
Special Considerations for Prescribing Exercise in Coronary Artery Disease Patients 1024
Myocardial Ischemia/Infarction 1024
Surgical/Catheter-Based Revascularization 1024
Implanted Pacemaker/Defibrillator 1024
Diabetes (Type 1 and 2) 1024
Hypertension 1025
Summary 1025
References 1025

INTRODUCTION

Exercise professionals working with patients with coronary artery disease (CAD), both in (inpatient) and out of hospital (outpatient), must possess the knowledge to develop and modify exercise prescriptions for both cardiorespiratory (CR) endurance and musculoskeletal resistance training (RT). Exercise training prescriptions for CR-type exercise should include an individualized intensity, frequency, duration, mode, and rate of progression. This process involves more than target heart rate (HR) ranges and should emphasize the importance of total energy expenditure for the secondary prevention of CAD. This chapter will also address the issue of generating an exercise prescription in the absence of maximal exercise "stress" test data, a common occurrence in this era of cost containment. Prescribing RT for CAD patients requires careful consideration and will be discussed in this chapter. Finally, this chapter will conclude with a section that describes the special considerations and/or modifications of the exercise prescription for some of the more common conditions/comorbidities seen in CAD patients, including those with a history of (1) myocardial ischemia/infarction, (2) postcoronary revascularization, (3) implanted pacemakers and/or defibrillation, (4) heart failure, (5) diabetes, or (6) hypertension.

The optimal exercise prescription should be determined from an objective evaluation of an individual's responses to graded exercise and should take into account an individual's health status, chronic disease risk factors, behavioral readiness for change, personal goals, and exercise preferences. The purpose of an individualized exercise prescription is to (1) enhance some facet of physical fitness (e.g., CR endurance, muscular strength/endurance), (2) promote health by modification of chronic disease risk factors (e.g., decrease excess body fat, normalize blood lipids or blood pressure), and (3) ensure safety during exercise participation (i.e., decrease incidence of cardiovascular complications and/or musculoskeletal injuries) [1].

The American College of Sports Medicine (ACSM) [2], American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) [3], and American Heart Association [4] have each published exercise prescription guidelines for CAD patients participating in rehabilitative

exercise programs. A review of these documents reveals that the basic principles related to exercise prescription are generally similar for primary and secondary prevention of CAD, yet some important differences exist. This chapter will describe and illustrate guidelines for prescribing CR and RT exercise programs and begins by looking at the current model of cardiac rehabilitation and discuss how the principles of exercise prescription are applied in this setting.

Beginning in the 1970s, cardiac rehabilitation programs were often divided into four sequential phases (I, II, III, and IV) based on the need for medical supervision and patient monitoring during exercise sessions [3]. Although most cardiac rehabilitation programs still contain the essential elements of these traditional phases, the time periods for the phases have become much less distinct in recent years, and for the most part, the terms *inpatient* and *outpatient rehabilitation* have replaced the Phase I–IV terminology. The combination of cost containment measures by medical insurance providers, along with the realization that many low-risk cardiac patients don't necessarily need the more costly elements of the rehabilitation program (i.e., direct medical supervision and continuous ECG monitoring), has led to a new paradigm for delivery of cardiac rehabilitation services [3]. The contemporary approach to the management of cardiac patients focuses more attention and resources on modification of CAD risk factors in an attempt to lower the patient's risk for disease progression and recurrent cardiac events [1]. Thus, the elements of the exercise prescription are designed to promote safety and to slow/reverse the progression of CAD. This chapter focuses on the exercise prescription guidelines for inpatient and outpatient cardiac rehabilitation programs. Other elements of a comprehensive rehabilitation program (patient education and counseling, risk factor intervention strategies, etc.) are discussed in other chapters.

INPATIENT CARDIAC REHABILITATION

The recommended physical activities and length of hospital stay for cardiac patients will vary depending on the nature of the clinical event precipitating hospitalization (i.e., MI, revascularization, etc.). Historically, Phase I typically lasted from 7 to 14 days and involved a gradual but systematic increase in activities of daily living (ADLs) and low-intensity exercise [3]. While ADLs and low-intensity exercise are still an important part of inpatient rehabilitation, the length of hospitalizations has shortened considerably in recent years, and in many cases, patients are in the hospital only for several days. Thus the amount of time available for inpatient rehabilitation is considerably shorter, and the goals for the program focus more on educating the patient about the disease process, offsetting the deleterious effects of prolonged best rest, assessing the patient's ability to complete ADLs safely prior to discharge, and perhaps most importantly, referral to the outpatient cardiac rehabilitation program. Extensive guidelines for *inpatient* physical activity can be found in the ACSM and AACVPR Guidelines [2,3] and should be reviewed thoroughly. Table 81.1 provides recommendations for the type, intensity, frequency, duration, and progression of physical activities during the inpatient phase [2]. Although structured, multistep inpatient exercise routines are available [2,3] and have been used within rehabilitation programs for years, many patients are now being discharged well before completing such routines. Before hospital discharge, patients should receive instructions outlining physical activities that are appropriate while they are at home, as well as any restrictions in physical activity based on their clinical status. They should also leave the hospital with an outline of physical activities including progressions for completion at home. Finally, all patients should be apprised of outpatient rehabilitation (Phase II) opportunities and encouraged to participate if at all possible. In order to enhance referrals, many hospitals now utilize an "automatic" referral to outpatient cardiac rehabilitation that is triggered when a patient enters the hospital with the appropriate diagnosis [5].

TABLE 81.1
Elements of the Exercise Prescription for Inpatient Cardiac Rehabilitation

Variable	Recommendation
Mode	Self-care activities, ROM, postural changes, walking (hallway or treadmill), stationary cycling, stair climbing
Intensity	Post-Ml: HR < 120 bpm or HR rest + 20 bpm (arbitrary upper limit)
	Postsurgery: HR rest + 30 bpm (arbitrary upper limit)
	RPE < 13 (Borg 6–20 scale)
	To tolerance if asymptomatic
Frequency	Early mobilization: three to four times per day (days 1–3)
	Later mobilization: two times per day (beginning on day 4)
Duration	Intermittent bouts lasting 3–5 min
	Rest periods at patient's discretion, last 1–2 min (shorter than exercise bout duration)
	Total duration of up to 20 min
Progression	Initially increase duration to 10–15 min, then increase intensity

HR, heart rate; ROM, range of motion; RPE, rating of perceived exertion.

OUTPATIENT CARDIAC REHABILITATION

Soon after hospital discharge, eligible cardiac patients should enter a structured outpatient cardiac rehabilitation exercise program designed to meet the following goals [3]:

- Optimal management of CAD risk factors to maximize secondary prevention
- Implementation of a safe and effective exercise program that is ultimately self-monitored
- Return to pre-event vocational and/or recreational activities with modifications when necessary

TABLE 81.2
Elements of the Aerobic Exercise Prescription

Variable	Recommendation
Mode	Aerobic: rhythmical and continuous in nature
Intensity	55/65 to 90% maximal HR
	40/50 to 85% maximal VO_2R or HR reserve
Frequency	Three to five sessions per week
Duration	20–60 min of continuous or intermittent aerobic activity
Progression	Individualized based on tolerance and adaptation
	Optimally. Maintenance programs should include energy expenditure threshold of >1500 kcal/week

HR, heart rate; VO_2R, oxygen uptake reserve.

An additional goal of the outpatient cardiac rehabilitation program is to provide appropriate medical surveillance for detection of a significant deterioration in the patient's clinical status, whereupon the program staff can alert the appropriate medical professional for assessment and treatment of the patient if necessary. Also patients entering cardiac rehabilitation programs should be "stratified" based on (1) their risk of "untoward events" during exercise training and (2) their risk of CAD progression. The AACVPR Guidelines [3] provide excellent approaches/models for this important aspect of the rehabilitative exercise program. General elements (mode, intensity, frequency, duration, progression) for prescribing CR exercise can be found in Table 81.2 and are discussed in the following text.

Cardiorespiratory Exercise Training

Mode of Cardiorespiratory Exercise

Cardiorespiratory (i.e., "cardio" or "aerobic")-type exercise includes a variety of physical activities that require the use of oxidative aerobic energy pathways and use large-muscle groups continuously and rhythmically. Traditionally, activities such as walking, jogging, cycling, swimming, cross-country skiing, and aerobic dancing are the primary modes for CR exercise training [2]. Moreover, a variety of indoor exercise machines such as stair climbers, recumbent leg cycles, and elliptical trainers, and the like are appropriate and quite popular in cardiac rehabilitation programs. Perhaps the most important consideration in choosing the mode of exercise for a given patient is their level of enjoyment and comfort. If a patient does not enjoy, or at least tolerate, a particular mode of exercise, it is unlikely that they will maintain sufficient compliance to this mode of exercise over time.

Intensity of Cardiorespiratory Exercise

Guidelines for defining an appropriate CR exercise training intensity for patients in secondary prevention programs vary based mainly on the clinical status of the patient (low, moderate, or high risk for exercise complications) [3]. While the general guidelines for prescribing exercise intensity apply to secondary prevention patients, the risks associated with exercise training are greater for those with a history of CAD [6]. For patients with normal responses to graded exercise, the appropriate CR exercise intensity can be based on a percentage of maximal heart rate reserve (MHRR) or percentage of maximal oxygen consumption reserve (VO_2R) [7,8]. For cardiac patients who have normal ECG and hemodynamic responses to graded exercise, the ACSM Guidelines [2] indicate that a minimal-intensity threshold lies between 40% and 50% of a patient's MHRR or VO_2R, with the upper end of the range set at approximately 85%. Once the relative intensity is defined (% VO_2R), a target VO_2 and/or HR range can be calculated (see Table 81.2).

However, for patients who have exercise-induced signs or symptoms (such as angina, hypotension, arrhythmia), the CR exercise training intensity needs to be set below the abnormal response in order to provide a safety buffer during training [2]. Table 81.3 provides a list of abnormal signs and symptoms for which an upper limit for exercise intensity should be set, regardless of the calculated MHRR or VO_2R. In such cases, the CR training intensity should be set at least 10 bpm below the exercise HR associated with any of the signs or symptoms listed in Table 81.3 [2]. In addition, careful monitoring of the patient's symptoms, HR, BP, and ECG is recommended to ensure that the intensity of exercise remains at a safe level.

Most of the medications used to control blood pressure and cardiac arrhythmias do not affect exercise tolerance and have minimal impact on HR and myocardial contractility. However, beta-blockers and some calcium channel blocker (i.e., Diltiazem and Verapamil) will likely decrease HR at rest and during exercise [8]. Consequently, HR ranges calculated to guide CR exercise intensity should be based on exercise test data obtained while patients are taking their standard regimen of medications. If the patient did not take his or her medication before the exercise test (commonly done for "diagnostic" stress tests) or when medication dosage changes, one option is to conduct an exercise "evaluation" (on a bike or treadmill) where patient exercises for several

TABLE 81.3
Signs and Symptoms for Which an Upper Limit for Exercise Intensity Should Be Set

Onset of angina or other symptoms of CV insufficiency
Plateau or decrease in SBP, SBP > 240 mmHg, or DBP > 110 mmHg
≥1 mm ST segment depression, horizontal or downsloping
Radionuclide evidence of LV dysfunction or onset of moderate to severe wall motion abnormalities during exertion
Increased frequency of ventricular arrhythmias
Other significant ECG disturbances (e.g., second- or third-degree AV block, atrial fibrillation supraventricular tachycardia, complex ventricular ectopy)
Other signs or symptoms or intolerance to exercise

minutes at approximately 40% and 80% of VO_{2peak}. HRs obtained at these intensity levels should provide the appropriate exercise intensity [1].

In addition to objective measures of HR and/or VO_2R, ratings of perceived exertion (RPEs) may be used as an adjunct to guide CR exercise intensity in cardiac patients [1–3]. The 15-point [6–20] RPE scale [9,10] is typically used for this purpose with RPE values of 11–13 being recommended for the early outpatient exercise sessions, whereas a range of 12–15 is recommended for the higher training intensities during subsequent exercise training sessions [2,3]. Use of such generalized RPE ranges for monitoring training intensity, such as those reflected earlier, is based on the assumption that a number on the RPE scale equates to a relative physiological intensity (% MHRR or VO_2R) [2]. However, within a given patient, specific RPE values do not always match with a given relative physiological intensity during exercise especially when attempting to transfer RPEs from exercise testing to the exercise training environment [11,12]. To use RPEs effectively for guiding the exercise intensity in cardiac rehabilitation programs, the following are recommended [11]:

- The RPE scale should be described providing explanations of the resting and maximal numbers (6–20, respectively) and reviewing the descriptors assigned to each number on the scale.
- Monitoring takes place in a discreet manner to avoid influence by ratings of other patients exercising in the same area.
- Once the patient reaches a steady-state level during exercise, have the individual rate his or her perceived exertion using the RPE scale. If over the course of several exercise sessions the patient reports a consistent RPE at the same physiological intensity, that RPE may be used, in conjunction with physiological markers, for monitoring the patient's training intensity.
- If the patient's RPEs vary considerably from day to day (at the same physiological intensity) after adequate acclimation, perceived exertion may not be an appropriate means for monitoring physiological intensity for this patient.

Prescribing Exercise Intensity without Exercise Test Data

The use of MHR and/or VO_2 to prescribe the intensity for CR exercise training intensity requires access to data obtained from an exercise "stress" test, preferably one with a "sign/symptom-limited" endpoint. However, a survey [12] of outpatient cardiac rehabilitation programs indicated that 60% do not require exercise stress test at entry to the program. Consequently, in lieu of "objective" exercise test data, the exercise prescription must be generated through other less objective methods. It has been well established that calculating exercise HR ranges based on age-predicting maximal HR formulae (i.e., 220-age) is inappropriate for CAD patients, particularly those on beta-blockers [13,14]. However, there are several "evidence-based" options [2,3] for prescribing exercise without exercise test data, including use of RPEs (as described earlier), resting HR plus an arbitrary value (generally 20 bpm for post-MI or post-CABG patients on beta-blockers or 30 bpm for non-beta-blocked patients), or data form the "talk test" [15,16] to regulate the CR exercise intensity in cardiac rehabilitation programs. Another approach is to perform a submaximal exercise assessment or conduct a 6 min walk test during one of the first outpatient exercise sessions and use HR and/MET levels derived from these tests as target intensities for early training sessions [1].

Joo and colleagues [17] evaluated the common practice of regulating CR exercise intensity using RPE as well as resting HR + 20 bpm in a group of patients entering an outpatient cardiac rehabilitation program. After two introductory/familiarity exercise sessions, patients wore a portable Cosmed ambulatory oxygen uptake analyzer while performing 10 min of continuous track walking at two different (and randomly ordered) exercise intensity levels: RPE levels of 11–13 and rest HR + 20 bpm (or for non-beta-blocked patients). The results demonstrated that prescribing CR exercise, in early outpatient cardiac rehabilitation participants, based on RPE and resting HR + 20/30 resulted in an average VO_2R of 42% and 71%, respectively (Figure 81.1). While the average exercise intensity from both techniques was at appropriate levels (Figure 81.1), using HR + 20/30 patients often exercised at a significantly lower (≤40% of VO_2R) intensity level whereas using RPE 11–12 patients commonly exercised at significantly higher (≥90% VO_2R) intensity levels. These findings suggest that prescribing CR endurance exercise using RPE and rest HR + 20/30 results in a significant amount of intersubject variability (Figure 81.1) and that caution should be used when guiding CR exercise intensity with either of these approaches. Brawner et al. [14] demonstrated that the exercise intensity calculated from resting HR + 20 corresponded with 45% and 31% of HR reserve of beta-blocked and non-beta-blocked CAD patients, respectively.

Pharmacologic stress tests are commonly conducted in patients whose inability to exercise adequately (due to

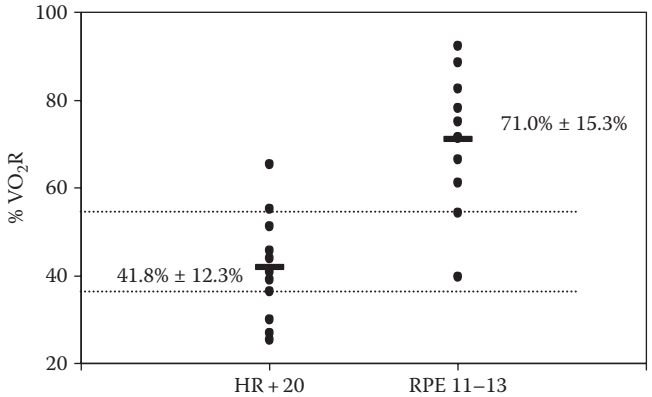


FIGURE 81.1 Average (41.8 ± 12.3% and 71.0 ± 15.3%, respectively) and individual % VO_2 of cardiac rehabilitation participants when exercising at HR + 20 or RPE 11–13.

neurological, vascular, or orthopedic) may compromise the predictive accuracy of the test [2]. Pharmacologic stress tests involve the infusion of medications that either increase myocardial demand (dobutamine) or reduce myocardial supply (dipyridamole or adenosine) by vasodilating non-occluded coronary arteries (e.g., coronary "steal") to induce myocardial ischemia with concomitant echocardiography or myocardial perfusion imaging, respectively. Although pharmacologic tests increase the sensitivity and specificity for myocardial ischemia, they do not provide an assessment of functional capacity, hemodynamic responses to progressive exercise, or an indication of the ischemic "threshold." Consequently, data from these tests are of little value in the determination of appropriate CR exercise training intensity. If the test was negative for ischemic abnormalities and symptoms, the highest HR obtained during the stress test can be used to guide the initial exercise training intensity. However, data obtained from a positive test will be more difficult to use since it will not be possible to determine the level of exertion where ischemic abnormalities begin to occur. Consequently, for patients with positive "non-exercise" stress tests, it will be necessary to use other complimentary methods (e.g., signs/symptoms and/or perceived exertion) to guide the exercise intensity in their initial exercise sessions.

One study [18] compared the rehabilitation outcomes of 229 post-MI and post-CABG that had undergone preliminary symptom-limited exercise testing with 271 matched patients who do not. All subjects underwent a 12-week exercise-based cardiac rehabilitation program (including ECG-telemetry monitoring for first 3–6 weeks). The group without a preliminary exercise test started at exercise levels of 2–3 Mets and progressed using HR and perceived exertion. Both groups showed similar physiologic improvement, and no complications were observed in either group. This study suggests that CAD patients, without preliminary exercise test data, can still participate safely and effectively in a cardiac rehabilitation program if proper monitoring of signs/symptoms and guidance on exercise training are provided.

Duration of Cardiorespiratory Exercise

The recommended CR exercise duration for CAD patients in outpatient cardiac rehabilitation programs is similar to that for apparently healthy participants in prevention programs [19]. Although 20–60 min of continuous CR exercise is the standard recommendation, recent guidelines [2] suggest that an accumulation of shorter exercise sessions throughout the day (i.e., three 10 min bouts) is comparable to a single, continuous session. Both of these approaches provide an increase in daily energy expenditure and can lead to improvements in functional capacity as well as other physiological benefits [20]. However, there is a need for more studies that directly compare the two training models (i.e., continuous vs. intermittent) in CAD patients before clear conclusions can be reached regarding comparable training adaptations. Finally, the exercise professional must recognize that CR exercise intensity and duration are generally inversely related; consequently, the standard recommendation is to have the patient start with a light to moderate exercise intensity and increase duration until the desired level (30–40+ min) is attained before increasing intensity [1,2].

Frequency of Cardiorespiratory Exercise

The recommendation for exercise training frequency for primary prevention programs [19]—3–5 days per week—is also appropriate for CAD patients in outpatient cardiac rehabilitation. Most outpatient programs offer two to three supervised exercise sessions per week and should also encourage their patients to be physically active—within prescribed limits—on most days of the week. The appropriate frequency for a given patient will depend on the individual's goals. Most CAD patients can achieve improvements in functional capacity (increased VO_2 max; decreased HR at given workload) with two to three sessions per week, provided that the intensity and duration of these sessions are adequate. However, patients in need of aggressive risk factor intervention (i.e., to decrease obesity or hypertension, normalize blood lipids, improve glucose tolerance, etc.) will likely benefit from a greater frequency of CR exercise [2]. Increasing the number of sessions per week (to four to five) will help to modify these risk factors over time; however, the exercise professional should be able to recognize that there is a direct relationship between the frequency of exercise and the risk of orthopedic injury [2]. Thus, patients must be instructed to slowly increase the frequency (and duration) of CR exercise and watch for signs of overuse injuries. Alternating modes of exercise may help reduce risk of overuse injuries [21].

Progression of Cardiorespiratory Exercise

As described, the general recommendation is to increase the CR exercise training duration and/or frequency before increasing the intensity. More specifically, patients should be able to achieve a duration of ≥20–30 min of continuous CR exercise before increasing the intensity [2]. Because many cardiac patients begin outpatient programs with a significantly lower functional capacity compared to their healthy counterparts, their rate of progression will likely be slower. In fact, as a consequence of extremely low functional capacity or limiting symptoms (i.e., claudication), some patients may need CR exercise to be intermittent during the early stages. The goal is to gradually work toward 15–20 min of continuous CR exercise at the target intensity. However, patients limited by symptoms will continue to need a more conservative rate of progression and may never reach the desired duration [2].

Prescribing Exercise Based on Total Energy Expenditure

Accumulating evidence suggests that specific health outcomes, including cardiovascular morbidity and mortality, are directly related to the total "volume" of physical activity, most accurately quantified in kcal/week [2]. Weekly energy expenditures exceeding 1000 kcal/week are more effective in modifying risk factors associated with obesity (hypertension, impaired glucose tolerance) and may also contribute to a slower progression of coronary disease. Hambrecht and colleagues [22] assessed the relationship between leisure-time

physical activity and coronary artery progression in 62 cardiac patients before and after a year of lifestyle intervention. Results showed an inverse dose–response relationship between the amount of physical activity and coronary disease progression. Patients who reported >2200 kcal of activity per week were found to be more likely to have regression of their CAD lesions. This amount of energy expenditure equated to approximately 5–6 h of physical activity per week. Patients who reported <1000 kcal/week were more likely to have progression of their lesions. The middle group of patients—those reporting an average of 1500 kcal/week—showed no progression (but no regression either) of CAD. It should be noted that the physical activity estimates in the study were derived from activity-recall instruments that rely on the patient's self-report of activity habits. Thus, there may be inaccuracies with these self-reported estimates (i.e., precise number of kilocalories expended per week). More studies on this issue are needed before the definitive dose of physical activity associated with the regression of coronary artery (if any) can be identified. Nevertheless, the results of Hambrecht et al. [22] study suggest that a threshold of approximately ≥1500 kcal/week can slow disease progression in cardiac patients. Consequently, cardiac rehabilitation professionals should encourage patients to achieve a volume of physical activity that will meet/exceed these caloric thresholds. Unfortunately, several studies [23–26] indicate that traditional cardiac rehabilitation exercise sessions usually result in <300 kcal/session. Thus, participating in three cardiac rehabilitation exercise sessions per week, without any additional lifestyle physical activity, will expend only 1000 kcal/week [27]. At this level of energy expenditure, CAD progression is likely to occur.

Prescribing Exercise for Weight Management in Cardiac Rehabilitation

Cardiac rehabilitation participants are certainly not immune to the "obesity epidemic," and >80% of patients entering cardiac rehabilitation are overweight and >40% are obese [28,29]. Accumulating evidence [30] indicates that the amount of exercise/physical activity required to sustain weight loss and prevent weight gain is considerably more than the general recommendation of 150 min/week. Overweight and obese individuals will benefit from progression to approximately 250–300 min/week (e.g., 50–60 min/week, 5–6 times/week) or ≥2000 kcal/week. For some individuals, progression to 60–90 min/day of exercise/physical activity may be necessary to promote and/or maintain weight loss. As discussed earlier, performing just three cardiac rehabilitation exercise sessions per week is unlikely to expend enough energy to reach these target levels. Thus, exercise/physical activity must be obtained outside of the center-based cardiac rehabilitation program if these target levels are to be achieved. Current research suggests that "bouts" of exercise/physical activity, as little as 10 min and distributed throughout the day, can be an effective strategy for weight loss as long as the total volume (or "dose") that is accumulated [31] achieve the levels described earlier. Thus, in addition to structured bouts of exercise, an increase in lifestyle physical activity should also be encouraged for overweight/obese patients with an overall goal of constructing a physical activity "pyramid" (Figure 81.2). The exercise professional must establish appropriate weight loss goals and convey to patients that a 5%–10% reduction of body weight during a 12-week cardiac rehabilitation program is considered successful and likely to produce significant health benefits [32].

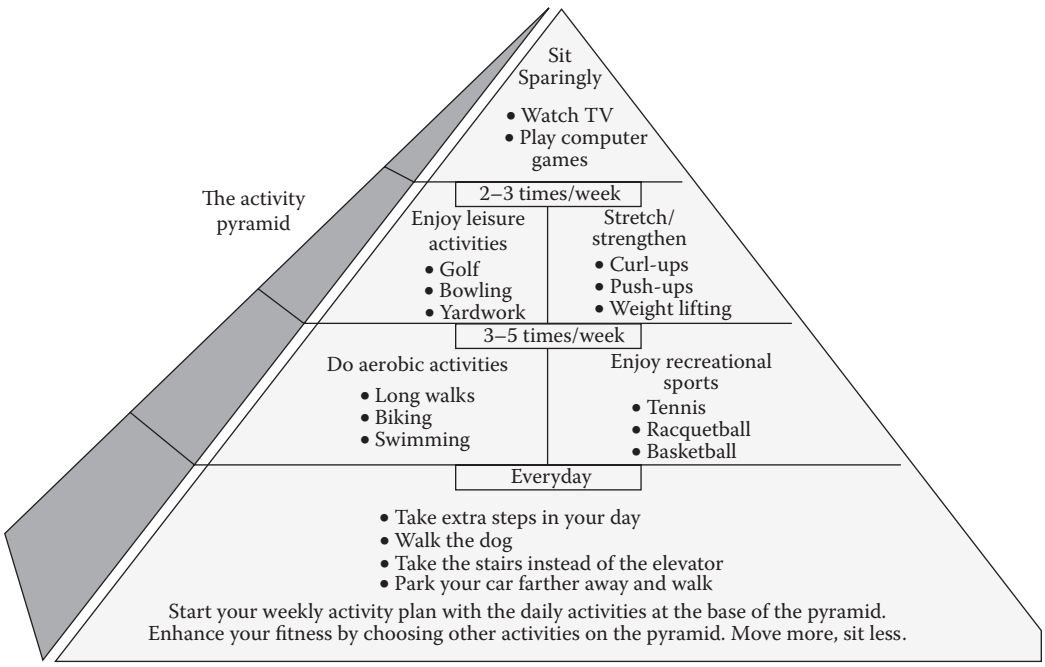


FIGURE 81.2 The Activity Pyramid, analogous to the USDA's Food Guide Pyramid, has been suggested as a model to facilitate public and patient education for the adoption of a progressively more active lifestyle. (Copyright 1997 Park Nicollet Health Source® Institute for Research and Education. Reprinted by permission.)

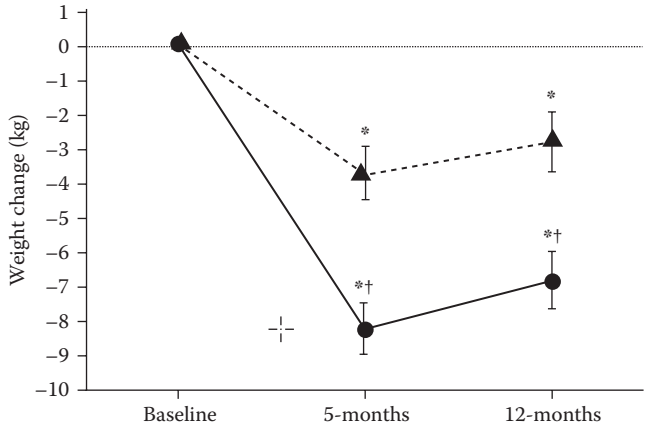


FIGURE 81.3 Demonstrates the change in bodyweight (kg) for cardiac rehabilitation (CR) patients in standard (triangles) and high-calorie-expenditure CR program after 5 and 12 months.

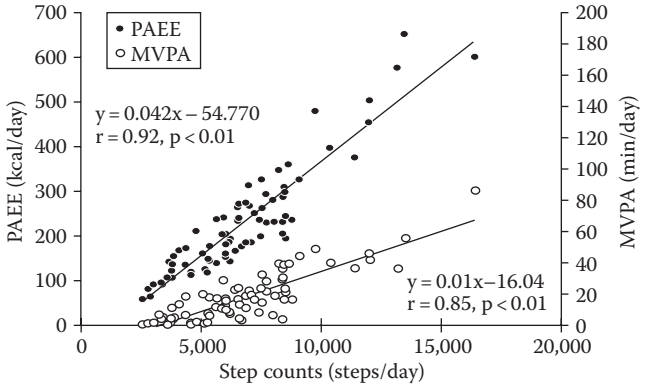


FIGURE 81.4 Demonstrates the relationship between levels of physical activity energy expenditure (PAEE in kcal/day) as well as minutes of moderate-vigorous physical activity (min/day) compared to steps/day.

Ades and colleagues [26] have recently demonstrated that a high-calorie-expenditure exercise (3,000–35,000 kcal/week of exercise-related energy expenditure) compared with standard cardiac rehabilitation exercise (>800 kcal/week) resulted in twice as much weight loss (Figure 81.3) and better cardiometabolic risk factor control, at 5 and 12 months, in overweight CAD patients. Furthermore, several studies have used physical activity monitors, such as pedometers and/or accelerometers, to help individuals achieve these higher volumes of physical activity [33,34] and successfully lose weight [35]. As shown in Figure 81.4, we recently demonstrated that accumulating 6500–8500 steps/day appears to be an appropriate target level of physical activity for cardiac rehabilitation participants as these levels are associated with approximately 1500–2200 kcal/week of energy expenditure [36]. As previously indicated, these levels of physical activity appear to be required for CAD stability/progression as well as weight loss in CAD patients.

Resistance Exercise Training

Since their inception in the 1970s, cardiac rehabilitation programs focused mainly on CR exercise training. Despite initial concerns regarding potential negative consequences on myocardial function, resistance exercise training (RT) has been shown to provide many important benefits for CAD patients in secondary prevention programs [3]. While the basic principles for prescribing RT apply to most stable CAD patients, the potential for complications should dictate who participates (i.e., patient eligibility) and when (i.e., time course following a cardiac event) as well as specific prescriptive guidelines [37].

Most CAD patients can participate in resistance exercise programs safely, as long as they receive instruction on appropriate lifting techniques and use loads appropriate for their capacity. In addition, CAD patients should be instructed to avoid the excessive isometric contraction associated with gripping too tightly and straining. A well-rounded RT program should include one to two sets of 10–15 exercises that work the major muscle groups, with a training frequency of 2–3 times/week. The decision to initiate an RT program should be made by the program staff in consultation with the medical director and/or surgeon. However, RT is generally contraindicated for CAD patients with the following clinical conditions [2]:

- Unstable angina
- Uncontrolled arrhythmias
- Left ventricular outflow obstruction
- Symptomatic heart failure
- Severe valvular disease
- Uncontrolled hypertension (i.e., systolic BP ≥ 160; diastolic BP ≥ 105 mmHg)

In addition to these clinical conditions, it is also advisable for CAD patients to have normal or only slightly reduced left ventricular function (EF > 35%) and a functional capacity >5 METs before starting a RT regimen.

As described earlier, range of motion (ROM) exercises are often initiated during the inpatient stage of rehabilitation. During the early outpatient stage (i.e., first few weeks), many cardiac rehabilitation programs incorporate very low-intensity RT using elastic bands, hand weights, etc. Most low-risk patients tolerate these activities without any problems. While these activities can be initiated at entry to outpatient cardiac rehabilitation, the ACSM and AACVPR guidelines [2,3] recommend the following for starting a traditional RT program (defined as lifting ≥50% of his or her 1-repetition [RM] maximum):

- Post-MI and postsurgical patients should defer traditional RT for at least 5 weeks after their event/surgery.
- Post-PCI (percutaneous coronary intervention = angioplasty, stent) patients should defer traditional RT for at least 2–3 weeks after the revascularization procedure.
- It is recommend that CAD patients complete a minimal period (i.e., 2 weeks for post-PCI and 4 weeks for post-MI/surgery) of supervised CR endurance training before starting a traditional RT.

SPECIAL CONSIDERATIONS FOR PRESCRIBING EXERCISE IN CORONARY ARTERY DISEASE PATIENTS

Myocardial Ischemia/Infarction

Although mode, duration, and frequency of the exercise prescription are similar to recommendations for other CAD patients, identifying the appropriate exercise intensity for ischemic or post-MI patients may be difficult when signs or symptoms arise. Myocardial ischemia is arrhythmogenic regardless of whether symptoms are present or not, thus the target HR for exercise should be set ≥10 bpm below the ischemic ECG or angina threshold [2]. The following are recommendations for prescribing exercise for the patient with myocardial ischemia [2,38]:

- Patients with angina should be instructed to recognize symptoms and avoid exercise interventions higher than level 2 (on 1–4 angina scale) during exercise, physical activity, or ADLs. Angina symptoms not relieved by cessation of exercise and/or the use of three sublingual nitroglycerin tablets (one every 5 min) require an emergent response.
- Exercise may be inappropriate for patients with angina and poor fitness levels or very low ischemic thresholds. However, non-weight-bearing exercise at very low levels may be appropriate to improve function.
- Exercise sessions should start with an extended warm-up and cooldown (10–20 min), which may decrease episodes of angina. The goal of the extended warm-up is to increase HRs ~10–15 bpm.
- Upper-body aerobic or RT may evoke early-onset angina, and caution should be used when RT programs are initiated. Patients also need to be advised that any physical activity in cold weather may also exacerbate symptoms of angina.

Surgical/Catheter-Based Revascularization

In 2007, more than 622,000 and 408,000 Americans underwent PCI and coronary artery bypass graft (CABG) surgery, respectively [39]. The majority of participants in cardiac rehabilitation programs have undergone surgical and/or percutaneous revascularization [40]. While the "standard" exercise prescription is generally appropriate for the postsurgical/PCI patient, the following are some specific modifications that should be made for these patients [2,41]:

- As there is often significant soft tissue and bone trauma to the thoracic cavity after CABG, ROM exercise should be undertaken in the early postsurgical period. ROM should be performed without feelings of pulling on the incision or mild pain.
- CABG patients that experience sternal movement or wound complications should not perform upper-body ergometry or RT until healing is complete. As described earlier, the CABG patient should perform 3–4 weeks of CR endurance exercise before initiating traditional RT.
- Asymptomatic PCI patients can begin RT after 2 weeks of CR endurance exercise training.
- Walking is a highly recommended and beneficial mode of exercise that can be initiated within a few days of the CABG or PCI procedure.

Implanted Pacemaker/Defibrillator

The number of patients receiving implanted pacemakers and/or defibrillator continues to increase as does the complexity of the devices. Exercise professionals working with these patients should consider a recent evidence-based review [42] and develop a solid understanding of these devices (including the four-letter code system used to describe the device functions) and their potential impact on exercise training programs. The following is a brief list of specific recommendation/considerations for these patients [2,43]:

- The device discharge thresholds must be known so that HR levels during exercise can be kept safely below this value (~10–20 bpm) to prevent inappropriate shocks.
- RPEs should be used in conjunction with HR to regulate exercise intensity.
- Upper-body/shoulder motion should be limited initially to prevent dislodging of the leads, and traditional RT should not be performed until 4–6 weeks postimplantation.

Diabetes (Type 1 and 2)

Diabetes leads to a number of pathological complications that result from chronically elevated blood glucose and/or insulin concentrations. Specifically, individuals with diabetes may develop conditions such as retinopathy, nephropathy, end-stage renal disease, and complications associated with neuropathy, which have the potential to impact the exercise prescription. While a comprehensive overview of exercise prescription for individuals with diabetes is provided by the ADA and ACSM [2,44,45], a summary of recommendations from these organizations for prescribing exercise for the patient with diabetes is listed in the following:

- In addition to traditional HR/BP monitoring, pre- and post-blood glucose monitoring is recommended during the initial weeks of the exercise program until glucose control has been established.
- The goal is to avoid postexercise hypoglycemia; thus, pre-exercise glucose levels should be ≥100 mg/dL. Low pre-exercise glucose levels should be increased with 20–30 g of carbohydrates before starting the exercise bout.
- Patient should not exercise if blood glucose levels are ≥300 mg/dL (or ≥250 with the presence of urinary ketones).

- The primary goal for individuals with type 1 diabetes is to develop a consistent "pattern" of exercise, carbohydrate intake, and insulin dosing.
- During exercise, autonomic neuropathy may cause chronotropic incompetence and/or a blunted blood pressure. Diabetics may also have difficulties with thermoregulation and dehydration and should avoid exercise in extreme hot/cold environments.
- Type 2 diabetics will benefit from participation in RT when contraindications such as retinopathy are not present. Emphasis must be placed on good technique to avoid straining and proper breathing to prevent the exaggerated BP responses associated with the Valsalva maneuver.
- Diabetics with peripheral neuropathy may need to avoid weight-bearing activity and regularly inspect their feet. Caution should be used for those with autonomic neuropathy while exercising in hot or cold environments.

Hypertension

The ACSM has published recommendations for exercise training of hypertensive individuals in a position stand [46] as well as within its Exercise Testing and Prescription Guidelines [2]. Hypertensive patients should be screened for contraindications to exercise and those with a resting BP $\geq$ 180/110 mmHg should be encouraged to see a physician for improved blood pressure control prior to beginning an exercise program. The following is a summary of the ACSM recommendations [2,46] regarding the prescription of exercise in hypertensive patients:

- Consistent monitoring of pre- and postexercise BP is important during the initial stages of the exercise program, and hypertensive patients should perform an active cooldown to avoid the risk of postexercise hypotension.
- CR exercise, performed at a lower intensity training (40%–60% of VO_2R), has been showed to effectively lower BP in hypertensive individuals [2]. The lower intensity training may also facilitate increased duration and total energy expenditure in patients that are overweight or obese.
- Do not exercise if resting blood pressure >200/110 mmHg. During exercise, blood pressure should remain $\leq$220/105 mmHg.
- Patients with hypertension should be advised to avoid isometric hand gripping during all RT exercises to avoid a disproportionate increase in SBP. Proper breathing techniques during RT should be encouraged to avoid the Valsalva maneuvers.

SUMMARY

This chapter presented the basics of exercise prescription principles pertaining to CR and RT programs in patients with CAD. While objective data from a GXT are preferred for developing the exercise prescription, often the exercise professional will have to rely on more "subjective" or arbitrary techniques. Consequently, prescribing exercise for CAD patients is often "more of an art than a science." This chapter also described the appropriate volume/dose of physical activity that is associated with CAD stability/regression and weight management in cardiac rehabilitation program participants. Finally, specific modifications to the standard exercise prescription were reviewed for some of the more common subgroups of CAD patients. Despite the potential for untoward events, there is considerable evidence to suggest that properly prescribed and monitored exercise therapy is not only safe but highly beneficial in patients with CAD.

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82 Contemporary Guidelines for Cardiac Rehabilitation

Randal J. Thomas, MD, MS

CONTENTS

Abbreviations 1027
Introduction 1027
Guiding Principles for Contemporary Cardiac Rehabilitation 1028
Timing: Windows of Opportunity 1028
Coordination and Continuity: Bridging the Gaps in SP 1029
Delivering Evidence-Based SP Care 1030
Accountability 1031
Putting It All Together: Cardiac Rehabilitation Programs as SP Centers 1032
Challenges and Potential Solutions 1033
Adherence 1033
Health Care Policy and Reimbursement 1033
Financial Viability of CR/SP Programs 1033
Summary 1034
References 1034

ABBREVIATIONS

AACVPR	American Association of Cardiovascular and Pulmonary Rehabilitation
ACC	American College of Cardiology
AHA	American Heart Association
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CMS	Centers for Medicare and Medicaid Services
CR	Cardiac rehabilitation
CR/SP	Cardiac rehabilitation/secondary prevention
CVD	Cardiovascular disease
MI	Myocardial infarction
NQF	National Quality Forum
PCI	Percutaneous coronary intervention

INTRODUCTION

For a number of reasons, cardiac rehabilitation/secondary prevention (CR/SP) services have experienced an important evolution over the past 30 years, similar in many ways to the evolution in health care services and policies that have generally occurred during that same time period. Once a service that was often an afterthought for most clinicians, a service focused on the rehabilitative episode of care during the hospitalization and subsequent 8–12 weeks following cardiac surgery or myocardial infarction, CR/SP has now transformed into a service that encompasses a multidisciplinary, evidence-based, and cost-effective approach for both short- and long-term care for a wide variety of patients with cardiovascular disorders. Current clinical practice guidelines for patients with coronary artery disease (CAD), percutaneous coronary intervention (PCI), or coronary artery bypass graft surgery (CABG) now rate the level of evidence for CR/SP at the highest rating possible (1A) [1–3].

Several important factors have prompted this transformation of CR/SP, including the following:

1. Changes in the science and practice of medicine
   a. Improved treatment options have been developed and implemented, leading to improved survival of patients who experience an acute cardiac event, such as MI, PCI, CABG, heart valve surgery, heart transplantation.
   b. Evolving treatment strategies that have increased the efficiency of inpatient management of patients with acute cardiac events, leading to a reduction in the hospitalization time and greater reliance on outpatient follow-up and management of patients with CVD.
   c. A widening array of evidence-based, lifestyle-based, and medication-based treatments have been developed that help to slow or reverse the effects of atherosclerotic CAD.
2. Changes in the science and practice of CR
   a. Growing evidence has emerged, over the past three decades, that multidisciplinary, short-term, and long-term approaches to CR/SP

and SP help improve both the quality and the quantity of life, for patients with a recent cardiac event.
   b. Technological innovations have opened new opportunities for CR/SP.
3. Changes in the types and complexity of patients in CR
   a. The number of patient groups eligible for CR/SP has expanded, now including six different groups: MI, PCI, CABG, heart valve surgery, heart transplantation, and chronic stable angina.
   b. The complexity of patients who participate in CR/SP and SP programs has increased (e.g., patients with concomitant heart failure, left-ventricular assist devices, those of older age, and those who are obese, have diabetes, or have musculoskeletal limitations).
4. Changes in expectations for health care quality and outcomes
   a. Health care policymakers have identified important gaps in the quality of health care that is delivered in the United States and have helped to increase societal awareness of potential and importance of reducing those gaps in care.
   b. Consumer advocacy groups, third-party payers, health care organizations, and governmental leaders have raised levels of expectations for the quality and outcomes of the care provided by health care professionals.
   c. Research has found that systematic approaches to health care delivery help to reduce inappropriate variability in health care services and increase the quality outcomes of those services.

These, and other factors, have paved the way for CR/SP services to transform and evolve, resulting in the contemporary model of CR/SP care that is practiced throughout the world today—a systematic approach to evidence-based, multidimensional, short-term, and long-term services that significantly improve both the quality and the outcomes of SP services for patients with CVD.

GUIDING PRINCIPLES FOR CONTEMPORARY CARDIAC REHABILITATION

Contemporary CR/SP programs fill an important role that is unique in health care systems—that of providing services that are aimed at optimizing a patient's short- and long-term health following a cardiac event. Research has shown that, for the most part, CR/SP programs have been very successful in filling that role, resulting in a reduction in the short- and long-term morbidity and mortality for patients who receive CR/SP services [4–15].

Several principles guide the way for effective CR services today. Those principles include the following.

Timing: Windows of Opportunity

CR services are effective at helping to improve patient outcomes primarily because they deliver important preventive services at key times in a patient's life (see Figure 82.1). These windows of opportunity result when a patient passes through a life-threatening and life-changing cardiac event, from which many emerge more committed to do whatever is necessary to improve health and well-being, and thereby reduce the risk of future cardiac events. These important times are sometimes referred to as "teachable moments" in which the patient becomes more open and more committed to adopt healthier lifestyle habits [16,17] as depicted in Figure 82.2.

These critical times of opportunity, in the case of the cardiac patient, usually occur at the time of the initial diagnosis of cardiovascular disease—usually a cardiac event—but can also occur soon after hospital discharge and at later times, such as during the transition from hospital to outpatient care, and from early outpatient care to long-term follow-up and treatment. During each of these times, patients find themselves in a particularly fragile and vulnerable point—both literally and figuratively. They have been diagnosed, for the first time in many cases, with a life-threatening medical condition, one that produces concerns about their current and future health, about their ability to participate in meaningful life activities,

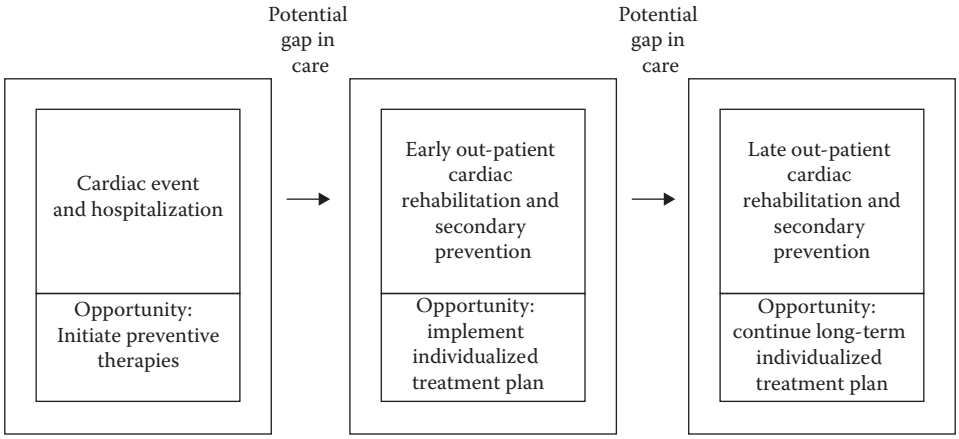


FIGURE 82.1 Windows of opportunity and potential gaps in care for cardiac rehabilitation and secondary prevention services.

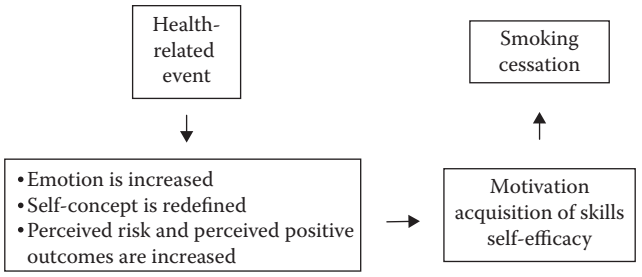


FIGURE 82.2 Conceptual model for the teachable moment for patient lifestyle change, using the example of smoking cessation. (From McBride, C.M. et al., *Health Educ. Res*., 18(2), 156, 2003.)

and about the financial and emotional challenges that are very likely to cross their path.

Just as there is an important therapeutic window of opportunity for the application of important lifesaving acute-care treatments (e.g., thrombolytic therapy and PCIs during acute coronary syndromes), research suggests that important therapeutic windows of opportunity exist for applying preventive therapies as well [18–22].

The Cardiovascular Hospitalization Atherosclerosis Management Program (CHAMP) study, for example, has shown that when hospitalized patients are treated using a standardized and systematic approach to SP, they are more likely to be started on appropriate preventive therapies during their initial hospitalization, are more likely to continue those therapies following hospital discharge, and are more likely to receive the health benefits associated with those therapies [19,20].

The CHAMP study was a landmark study that illustrated the impact of a systematic, evidence-based approach to help patients receive appropriate therapies during the window of opportunity that occurs in the hospital at the time of a myocardial infarction. Not only did the CHAMP investigators find that the CHAMP systematic processes of care helped to increase both the prescription of appropriate therapies during the patient's hospitalization and the adherence to those therapies after hospital discharge. Understandably, patients in the CHAMP system of care also were more likely to have favorable clinical outcomes, compared to patients who were managed prior to the initiation of the CHAMP system (see Tables 82.1 through 82.3).

Effective contemporary CR/SP programs take full advantage of the windows of opportunity for initiating and maintaining lifesaving preventive therapies—both in the hospital and in the outpatient setting.

TABLE 82.1
Percentage of Patients on Preventive Treatments at Hospital Discharge and 1 Year later, before, and after Initiating the CHAMP Inpatient System

	Pre-CHAMP (%)		Post-CHAMP (%)	
Therapy	At Hospital Discharge	1 Year Later	At Hospital Discharge	1 Year Later
Aspirin	78	68	92*	94*
β–blocker	12	18	61*	57*
Nitrates	62	42	34*	18*
Calcium blocker	68	58	12*	6*
ACE inhibitor	4	16	56*	48*
Statin	6	10	86*	91*

Source: Fonarow, G.C. et al., *Am. J. Cardiol*., 87(7), 819, 2001.
* $p < 0.01$, for findings before and after initiating the CHAMP system, for percentage of patients on preventive treatments at hospital discharge and 1 year later.

TABLE 82.2
Posthospital LDL Cholesterol Levels for Patients in CHAMP Study, Comparing Data before and after Initiation of CHAMP System

LDL Cholesterol (mg/dL)	Before CHAMP System Initiated 1992/1993 (%) (n = 256)	After CHAMP System Initiated 1994/1995 (%) (n = 302)
≤100	6	58
101–130	15	16
131–160	18	4
>160	14	0
Not documented	48	22

Source: Fonarow, G.C. et al., *Am. J. Cardiol*., 87(7), 819, 2001.

Coordination and Continuity: Bridging the Gaps in SP

A natural corollary to windows of opportunity is the concept of windows of *missed* opportunity, when patients don't receive the care they need at critical junctures and dangerous gaps occur in the delivery of SP care (see Figure 82.1). These gaps in care can occur even for health care providers with the best intentions or at the best health care centers and can occur for a number of reasons [23–26], including the following:

- *Provider barriers*: Health care providers are often unaware that CR/SP services provide numerous health benefits to participants, that CR/SP services are generally covered by most health care insurance companies, and that the process of enrolling a patient in a CR/SP program involves only a few relatively simple steps that start with an order from the patient's health care provider. In addition, providers are also often distracted at the "teachable moments" and at the "CR/SP referral moment" due to a large number of competing demands and a relatively short time with which the provider typically has to interact with the patient in the inpatient or outpatient setting.

TABLE 82.3
Clinical Events 1 Year Following Hospital Discharge for Patients in CHAMP Study, Comparing Results before and after Initiation of CHAMP System

	Pre-CHAMP 1992/1993 (n = 256)	Post-CHAMP 1994/1995 (n = 302)
Recurrent myocardial infarction	20 (7.8%)	10 (3.1%)*
Heart failure	12 (4.7%)	8 (2.6%)
Hospitalization	38 (14.8%)	23 (7.6%)*
Sudden death	3 (1.2%)	2 (0.6%)
Cardiac mortality	13 (5.1%)	6 (2.0%)*
Noncardiac mortality	2 (0.8%)	2 (0.6%)
Total mortality	18 (7.0%)	10 (3.3%)*

Source: Fonarow, G.C. et al., *Am. J. Cardiol*., 87(7), 819, 2001.
* $p < 0.05$.

- *Patient barriers*: Patient-oriented barriers contribute commonly to gaps in preventive care, including language and health literacy barriers, competing time and financial demands, and lack of understanding about the need for and benefits of CR/SP.
- *Health system barriers*: Health system barriers include lack of focus on SP policies and procedures, lack of appropriate inpatient staffing and resources to educate and refer patients to CR/SP, lack of CR/SP facilities in the vicinity of a patient's home, and lack of CR/SP resources for uninsured patients [24,26,27].

Standardized CR/SP processes of care, such as the CHAMP system described earlier, are the perfect remedy to the challenges listed earlier. A systematic approach that includes "automatic" and personalized processes of care helps reduce inappropriate variability in patient care and increases the appropriate use of preventive therapies for patients with CVD [21,22,28,29].

The American Heart Association's Get With The Guidelines (GWTG) is yet another example of an effective and systematic inpatient approach to SP care. The GWTG system includes materials, tools, and process steps that help hospital staff implement important preventive strategies for patients who are hospitalized with CVD. Studies involving GWTG hospitals have shown that appropriate SP therapies are provided to patients at much higher rates than that in non-GWTG hospitals [30,31]. For example, a study by Mazzini and colleagues evaluated patients who had been hospitalized with a cardiac event in a hospital that utilized the American Heart Association's GWTG system for standardized processes of care [31]. Among other things, the study found that patients in GWTG hospitals were more likely to be referred to outpatient CR/SP programs than patients who are in hospitals that did not use the GWTG system.

Unfortunately, however, there are occasional challenges to the full implementation and long-term impact of inpatient systems of care. The study by Mazzini and colleagues provides an excellent example of those challenges. When investigators evaluated the longer-term effectiveness of the GWTG system in the Boston area hospitals they studied, they found that the percentage of patients who actually enrolled in a CR program did not differ significantly between the two hospital groups (approximately 18% of all patients and approximately 33% of those who had been referred to CR). In other words, treatments initiated or recommended in the hospital may not necessarily translate into their application in the outpatient setting. Some patients—approximately 25% of those who did not enroll—reported that they did not remember being referred to a CR/SP program while they were in the hospital. Whether this is due to faulty patient memories or faulty referral processes in those hospitals is unclear, but it appears likely that inpatient systems aimed at improving the delivery of SP therapies must include steps that strengthen the link between inpatient recommendations and outpatient adherence to those recommendations. Simple "check box" processes of care may not be sufficient to bridge potential gaps between inpatient and outpatient preventive care.

Medication adherence is another important concern. An illustrative study by Shah and colleagues found that in insured, post-MI patients from Olmsted County, Minnesota, approximately 25% of patients did not even fill their prescription following hospitalization for their statin, ACE inhibitor, or beta-blocker medications [32]. Furthermore, only 45% of patients were taking these medications 3 years following their MI. Patients who were smokers were particularly at risk for non-adherence to their medications, while those who attended CR/SP were significantly more likely to remain adherent to their prescribed medications during the follow-up period.

This study is important because it highlights two important principles that argue for the important role of the multidisciplinary and long-term approach to contemporary CR/SP: (1) Patients, on their own, often fall into "prevention gaps," especially when attempting to start or continue with complex and expensive SP regimens, and (2) CR/SP services help improve patient outcomes, at least in part because they appear to help improve patient adherence to prevention-oriented therapies.

Delivering Evidence-Based SP Care

One of the major accomplishments in cardiovascular medicine over recent times has been the dramatic drop in cardiovascular mortality that has been observed in the United States over the past 50 years. A large percentage of this drop has been due to effective treatments aimed at controlling cardiovascular risk factors [33]. Unfortunately, however, the true impact of the wide array of efficacious preventive therapies has been dampened by the fact that these therapies are underutilized [34–38].

Contemporary CR/SP services are aimed at delivering evidence-based preventive therapies—lifestyle and medication therapies—that help to reduce the morbidity and mortality for patients with documented CVD. The core components and competencies of CR/SP, in fact, include a specific treatment plan that initiates, evaluates, and adjusts evidence-based treatments for participating patients [39,40]. It has been estimated, in fact, that at least half of the benefits that result from CR/SP are the likely result of improved cardiovascular risk factor control [14].

Evidence-based therapies that are delivered through CR/SP services include the following:

- Lifestyle modification counseling to initiate and maintain healthy lifestyle habits
- Initiate appropriate SP medications and help with adherence to those medications, in coordination with the patient's primary health care providers
- Identification, assessment, and management of comorbid conditions, such as diabetes, hypertension, depression, and musculoskeletal disorders
- Assessment of patient responses to lifestyle and medication therapies, assisting with adjustments to the patient's individualized treatment plan as needed

Accountability

Published research has clearly documented significant gaps in the quality of health care delivery—that the health care services we actually deliver are lacking for a large percentage of the population [36–38]. This evidence has led to the relatively slow realization by health care organizations, governmental organizations, and health care practitioners themselves that gaps in the quality of care do exist and that the health care providers and the health care systems are two of the major reasons for such gaps. However, lessons from the world of Total Quality Management have taught that problems with quality are not always due to "people problems" but are often the result of "process or system problems."

A good example of this fact comes from the work of W. Edwards Deming, a major force in the Total Quality Management movement. He related a classic case of a system problem involving a company that used a number of flammable materials in its production line [41]. To combat the numerous fires that were occurring in the production plant, the leaders of the company pushed the employees to set fewer fires while they were working. What the company perceived as a "people problem"—that their employees were setting too many fires—was, in fact, a situation or system problem. The production line used flammable materials!

Quality improvement efforts within the field of medicine have led to recent efforts to introduce new systems of accountability into the practice of medicine. Clinical practice guidelines have long been published in hopes of setting the basic standards for high-quality care. Such hopes have largely been unfulfilled, however, due to a number of shortcomings with clinical guidelines, including the lack of full and consistent implementation of clinical practice guidelines into clinical practice [42–44].

Following the example of quality improvement efforts in the field of business, health care organizations have in recent years begun to utilize quality improvement methods, including, among other things, quality of care indicators, scorecards, and performance measures to help improve clinician accountability for the quality of the care that they provide [45,46]. CR performance measures, jointly developed by AACVPR, ACCF, and AHA, were published originally in 2007 and updated in 2010. These performance measures are designed as quality of care indicators and hold clinicians and health care systems accountable for referring eligible patients to CR/SP programs and at the same time hold CR/SP programs and professionals accountable for the delivery of high-quality CR/SP services to the patients referred to them [47,48]. These measures have been endorsed by the National Quality Forum and are now in the process of being disseminated and implemented.

The Centers for Medicare and Medicaid Services (CMS) have announced their plans to begin abstracting the outpatient CR/SP referral performance measure as one of their reportable performance measures, starting in 2014. Plans for the inclusion of the inpatient CR/SP referral performance measure as a chart-abstracted performance measure are currently under review by CMS. Whether or not the CR/SP performance measures will be included in "pay for performance" strategies is yet to be seen. It is anticipated that the implementation of these performance measures will help reduce the gap in CR/SP referral and enrollment, much in the same way that gaps in the inpatient prescription of aspirin, beta-blocker, and statin therapy to MI patients improved when CMS and other organizations began assessing and reporting how well clinicians and health care systems were providing these medications to eligible MI patients [49,50].

Three national data registries include the CR/SP performance measures: (1) the American College of Cardiology's National Cardiovascular Data Registry, (2) the American Heart Association's Get With The Guidelines and The Guideline Advantage (the latter done in cooperation with the American Cancer Society, the American Diabetes Association, and the American Stroke Association), and (3) the American Association of Cardiovascular and Pulmonary Rehabilitation's National Cardiac Rehabilitation Data Registry (soon to be launched). These data registries, ideally, will continue to evolve and interface in ways that will help to connect inpatient and outpatient data with data from CR/SP programs. Such links will be important tools to clinicians, health care systems, and patients to help improve the coordination and continuity of preventive care provided to patients with CVD.

CR/SP programs will continue to be a key factor in helping clinicians and health care systems improve the quality of SP care that is provided to patients with CVD. The contemporary CR/SP program will capitalize on this opportunity—to

serve as an "accountability resource" to clinicians and health care system, assisting them by providing standardized, systematic, evidence-based, and collaborative model of coordinated care resulting in high-quality SP services and high levels of CMS-measured quality of care performance.

Putting It All Together: Cardiac Rehabilitation Programs as SP Centers

Contemporary CR/SP programs, when ideally organized and operational, are specialized centers of SP [51]. They are designed and operated in a variety of different ways, but generally, to be most effective, will include the following operational parts:

1. Inpatient CR/SP services
   a. *Window of opportunity*: Members of the CR/SP team take full advantage of the "window of opportunity" and "teachable moments" by assuring that patients who have a new cardiac event or diagnosis (MI, PCI, CABG, heart valve surgery, heart transplantation, or a new diagnosis of stable angina) are started immediately on the path of SP, initiating preventive medications and referring the patient to an outpatient CR/SP program.
   b. *Systematic and automatic process steps*: Effective process steps include the use of standing orders, clinical pathways, and automatic processes for CR/SP assessment and referral [25]. Liaisons, health care professionals who help guide and "coach" the new CR/SP patient as they initiate the new preventive therapies and transition to an outpatient CR/SP program, have been shown to help improve uptake of outpatient CR/SP services [52].
2. Early outpatient CR/SP services
   a. *Seamless transition from inpatient to outpatient setting*: Effective contemporary CR/SP programs have a system in place to smooth the transition time between the inpatient and outpatient settings. Effective methods start in the hospital, as noted earlier, as the hospital team completes the patient referral process by communicating the patient's information and referral order to the receiving CR/SP program.
   b. *Enrollment and adherence enhancement*: The receiving CR/SP program contacts the enrolling patient soon after hospital discharge—usually within the first week—to confirm their enrollment in the CR/SP program and to help them with the specific steps they will need to take to attend their first visit (appropriate clothing to wear, time to report, directions to the CR/SP program, parking locations, reporting location, etc.).
   c. *Core components and competencies*: The CR/SP program incorporates the core components [39] and core competencies [40] that are considered to be the standard of care for CR/SP programs.
   d. *Case management to provide full dose of CR/SP*: The CR/SP staff assigns a case manager or case management team to provide a personal assessment and individualized treatment plan for the patient to follow. The case management team encourages patient participation and completion of early outpatient CR/SP by using a number of potential tools, including phone calls when the patient misses a CR/SP visit or incentive programs that encourage patients to complete their prescribed course of early outpatient CR/SP (usually consisting of up to 36 sessions over a period of 12–36 weeks). Delivery of the "full dose" of early outpatient CR/SP is an important responsibility of the patient's case management team, since receiving the "full dose" is associated with improved patient outcomes, as shown in a study by Hammill and colleagues. Patients who attend all 36 sessions of early outpatient CR/SP had a 4-year mortality rate that was 14% lower than those who attended 24 sessions, 22% lower than those who attended 12 sessions, and a 47% lower than those who attend only one session [7].
   e. *Tracking of progress*: The CR/SP staff assesses the patient's progress in achieving treatment and prevention goals, and gives feedback to the patient and adjusts treatment plans if the goals are not met, or else encourages continuation of efforts if treatment goals are met.
   f. *Care coordination and transition*: Finally, the CR/SP staff helps to transition the patient from the early outpatient phase of CR/SP to the long-term follow-up phase by coordinating those plans with the primary care provider and with long-term case management services that may be available in their community.
3. Late outpatient CR/SP services
   a. *Long-term case management*: Long-term case management services for CR/SP are designed to continue with patients for the rest of their lives. Long-term case managers (nurses and other nonphysician providers) meet with and/or contact the patient at set intervals to help the patient maintain healthy lifestyle habits, continue to adhere to their preventive medications, and monitor symptoms, possible disease progression, and important comorbid conditions. The case manager helps to arrange for additional evaluation or treatment, if indicated, for new symptoms, abnormal findings, or other patient concerns. Such long-term systems of follow-up care have been found to help patients achieve excellent control of their cardiovascular risk over time and to optimize their cardiovascular health and survival [5,13,53].

CHALLENGES AND POTENTIAL SOLUTIONS

Adherence

Studies in the United States and in other countries have shown that a surprisingly low percentage of eligible patients actually receive CR/SP services. In the United States, there is considerable regional variation in CR/SP uptake by eligible patients, ranging from a low of 6.6% in Idaho to a high of 53.5% in Nebraska [54]. Participation rates for CR/SP appear to be even lower for women, the elderly, and for racial and ethnic minorities [55]. Clearly, important gaps in the delivery of CR/SP are taking place, which limit the significant potential of CR/SP to reduce morbidity and mortality for eligible patients.

Fortunately, a number of innovative investigators have helped to identify methods that can help improve the delivery of CR/SP care (as described earlier in this chapter). A systematic approach to starting CR/SP in the hospital is a critical component to improving the delivery of CR/SP services. This approach generally includes a standardized patient risk factor assessment, initiation of appropriate preventive medications, automatic referral to CR/SP, and predischarge assistance by a "liaison" or health care professional to help the patient with steps to begin and continue with their preventive medications, steps to begin and maintain healthy lifestyle changes, and steps to enroll in an outpatient CR/SP program [23,25,52,56,57]. A strong recommendation for CR/SP by the patient's physician has also been shown to be a very strong predictor of subsequent CR/SP participation [23].

Some barriers to CR/SP participation continue to be a challenge, including the fact that many patients do not have a CR/SP program close to where they live or have difficulty attending the CR/SP program during the hours of operation, due to work and/or family responsibilities. Potential solutions for these barriers include the use of alternative delivery models of care, such as home-based CR/SP [58–60] and Internet-based CR/SP [61,62]. In addition, CR/SP programs can help improve availability to patients by offering expanded hours of operation, to include early morning, evening, and weekend hours.

Unfortunately, the full implementation of new and innovative methods to delivery CR/SP, and thereby reach the "unreachable" patients who do not receive CR/SP services, is highly dependent upon health care policy that supports reimbursement for such programs. The MULTIFIT [58] and SCRIP [59] models are excellent examples of innovative CR/SP programs that could help expand the reach of traditional CR/SP programs and improve delivery of CR/SP services to patients who are currently not receiving those services, but are falling instead into the CR/SP "gap."

Health Care Policy and Reimbursement

While improvements in the systematic approach to inpatient, early outpatient, and long-term case management will increase the number of eligible patients who receive CR/SP services, these improvements alone will not be sufficient to provide CR/SP services to all eligible patients. As mentioned earlier, innovative models of CR/SP delivery will be essential in order to reach the "unreachable." And to make innovative models of care feasible, health care policy will need to change so that reimbursement for such models is provided to CR/SP professionals. As an example, CMS and most health care insurance companies currently do not provide consistent coverage for home-based CR/SP services, despite the fact that they have been shown to be effective in delivering CR/SP care, perhaps at an even more cost-effective level than that observed in the delivery of traditional "in-center" CR/SP services [60].

A major opportunity for health care policy makers and health care providers is the provision of CR/SP to patients *before* a cardiac event, when the patient is first diagnosed with atherosclerotic CVD. The COURAGE trial shed important light on this approach to CR/SP by comparing the use of optimal medical/lifestyle therapy alone with optimal medical/lifestyle therapy plus PCI in patients who had CAD with stable angina [53]. While angina control improved more quickly in the PCI group, the overall symptom control, morbidity, and mortality outcomes were similar in the two groups, over a 2-year follow-up. Similarly, a study from Germany has also suggested that lifestyle approaches to CR/SP may be superior to PCI with regard to patient outcomes in patients with stable CAD [63]. It is still unknown whether or not CMS and other health care insurance providers will set as a policy to provide or even require CR/SP services for patients with CAD before PCI or other more expensive and interventional approaches would be approved. A recent Presidential Advisory from the American Heart Association on the referral, enrollment, and delivery of CR/SP programs at clinical centers and beyond highlights the urgent need for CR/SP professional and health care policymakers to work together to take bold steps forward to expand the reach and impact of CR/SP services to all eligible patients [27].

Financial Viability of CR/SP Programs

There is an old adage that an ounce of prevention is worth a pound of cure, and health care policy for reimbursement has generally operated in the opposite direction—willing to pay high prices for the "cures" and yet not willing to cover prevention at a much lower cost.

CR/SP programs have been shown to reduce mortality as much as, or more than, other treatments of CVD [6,11,12,14,53,64] and at a cost that is equal to or better than most treatments for CVD [65].

While CMS has recently increased reimbursement for early outpatient CR/SP services, rates of reimbursement still fall well below operational costs for many programs. Some health care plans require high co-pays for CR/SP patients, in some regions charging patients high co-pays for *each CR/SP session*. Clearly, to help expand the reach of CR/SP services, health care policy will need to change to reduce disincentives for CR/SP participation, such as co-pays, and to increase the use of appropriate incentives to patients and health care professionals alike.

SUMMARY

Contemporary CR/SP services hold a unique and important role in health care today. Increasing evidence suggests that CR/SP services improve short- and long-term outcomes for patients with CVD by delivering evidence-based and cost-effective care during important "windows of opportunity" during and after a cardiac event. Systematic approaches to the delivery of CR/SP increase the percentage of eligible patients who receive evidence-based CR/SP services and their associated benefits. CR/SP programs, when ideally designed, can serve as important quality of care resource to health care providers and health care systems, an important fact during these times of increasing expectations and accountability for the provision of high-quality patient care and optimal patient outcomes.

The contemporary CR/SP program is an SP center that uses systematic approaches to patient care and outcome assessment that begin in the hospital, transition to the outpatient setting, and continue lifelong to help patients enjoy optimal cardiovascular health despite having CVD.

Efforts to expand CR/SP services in order to reach all eligible patients are taking place, but will have only moderate impact unless health care policymakers appropriately support and encourage new and innovative approaches to reach patients who do not currently receive CR/SP services. The full impact of CR/SP services will be seen as health care systems and CR/SP programs adopt methods that increase the uptake of CR/SP services, increase the quality of CR/SP services delivered, and track and report quality of care metrics through collaborative data management systems.

CR/SP programs have evolved significantly over the past 30 years and will continue to evolve as CR/SP services adapt to meet the ongoing challenges and opportunities that are sure to come as changes in technology, health care services, and health care policies continue to occur.

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83 Benefits and Risks of Exercise for the Coronary Patient

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CONTENTS

Cardioprotective Effects of Structured Exercise and/or Lifestyle Physical Activity 1038
Anti-Atherogenic 1039
Anti-Ischemic 1040
Anti-Inflammatory 1040
Anti-Thrombotic 1040
Anti-Arrhythmic 1041
Regenerative Capacity 1041
Heart Function 1041
Behavioral 1041
Health Risks of Physical Activity and/or Structured Exercise 1042
Pathophysiological Basis for Exercise-Related Cardiovascular Events 1042
Exercise-Related Cardiovascular Events 1042
Morning versus Afternoon Exercise 1043
Risk–Protection Paradox 1043
High-Risk Activities 1044
Recommendations to Reduce the Risk of Exercise-Related Cardiovascular Events 1044
Exercise Testing to Identify Patients "At Risk" 1045
Other Exercise Risks 1046
Musculoskeletal Injuries 1046
Diabetes 1046
Asthma or Chronic Obstructive Pulmonary Disease 1046
Conclusions 1047
Acknowledgment 1047
References 1047

Cardiovascular mortality declined by ~31% over the last decade. Nevertheless, cardiovascular disease (CVD) still accounts for nearly one of every three deaths in the United States. In 2010, an estimated 785,000 Americans experienced a new coronary event, and 470,000 had a repeat acute myocardial infarction (AMI) [1]. With such an enormous burden of coronary heart disease (CHD), therapeutic strategies to reduce cardiovascular mortality are paramount for increasing life expectancy in the United States. Accordingly, for literally millions of previously affected adults, interventions that have been shown to reduce the risk of recurrent cardiovascular events, collectively referred to as secondary prevention (Figure 83.1) [2], are critically important.

Exercise training has been reported in numerous randomized controlled trials, "real-world" observational studies, and meta-analyses to reduce the overall morbidity and mortality associated with CHD [3–10]. Structured exercise after a coronary event is often prescribed as an integral component of a comprehensive secondary prevention program in outpatient cardiac rehabilitation (CR). This chapter details the benefits associated with regular exercise training and moderate-to-vigorous physical activity in patients with CHD, highlighting the underlying mechanisms and evidence for improvement in long-term cardiovascular outcomes. Additionally, we review the potential complications associated with exercise interventions, especially when concomitant chronic diseases or superimposed environmental stressors are involved, so as to enable physicians and allied health professionals to more accurately assess the risk–benefit ratio of exercise in the coronary patients they counsel.

The recently published American Heart Association/American College of Cardiology Foundation secondary prevention guidelines for patients with coronary or other atherosclerotic vascular disease list regular physical activity as a Class I indication for risk reduction. The guidelines recommend "30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, household work) to improve cardiorespiratory fitness and move patients out of

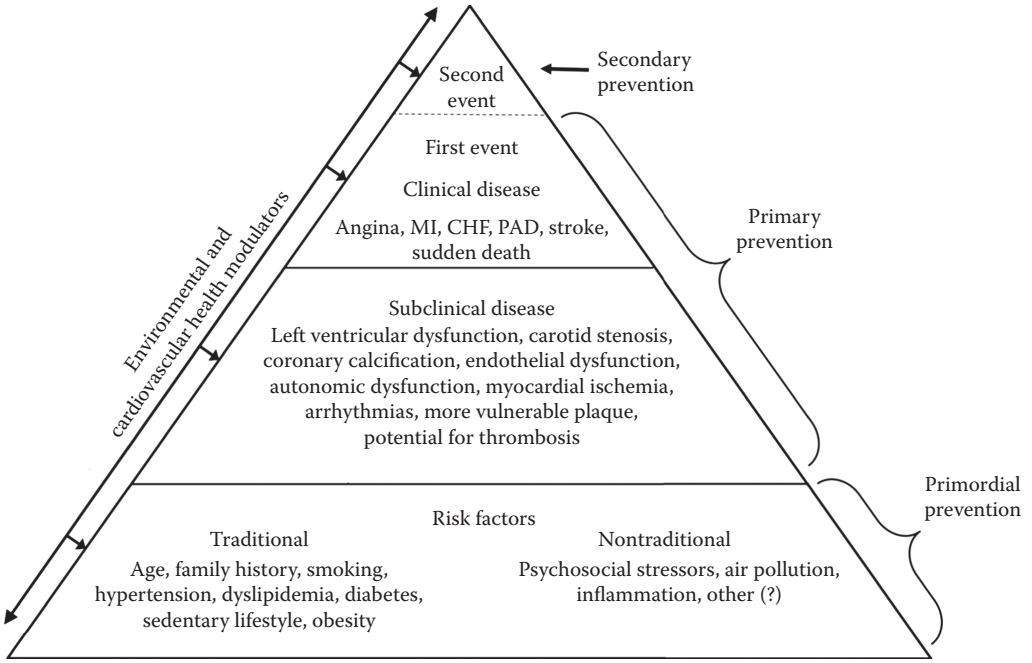


FIGURE 83.1 Multifactorial risk factor framework and the progression of CVD with corresponding primordial, primary, and secondary prevention. Environmental modulators include health care access, the built environment, advocacy/public policy initiatives, and potential intervention targets (e.g., personal, family, school, workplace). Cardiovascular health markers/interventions include smoking status, body mass index, physical activity, healthy diet score, total cholesterol, blood pressure, fasting plasma glucose, pharmacotherapies (e.g., aspirin, beta-blockers, statins, angiotensin-converting enzyme inhibitors), and coronary revascularization, when appropriate. MI, myocardial infarction; CHF, congestive heart failure; PAD, peripheral arterial disease. (From Franklin, B.A. and Cushman, M., *Circulation*, 123, 2274, 2011. With permission.)

the least fit, least active high-risk cohort (bottom 20%) [8]." Other contemporary guidelines recommend exercise training or exercise-based CR as a Class I indication after an AMI, percutaneous coronary intervention (PCI) [11], and coronary artery bypass graft surgery (CABG) [12].

In the most comprehensive and detailed meta-analysis of 47 studies that randomized 10,794 coronary patients (MI, PCI, CABG, angina pectoris, or angiographically documented coronary disease) to exercise-based CR or usual care, Heran et al. [6] reported a 13% relative reduction in all-cause mortality (RR 0.87, 95% CI 0.75–0.99) and a 26% relative reduction in cardiovascular mortality (RR 0.74, 95% CI 0.63–0.87) in patients with >12-month follow-up. In patients with short-term follow-up (≤12 months), a 31% relative reduction in hospital admissions (RR 0.69, 95% CI 0.51–0.93) was noted; however, no difference was observed in the risk of recurrent MI, PCI, or CABG between the exercise and usual-care groups. In another meta-analysis of secondary prevention programs including 63 randomized trials, a significant reduction in all-cause mortality and recurrent MIs was reported. Specifically, supervised exercise alone (17 trials, 2566 patients) was associated with a 28% reduction in all-cause mortality (RR 0.72, 95% CI 0.54–0.95) and a 26% reduction in recurrent MI (RR 0.74, 95% CI 0.57–1.01) [13].

The Exercise Training Intervention after Coronary Angioplasty trial randomized 118 patients who underwent PCI to exercise training versus usual care [14]. Exercise training was associated with a reduced incidence of subsequent cardiac events and/or revascularization procedures, including MI, PCI, and CABG (RR 0.71, 95% CI 0.60–0.91), and hospital readmissions (RR 0.69, 95% CI 0.55–0.93) at 33-month follow-up [14]. Recently, Goel et al. [4] reported that exercise-based CR was associated with significantly reduced all-cause mortality (RR 0.54, 95% CI 0.41–0.71) and cardiac mortality (RR 0.69, 95% CI 0.44–1.07) in a large community-based study of 2395 patients undergoing PCI. Studies in Medicare beneficiaries have also demonstrated a significant mortality reduction associated with participation in exercise-based CR [9]. More recently, the HF-ACTION randomized controlled trial in chronic heart failure patients with a left ventricular ejection fraction (LVEF) ≤35% found that exercise training reduced the incidence of combined all-cause mortality or hospitalization by 11% (HR 0.89, 95% CI 0.81–0.99), after adjusting for baseline prognostic variables [15]. Collectively, these data suggest that exercise training reduces all-cause mortality by up to 46% and decreases the risk of recurrent nonfatal MIs by ∼20% in patients with coronary disease. Several mechanisms have been suggested to explain the associated cardioprotective effects.

CARDIOPROTECTIVE EFFECTS OF STRUCTURED EXERCISE AND/OR LIFESTYLE PHYSICAL ACTIVITY

Longitudinal, observational, and experimental studies have now elucidated various biological and/or clinical mechanisms that may be responsible for the cardioprotective effects

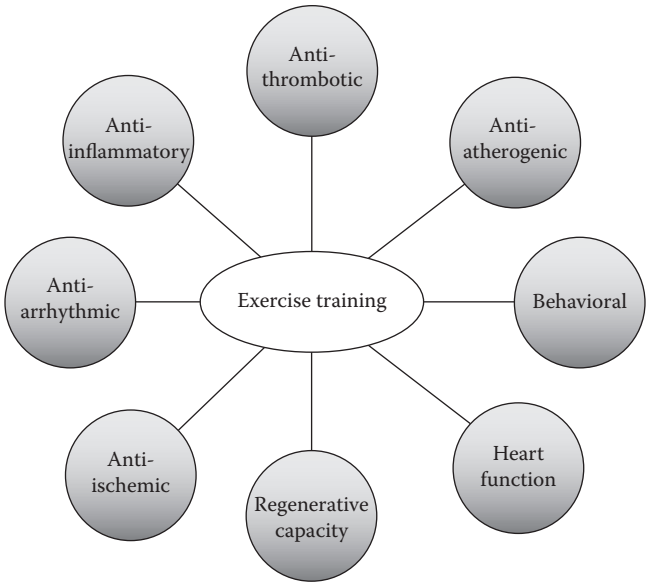


FIGURE 83.2 Potential cardioprotective effects of exercise training in coronary patients.

of exercise training. These are broadly summarized and outlined in Figure 83.2 and Table 83.1, respectively.

ANTI-ATHEROGENIC

Exercise training or regular physical activity has numerous anti-atherosclerotic effects that may reduce overall cardiovascular risk. In a meta-analysis of 48 trials including 8940 coronary patients, exercise-based CR was associated with significant mean reductions in total cholesterol (–14.3 mg/dL), triglycerides (–20.4 mg/dL), and systolic blood pressure (–3.2 mmHg) [16]. Similarly, another meta-analysis of 10 studies including 1260 patients with CVD who were randomized to aerobic exercise versus usual care for ≥4 weeks found that the exercise intervention was associated with significant increases and decreases in HDL cholesterol (9%) and triglycerides (–11%), respectively, with nonsignificant reductions in LDL and total cholesterol (–7.7 mg/dL and –8.8 mg/dL) [17]. Other studies, however, have reported significant reductions in LDL cholesterol with exercise training [18–20]. In addition, there is evidence that LDL heterogeneity may improve with regular aerobic exercise, transforming the more atherogenic small LDL particles into the larger less atherogenic form [21]. Physical conditioning also increases the resistance of LDL cholesterol to oxidation in previously sedentary subjects with CHD, highlighting the cardioprotective role of exercise in secondary prevention [22].

Previous studies and meta-analyses also report a modest, but significant reduction in systolic blood pressure with exercise training [16,23]. The underlying mechanisms may include a reduction in systemic vascular resistance, secondary to changes in sympathetic neural activity and/or the renin–angiotensin system [23]. Insulin resistance in coronary patients is associated with increased mortality [24]. Exercise training may have a beneficial impact on insulin sensitivity

TABLE 83.1
Pathophysiological Mechanisms Associated with Exercise Training in Coronary Patients

Anti-atherogenic
↑ Weight loss
↑ High-density lipoprotein cholesterol
↑ Coronary artery diameters
↓ Triglycerides and low-density lipoprotein cholesterol
↓ Arterial blood pressure
↓ Insulin resistance

Anti-ischemic
↑ Coronary flow reserve
↑ Coronary collateralization
↑ Myocardial capillary density
↑ Nitric oxide
↓ Myocardial oxygen demand
↓ Endothelial dysfunction

Anti-inflammatory
↓ hs-CRP
↓ TNF-α
↓ IL-6
↑ IL-10

Anti-thrombotic
↑ Fibrinolysis
↑ RBC deformability and tissue-level perfusion
↑ Plasma volume
↑ Endothelial tissue plasminogen activator
↓ Platelet aggregation
↓ Fibrinogen
↓ Blood viscosity

Regenerative Capacity
↑ EPC and CPC's
↑ Cardiac stem cells
↑ VEGF production
↑ Mesenchymal stem cells
↑Neoangiogenesis
↑Re-endothelialization
↓ Apoptosis
↓ Neointima formation

Anti-arrhythmic
↑ Vagal tone
↑ Heart rate recovery
↑ Heart rate variability
↑ Ventricular fibrillation threshold
↓ Adrenergic activity

Heart Function
↑ Improvement in diastolic function
↑ Cardiac output
↑ Ejection fraction
↑ Cardiac index

(*continued*)

TABLE 83.1 (continued)
Pathophysiological Mechanisms Associated with Exercise Training in Coronary Patients

Behavioral
↑ Social support
↑ Quality of life
↓ Depression
↓ Stress
↓ Hostility

hs-CRP, high-sensitivity C-reactive protein; TNF-α, Tumor necrosis factor; IL, Interleukin; EPC, Endothelial progenitor cell; CPC, circulating progenitor cell; VEGF, vascular endothelial growth factor.

and glucose metabolism [25]. The Diabetes Prevention Program Outcomes study showed that substantive lifestyle modification, including regular physical activity, reduced the incidence of new-onset diabetes, even at 10-year follow-up [26]. In contrast, another trial that randomized 55 cardiac patients to 12 weeks of exercise training versus usual care found insulin resistance unchanged in the absence of weight loss [27]. This suggests that adjunctive weight loss may be an essential component of some exercise training-induced adaptations, such as improved insulin sensitivity.

An "obesity paradox" has been reported in patients with CHD, wherein obese patients demonstrate a greater likelihood of survival as compared to their normal-weight counterparts [28–31]. Although a large body of evidence supports the obesity paradox when obesity is categorized using body mass index, central obesity as measured by waist–hip ratio or waist circumference has been shown to be directly associated with mortality [28]. Regardless of the adiposity indices employed, studies in coronary patients have shown that weight loss is associated with significant increases in HDL cholesterol [32] and brachial artery flow-mediated dilatation [33], and decreases in LDL cholesterol, triglycerides, C-reactive protein [32], major acute cardiovascular events, and total mortality [34]. Nevertheless, additional randomized controlled trials are needed to evaluate the short- and long-term effects of purposeful weight loss in secondary prevention programs.

ANTI-ISCHEMIC

Reduced myocardial oxygen demands and improvement in endothelial function are the epitome of anti-ischemic effects of exercise training in coronary patients. Exercise training decreases the heart rate and systolic blood pressure at a fixed level of submaximal exertion, reducing the rate-pressure product and associated myocardial oxygen demand. This allows selected patients to achieve greater workloads or metabolic equivalents (METs; 1 MET = 3.5 mL O_2/kg/min) before signs or symptoms of myocardial ischemia occur. The concept of "ischemic preconditioning" has also been described, primarily in animal models, and corresponds to increased tolerance of the myocardium to more prolonged periods of ischemic stress [35]. Physiological reduction in heart rate with regular physical activity allows for increased diastolic filling time, augmenting coronary perfusion during diastole. Finally, improvement in endothelial function with exercise training contributes significantly to the anti-ischemic effect. Hambrecht et al. [36] randomly assigned 19 patients with coronary endothelial dysfunction to exercise training or usual care. After 4 weeks, patients undergoing exercise training demonstrated significant improvement in endothelium-dependent vasodilatation in the epicardial coronary and resistance vessels, along with an increase in coronary blood flow reserve. Other studies have also reported that exercise training and/or habitual physical activity are directly associated with increased flow-mediated vasodilatation and exercise capacity [37,38]. Exercise training may also enhance coronary collateralization after an acute cardiac event [39].

ANTI-INFLAMMATORY

Subclinical inflammation measured by high-sensitivity C-reactive protein (hs-CRP) is associated with an increased risk of CVD and mortality [40]. Evidence also suggests that reduction of hs-CRP levels with cardioprotective medications (e.g., statins) has the potential to reduce long-term mortality [41]. Exercise-based CR programs have been shown to significantly reduce hs-CRP levels in patients with CHD [42]. Goldhammer et al. [43] reported that a 12-week aerobic exercise training program in coronary patients resulted in a significant reduction in the levels of CRP and pro-inflammatory cytokines, including IL-1, IL-6, and INF-γ, and significantly increased levels of the atheroprotective cytokine, IL-10. Walther et al. [44] randomized 101 men with moderately to severely obstructed coronary lesions to regular exercise training or PCI. At 2-year follow-up, exercise-trained patients demonstrated significantly reduced CRP levels and ischemic events as compared with patients who underwent PCI. Collectively, these findings suggest that exercise training and/or regular physical activity reduce chronic inflammation associated with coronary disease and that this adaptation may be responsible, at least in part, for the reduced long-term morbidity and mortality.

ANTI-THROMBOTIC

Exercise training produces intrinsic hemostatic effects that may reduce the plaque burden in coronary patients. The anti-thrombotic benefits of exercise training may include decreased fibrinogen levels, increased fibrinolysis, increased thrombolytic activity by increasing tissue plasminogen activator levels, decreased platelet aggregability, expansion of plasma volume, and reduction of blood viscosity [45–47]. A study of 23 nonsmoking coronary patients reported a significant reduction in the hematocrit standardized blood viscosity and plasma viscosity and an increase in red blood cell transport efficiency after a phase II exercise-based CR

program, thus improving blood rheology [48]. Short-term strenuous physical activity may be associated with increased platelet aggregation; however, this may be prevented with regular exercise [49]. Collectively, these data suggest that exercise training may reduce the incidence of recurrent cardiovascular events, possibly by attenuating the likelihood of plaque rupture and thrombus formation [14].

ANTI-ARRHYTHMIC

Threatening arrhythmias, including ventricular tachycardia and fibrillation, are directly associated with an increased incidence of sudden cardiac death (SCD), which is the most common cause of mortality in coronary patients. Exercise training may raise the threshold for ventricular fibrillation [50,51] by increasing vagal tone at rest while simultaneously decreasing the sympathetic drive [52,53]. Recently, Jolly et al. [54] found that CR participation was associated with improvement in heart rate recovery, which is considered to be reflective of vagal tone. In a classic experiment demonstrating the cardioprotective effect of exercise training in dogs, Hull et al. [52] reported heightened baroreflex sensitivity, a marker of the capability to reflexly augment vagal activity; increases in heart rate variability, an index of vagal tone; and increases in repetitive extrasystole threshold, an indicator of ventricular electrical stability. Subsequently, these adaptations were substantiated in patients with coronary disease [53,55]. In a randomized trial of 97 patients with CHD, a short-term residential exercise training program resulted in significant improvement in baroreflex sensitivity and heart rate variability [53]. In another randomized trial of post-MI and post-CABG patients, investigators reported that the observed increase in heart rate variability with exercise training persisted up to 1-year post-intervention [56]. These findings suggest that exercise-induced changes in cardiac autonomic control may create a myocardial milieu that is more resistant to the fostering of malignant ventricular arrhythmias.

REGENERATIVE CAPACITY

The number and morphology of endothelial progenitor cells (EPCs) in coronary patients are often low, more apoptotic, and functionally impaired [57,58]. One of the most important and emerging beneficial effects of exercise training may be the mobilization of progenitor cells from bone marrow. A randomized study of 37 patients with ST-segment elevation MI showed that regular exercise training was associated with a significant increase in the number and migratory capacity of the circulating progenitor cells [59]. Another investigation involving 19 stable coronary patients reported a significant increase in the number of EPCs and reduced apoptosis after 28 days of moderate-intensity exercise training [60]. Paul et al. [61] noted that participation in a 36-session CR program after a cardiac event led to a significant increase in the number of EPCs and EPC colony-forming units, and a significant reduction in the total number of apoptotic progenitor cells. Similar results have been replicated in experimental studies on exercise-trained mice [60]. These responses may serve to inhibit the progression of atherosclerosis in some patients by suturing the denuded endothelium, reducing neointima formation, promoting neoangiogenesis, and increasing re-endothelialization [60].

Mesenchymal stem cells are involved in the repair of myocardium via differentiation into cardiomyocytes, smooth muscle cells, and vascular endothelial cells, stimulating spontaneous cell fusion, endogenous repair, and local immunosuppressive properties [62]. Recent studies in patients with stable CHD have shown that brief bouts of high-intensity exercise (i.e., >90% peak heart rate) evoked a significant increase in mesenchymal stem cells [63]. Furthermore, growing evidence suggests that endurance exercise training may facilitate favorable cardiac remodeling by increasing the circulating and tissue-specific cardiac stem cells [64]. Experimental studies in mice have shown that exercise-induced hyperplasia may be due to the activation and differentiation of cardiac stem cells into cardiomyocytes [65].

HEART FUNCTION

Coronary artery disease is often associated with ischemic cardiomyopathy, systolic and/or diastolic dysfunction, and ultimately heart failure. Exercise training has the potential to enhance myocardial function with significant improvements in both systolic and diastolic functions. Oberman et al. [66] noted that high-intensity exercise training, as compared to low-intensity training, led to higher increments in rest–peak LVEF in sedentary men with coronary disease. Similarly, investigators recently reported a significant (31%) increase in LVEF after 12 weeks of exercise training in 42 cardiac patients [67]. Exercise training has also been consistently shown in numerous randomized controlled trials to improve indices of diastolic function in heart failure patients [68–70]. Wisløff et al. [70] randomized 27 patients with stable post-infarction heart failure to either high-intensity aerobic interval or moderate-intensity continuous endurance training and showed that the former intervention was more effective in promoting reverse left ventricular remodeling, reductions in left ventricular end-diastolic and systolic volumes, and increases in LVEF. Moreover, the Exercise Training in Diastolic Heart Failure pilot study showed that physical training improved exercise capacity, atrial remodeling, and indices of diastolic function in heart failure patients with preserved ejection fraction [68].

BEHAVIORAL

A high prevalence of psychosocial traits like anger, hostility, depression, and social isolation are often observed in patients who experience cardiovascular events. These behavioral characteristics are associated with a reduced quality of life and increased morbidity and mortality [47,71]. Recent data also show that positive recovery expectations at baseline are strongly associated with long-term survival and functioning in patients with angiographically documented

coronary artery disease [72]. Exercise training, especially in the form of comprehensive CR programs, has the potential to favorably modify psychosocial risk factors in patients with CHD. The Enhancing Recovery in Coronary Heart Disease Patients randomized trial showed that cognitive behavior therapy reduced depression and social isolation scores in 2481 post-MI patients; however, there was no difference in mortality between the intervention and usual-care control group [73]. Milani et al. [71] reported a 63% reduction in the prevalence of depressive symptoms following exercise-based CR as well as a significant reduction in long-term mortality. The Heart and Soul Study [74] raised the hypothesis that the increased risk of cardiovascular events associated with depression in stable coronary patients could be nullified by behavioral modification like regular physical activity, structured exercise, or both. To answer this question, the NIH-funded trial, Understanding Prognostic Benefits of Exercise and Antidepressant Therapy study, is under way, evaluating the effects of sertraline versus exercise on depressive symptoms and cardiovascular function in patients with CHD [75].

HEALTH RISKS OF PHYSICAL ACTIVITY AND/OR STRUCTURED EXERCISE

The risk of cardiovascular, pulmonary, musculoskeletal, and metabolic complications appears to increase transiently during strenuous physical activity compared with the risk at other times [76]. This seems particularly true when concomitant chronic diseases/medical conditions (e.g., diabetes, asthma, chronic obstructive pulmonary disease, coronary artery disease, orthopedic problems) are involved, especially among habitually sedentary, unfit individuals who were performing unaccustomed vigorous physical activity (i.e., 60%–89% of heart rate reserve or oxygen uptake [VO_2 reserve]) and/or ≥6.0 METs, where VO_2 reserve = percent intensity × (VO_2 peak − VO_2 rest) + VO_2 rest) [77–80].

This section reviews the pathophysiological basis for exercise-related untoward events, with specific reference to the absolute and relative risks for patients with known CHD, high-risk activities, identifying the "high-risk" patient, and recommendations to reduce the risk of activity-induced complications, including musculoskeletal injuries, cardiovascular events, adverse metabolic responses (e.g., hypoglycemia in diabetics), and/or the exacerbation of symptomatology related to asthma or chronic obstructive pulmonary disease.

PATHOPHYSIOLOGICAL BASIS FOR EXERCISE-RELATED CARDIOVASCULAR EVENTS

Pathophysiological evidence suggests that vigorous physical exertion may precipitate AMI or cardiac arrest in some persons with known or occult CVD [77–79]. Several hypotheses have been suggested as potential triggering mechanisms for plaque rupture (Figure 83.3) and acute coronary thrombosis, including abrupt increases in heart rate and systolic blood pressure, induced coronary artery spasm in diseased artery segments, or the twisting of epicardial coronary arteries [81,82]. An increase in platelet activation and hyperreactivity, which could contribute to (or even initiate) coronary thrombosis, has been reported in sedentary individuals who were engaged in sporadic high-intensity exercise, but not in physically trained individuals [83].

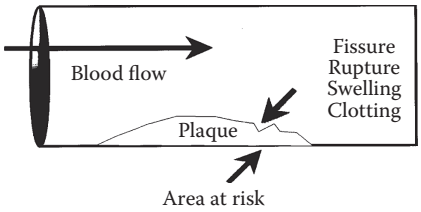


FIGURE 83.3 Atherosclerotic plaque can be either active and unstable or quiet and stable. If unstable, even mild-to-moderate blockages may fissure, rupture, or swell. Depending on the coagulative state of the blood, this cascade of events at vulnerable regions can induce thrombogenesis, triggering AMI. In some individuals, it appears that strenuous physical exertion can activate this sequence.

By increasing the rate-pressure product, a key index of myocardial oxygen consumption (r = 0.92) [84,85], and simultaneously shortening diastole and coronary perfusion time, exercise may evoke a temporary oxygen deficiency at the subendocardial level, which is exacerbated by abrupt cessation of exercise, arterial vasodilatation, or both. Because cardiac demands remain high in the immediate postexercise period, in the presence of known or occult coronary atherosclerosis, sudden decreases in venous return and coronary perfusion may increase the likelihood of myocardial ischemia, commonly manifested as significant ST-segment depression, angina pectoris, transient thallous (thallium) chloride-201 or technetium Tc99 m sestamibi (Cardiolite) perfusion defects, or combinations thereof. Ischemia can alter depolarization, repolarization, and conduction velocity (Figure 83.4), triggering threatening ventricular arrhythmias that, in extreme cases, may be harbingers of ventricular tachycardia or fibrillation. In addition, symptomatic or silent myocardial ischemia [86], sodium–potassium imbalance, increased catecholamine excretion, and circulating free fatty acids may heighten electrical instability.

EXERCISE-RELATED CARDIOVASCULAR EVENTS

For patients with known or occult CHD, the relative risk of experiencing cardiac arrest during vigorous exercise is estimated to be 6–164 times greater than that which might be expected to occur by chance alone [87]. Although isolated bouts of vigorous physical exertion may transiently increase the risk of cardiovascular events, the absolute risk associated with each episode of exercise remains extremely low. A large survey of cardiovascular events during rehabilitative exercise training in 142 U.S. CR programs (1980–1984) reported one cardiac arrest per 111,996 patient hours, one nonfatal MI per 293,990 patient hours, one major complication per

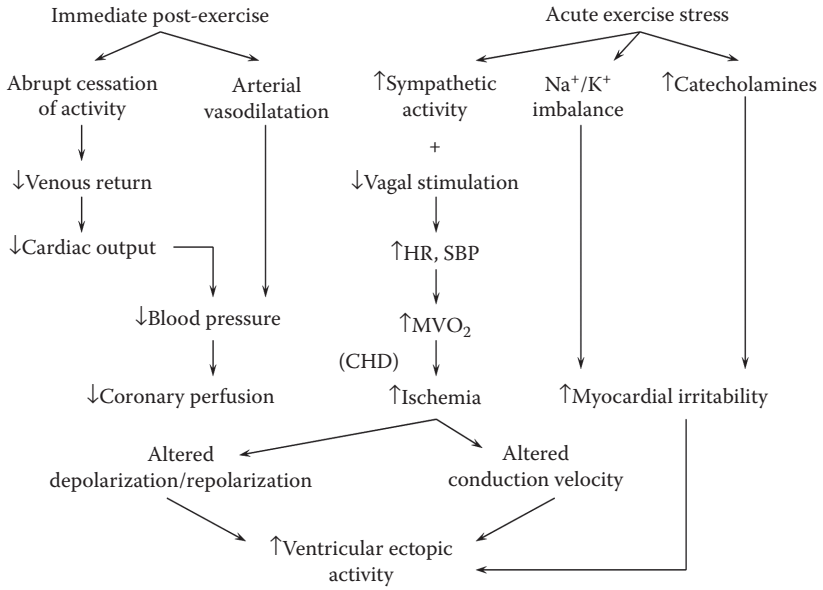


FIGURE 83.4 Physiological alterations accompanying acute exercise and recovery and their possible sequelae. HR, heart rate; SBP, systolic blood pressure; MVO_2, myocardial oxygen consumption; CHD, coronary heart disease.

81,101 patient hours, and one fatality per 783,972 patient hours of exercise [88]. However, these data antedate the current use of risk stratification procedures, emergent and elective coronary revascularization, newer cardioprotective pharmacotherapies, ablation techniques, ventricular assist devices, and antitachycardia pacemakers and implantable cardioverter defibrillators. Thus, these exercise-related complication rates may not necessarily apply to modern-day cardiac patients.

More recent studies suggest one major cardiovascular complication in every ~58,000 participant hours of outpatient cardiac exercise therapy, with no fatal events [89–91]. The French registry of complications during exercise-based CR reported a cardiac arrest rate of 1.3 per million patient hours of exercise [91]. It should be emphasized, however, that the absence of fatal cardiovascular events associated with CR applies only to medically supervised programs equipped with a defibrillator and appropriate emergency drugs. Numerous reports indicate that up to 90% of all patients with cardiac arrest occurring under such conditions are successfully resuscitated [88–91].

Morning versus Afternoon Exercise

During the early morning hours, a variety of pathophysiological mechanisms for AMI are more likely to be operative, including circadian surges in heart rate, blood pressure, catecholamines, and cortisol; platelet aggregability; coronary vascular tone; plasma viscosity; and fibrinolytic activity associated with awakening and assuming an upright posture [92]. Although it has been suggested that superimposed exercise training may accentuate these responses, and thus heighten the risk of activity-induced cardiovascular events, two studies of outpatient CR that compared morning-hour exercise with afternoon-hour exercise reported no difference in the overall cardiac complication rate [90,93].

Risk–Protection Paradox

Numerous independent studies have now shown that the relative risk of acute cardiovascular events is transiently increased by vigorous physical exertion, especially among habitually sedentary individuals with known or occult CHD and that the risk decreases with regular exercise participation [94]. To put these data into perspective, it is important to emphasize that the absolute risk associated with each bout of exercise is extremely low, the relative risk is inversely related to the habitual level of activity, and the long-term cardioprotective effect of regular physical activity and/or increased cardiorespiratory fitness is substantial. Two meta-analyses now suggest that regular exercise can reduce the long-term risk of cardiovascular events by up to 50% [95,96]. Moreover, recent studies in coronary patients have expressed exercise capacity in the context of survival benefit per MET [97]. These observations are noteworthy in that each 1-MET increase in exercise capacity appears to confer an 8%–55% reduction in mortality (Table 83.2) [15,98–103].

Based on data from the Onset study [104], the risk of AMI during each bout of physical activity is approximately doubled for an individual who participates in ≥5 vigorous 1-h exercise sessions per week. During the exercise bout, his or her risk will double and approximate the level that it would have been at all times if he or she were habitually sedentary. However, over the remaining 23 h of the day, his or her risk would be substantially lower, highlighting the clear net benefit of regular exercise and/or increased cardiorespiratory fitness, despite the modest, transient increased relative risk for a training-related cardiovascular event.

TABLE 83.2
Relation of Fitness or Exercise Tolerance to All-Cause or Cardiovascular Mortality in Secondary Prevention

Study	Population/Follow-Up Period	Fitness Measurement	Decrease in All-Cause or Cardiovascular Mortality
Vanhees et al. [98]	Male patients ≥4 weeks after MI (n = 312) or CABG (n = 215) for 6.1 years	Peak VO_2	71% per 1 L/min increase
Dorn et al. [99]	315 post-MI men randomized to a 6-month exercise program; patients followed over the course of 19 years	Peak METs	8%–14% per 1-MET increase
Kavanagh et al. [100]	12,169 men with CVD referred for exercise-based cardiac rehab; median follow-up was 7.9 years	Peak VO_2	9% per 1 mL/kg/min increase
Kavanagh et al. [101]	2,380 women with CVD referred for exercise-based cardiac rehab; average follow-up was 6.1 years	Peak VO_2	10% per 1 mL/kg/min increase
Kavanagh et al. [102]	6,956 men with CVD completing a 12-month walking-based training regimen; median follow-up was 9.0 years	Walking distance	20% per 1 mile improvement
O'Connor et al. [15]	2,331 medically stable outpatients with HF and reduced EF (≤35%), randomized to exercise training or usual care; median follow-up was 30 months	Peak VO_2	11% per 0.7 mL/kg/min increase
Feuerstadt et al. [103]	600 men and women with CVD who were referred to a 12-week exercise-based cardiac rehab program; mean follow-up was 4.4 years	Exit training MET level	34% per 1-MET increase 28% per 1-MET increase[a]

MI, myocardial infarction; CABG, coronary artery bypass graft surgery; CVD, cardiovascular disease; rehab, rehabilitation; HF, heart failure; EF, ejection fraction; VO_2, oxygen consumption; MET, metabolic equivalent, where 1 MET, 3.5 mL/kg/min.

[a] After adjustment for age.

HIGH-RISK ACTIVITIES

Although the incidence of cardiovascular events during very light-to-moderate-intensity activities is similar to that expected by chance alone [45], vigorous physical exertion, especially when it is sudden, unaccustomed, or involving interspersed, near-maximal to maximal exercise bouts (≥90% VO_2 reserve), may increase the risk of AMI and SCD [77–79]. For example, jogging [45], racquet sports [105], skiing [106], marathon running [107], and strenuous sports (e.g., basketball) seem to be associated with a greater incidence of acute cardiovascular events than other activities. The excitement of competition may increase sympathetic activity and catecholamine levels, and lower the threshold to ventricular fibrillation [108]. Other recreational and domestic activities that are associated with a greater incidence of cardiovascular events include deer hunting [109] and snow removal [110], both of which may involve isometric and/or heavy upper extremity exertion and substantial increases in left ventricular afterload [111,112]. These responses, coupled with the body's normal thermoregulatory responses to cold, including increased platelet aggregability and plasma viscosity [113], coronary spasm or vasoconstriction [114], and superimposed emotional/hyperadrenergic responses [115], may present a hazardous milieu for cardiovascular events. During the winter months, an increased incidence of AMI and SCD has been reported in both the medical literature and lay press after hunting excursions [116] and heavy snowfalls [117–120].

RECOMMENDATIONS TO REDUCE THE RISK OF EXERCISE-RELATED CARDIOVASCULAR EVENTS

Recommendations to potentially reduce the risk of exercise-related cardiovascular events and their sequelae in coronary patients include the following: mandate medical clearance for participation and follow-up evaluations, which may involve serial peak or symptom-limited exercise testing; provide on-site medical supervision during and after exercise, until all patients have exited the shower and changing areas; establish an emergency plan, with provisions for cardiopulmonary resuscitation practice, regular emergency drills, and defibrillator and outdated drug checks; encourage sedentary patients to initially engage in regular walking so as to move them out of the least fit, least active, "high-risk" cohort (i.e., the bottom 20%) [46,121]; counsel inactive patients to avoid unaccustomed, vigorous physical activity (e.g., racquet sports, waterskiing, snow shoveling) [78,79];

advocate appropriate warm-up and cooldown procedures [122,123]; promote education of warning signs/symptoms (e.g., chest pain or pressure, light-headedness, heart palpitations/arrhythmias; unusual shortness of breath) [105,124]; emphasize strict adherence to prescribed training pulse rates, using perceived exertion as an adjunctive intensity modulator; use continuous or instantaneous electrocardiographic (ECG) monitoring in selected coronary exercisers, including suspected intensity violators [125]; minimize competition and modify recreational games to decrease the energy cost and heart rate response to play (e.g., doubles as opposed to singles tennis; allow 1 bounce of the ball per side during volleyball play); and adapt the exercise to the environment.

Cardiac patients can exercise safely in cold weather if proper precautions are taken. Nevertheless, inhalation of or exposure to cold air may evoke ischemic ST-segment depression, angina pectoris, or both. A cold-weather "jogging mask" may be helpful in this regard by attenuating signs or symptoms of myocardial ischemia in selected coronary exercisers [126]. Hyperthermic conditions may pose an even greater hazard than cold weather for cardiac patients who exercise. As the temperature increases at a given workload, heart rate response and myocardial demands may increase disproportionately [127]. Accordingly, patients may need to reduce their exercise intensity in hot and/or humid conditions. Because symptomatic or silent myocardial ischemia may be highly arrhythmogenic, the prescribed heart rate for endurance exercise training should be set at least 10 beats/min below the ischemic ECG or anginal threshold [128].

EXERCISE TESTING TO IDENTIFY PATIENTS "AT RISK"

It is difficult to identify cardiac patients who may be predisposed to cardiovascular events during exercise training; however, certain risk factors have been reported. For example, patients with previous MIs who have impaired LVEF (≤35%), rest- or exercise-induced signs and/or symptoms of myocardial ischemia (angina, marked ST-segment depression (≥2 mm)), high-grade left anterior descending lesions and/or significant multivessel atherosclerosis on angiography, inotropic impairment (exertional hypotension), a very low or relatively high exercise capacity, or threatening rest- and/or exercise-induced ventricular arrhythmias (especially in patients with impaired left ventricular function) appear to be at increased risk for an exercise-related cardiovascular complication [129]. Today, the latter cohort is increasingly treated with an implantable defibrillator to potentially reverse the catastrophic sequelae of SCD. Cardiac arrest victims are more likely to be chronic intensity violators (i.e., exceeding the prescribed training heart rate), disregard appropriate warm-up and cool-down procedures, or participate in sporadic high-intensity exercise. Low serum potassium has also been associated with electrical instability and worrisome ventricular arrhythmias. Nevertheless, it should be emphasized that coronary patients who have one or more of these widely varied characteristics may never experience an exercise-related cardiovascular event.

It is not necessary that all cardiac patients beginning a moderate-intensity and moderately progressive exercise program undergo a peak or symptom-limited exercise stress test, although this issue remains controversial since no data from controlled trials are available [25]. Exercise testing is recommended (i.e., Class I, Level of Evidence: B) for prognostic assessment, activity prescription, evaluation of medical therapy, and exercise-based CR after hospital discharge in patients with coronary and other atherosclerotic vascular diseases [8,130]. Cardiac patients who may be at increased risk for exercise-related cardiovascular events should also be considered for exercise testing before beginning a vigorous exercise training program [79]. On the other hand, empiric experience and previous studies have demonstrated the safety and effectiveness of early outpatient medically supervised exercise rehabilitation, using adjunctive intensity modulators (e.g., rating of perceived exertion and/or the patient's resting heart rate plus 20 beats/min) and continuous ECG monitoring, without a preliminary exercise stress test [131]. Joo et al. [132] reported that, on average, this methodology corresponded to ~42% VO_2 reserve among patients entering a phase II CR program, an intensity that approximates the minimum or threshold intensity for improving cardiorespiratory fitness in this patient subset [133].

Although exercise testing may be helpful in identifying threatening ventricular arrhythmias, a truly positive exercise test requires a hemodynamically significant coronary lesion (e.g., >75% stenosis; Figure 83.5), whereas most AMIs in previously asymptomatic persons occur at mild-to-moderate obstructions, due to vulnerable plaque disruption [134]. Consequently, an exercise stress test with or without concomitant myocardial perfusion imaging can be normal despite the presence of coronary plaque that may rupture. This requires that physicians and allied health professionals employ comprehensive risk stratification methodologies when advising patients on the feasibility of a vigorous exercise program.

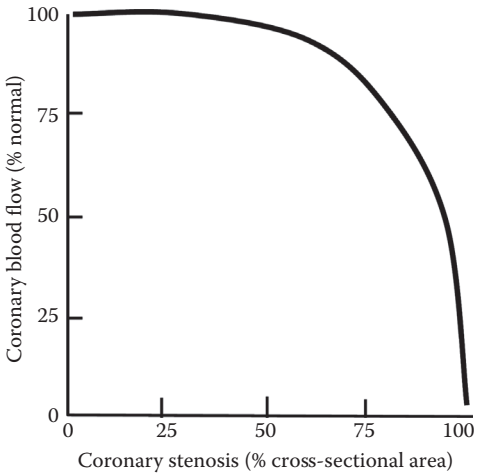


FIGURE 83.5 Relationship between coronary blood flow and coronary artery stenosis shows how perfusion is not significantly reduced until the obstruction exceeds 75% of the vessel's cross-sectional area.

OTHER EXERCISE RISKS

Although considerable epidemiologic evidence suggests that regular physical activity may help to protect against and treat aging-related chronic diseases, including CHD, cardiovascular, musculoskeletal, metabolic, and pulmonary complications appear to increase transiently during strenuous physical activity compared with the risk at other times. Accordingly, these risks must be considered when recommending the type and intensity of exercise for cardiac patients, especially those with concomitant orthopedic limitations, previous musculoskeletal injury, metabolic conditions, or pulmonary disease.

Musculoskeletal Injuries

Moderate-intensity physical activity, corresponding to between 40% and 59% of the heart rate reserve or VO_2 reserve, is associated with a relatively low risk of orthopedic complications [135]. On the other hand, the most common risk of vigorous physical activity is musculoskeletal injury, which can be as high as 55% among adults involved in jogging/running programs [136,137].

Jogging-related injury rates for novice exercisers are directly related to the intensity, frequency, and duration of exercise. Inordinate exercise demands, particularly during the initial weeks of a physical conditioning program, often result in muscle soreness, orthopedic injury, and attrition. An excessive frequency (≥5 days/week) and/or duration (≥45 min/session) of training offer the participant little additional gain in aerobic capacity (VO_2 max), whereas the incidence of orthopedic injury increases disproportionately (Figure 83.6) [138]. Similarly, near-maximal to maximal training intensities (≥90% of the heart rate reserve or VO_2 reserve) provide little additional improvement in cardiorespiratory fitness and are associated with an injury rate of ~50% [139]. Attention to warm-up, proper footwear, and terrain (avoiding hard and uneven surfaces) should aid in decreasing attrition due to injury.

Diabetes

For the diabetic who is adequately controlled or is only slightly hyperglycemic without ketosis, physical activity decreases blood glucose concentration, and a lower insulin dosage may be required. A lack of sufficient insulin before exercise may impair glucose transport into the muscles and lead to a cascade of potentially adverse metabolic responses, including ketosis and hyperglycemia. On the other hand, because exercise has an insulin-like effect, hypoglycemia is the most common problem experienced by exercising diabetics who take exogenous insulin or, to a lesser extent, oral hypoglycemic agents. Other precautions that should be taken include wearing proper footwear, practicing good foot hygiene, and recognizing that diabetic neuropathies can alter cardiovascular, skin blood flow, and sweating responses to exercise in hot/humid environments, increasing the risk of heat injury [128].

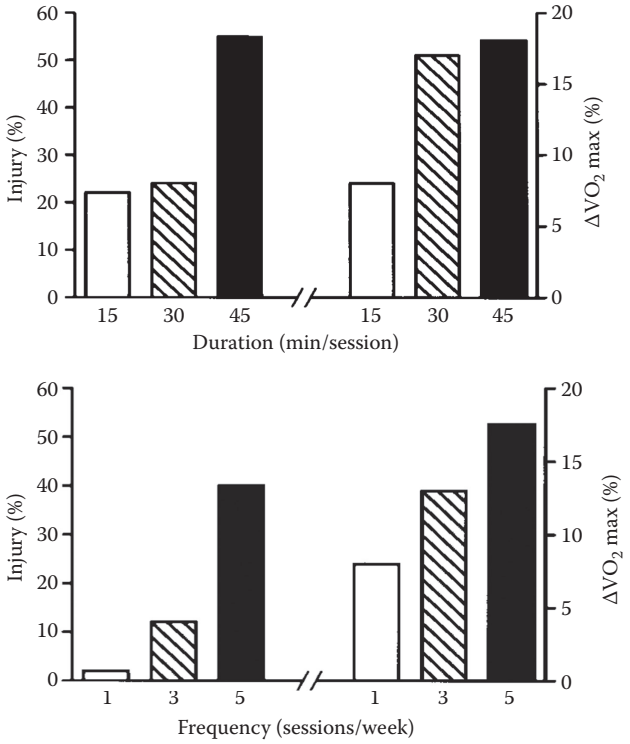


FIGURE 83.6 Relationships among exercise frequency and duration, improvement in maximal oxygen consumption (ΔVO_2 max), and the incidence of orthopedic injury in novice exercisers. Above an exercise duration of 30 min/session or a frequency of 3 sessions/week, additional improvement in VO_2 max is small, yet the injury rate increases disproportionately. (Adapted from Pollock, M.L. et al., *Med. Sci. Sports Exerc*., 9, 31, 1977.)

Selected recommendations and precautionary measures to reduce the likelihood of the previously referenced complications are outlined in Table 83.3.

Asthma or Chronic Obstructive Pulmonary Disease

Many coronary patients with moderate-to-severe asthma or chronic obstructive pulmonary disease may experience an exacerbation of pulmonary symptoms during exercise due to ventilatory limitations and/or oxygen desaturation. In patients in whom reactive airway disease is suspected or asthma has been documented, exercise-induced bronchoconstriction frequently occurs. Accordingly, such patients should be instructed in pursed-lip breathing during exercise, as well as the use of supplemental oxygen, especially those with a partial pressure of arterial oxygen of ≤55 mmHg, or a percent saturation of arterial oxygen of ≤88% while breathing room air [128]. Although there is no consensus as to the "optimal" intensity of exercise training for patients with cardiopulmonary disease, exercise at 50% of the peak VO_2 should improve exercise performance, and higher intensities may be periodically interspersed as tolerated by symptoms. Intermittent exercise, i.e., brief repetitive exercise–rest periods on alternate days, may be necessary for the initial training sessions until the patient can achieve 20–30 min of continuous exercise.

TABLE 83.3
Recommendations to Reduce the Risk of Exercise-Related Complications in Patients with Diabetes

- *Wear proper footwear and practice good foot hygiene*. Diabetics, especially those with impaired nerve conduction in their feet, should use cushioned shoes (gel or air soles) and avoid high-impact exercise. Because of their increased susceptibility to infection, diabetics should monitor their feet carefully for skin lesions, blisters, discoloration, or swelling and consult their physician if any of these appear
- Curtail outdoor exercise when the temperature is above 32°C (90°F), when the relative humidity is above 60%, or both, to decrease the likelihood of heat exhaustion or heat stroke
- *Monitor blood glucose before, during, and after physical activity when starting an exercise program*. Exercise at approximately the same time each day, ideally, 15–45 min after meals, when glucose levels are relatively high
- *Inject insulin in body areas that are not engaged by exercise*. For example, an inactive injection area like the abdomen should be used before walking, jogging, or stationary/outdoor bicycling
- *Avoid exercising during periods of peak insulin action*
- *Avoid exercise if the glucose level is below 100 mg/dL or above 300 mg/dL* (*or greater than 240 mg/dL with urinary ketone bodies*). Physical activity may be undertaken in insulin-dependent diabetics with low blood sugar, provided that 20–30 g of additional carbohydrate is ingested before exercise
- *Know the signs and symptoms of hypoglycemia*. These include heart palpitations, confusion, weakness, and visual disturbances, which, if left untreated, could lead to unconsciousness or convulsions. To reduce the likelihood of such adverse sequelae, diabetics should be instructed to always carry a form of fast-acting carbohydrate, e.g., juice, candy, glucose tablets, exercise with a partner, and wear a diabetic identification tag. Because the insulin-like effects of activity can persist for several hours after exercise, diabetics should also be counseled to eat more than usual or eat an extra carbohydrate-rich snack after working out
- *Monitor for symptoms of hyperglycemia, e.g., excessive thirst; frequent urination; blurred vision; itchy, dry skin; or a fruity odor or breath, which can lead to ketoacidosis, commonly called diabetic coma*

CONCLUSIONS

Although considerable epidemiologic and clinical evidence suggests that structured exercise, increased lifestyle activity, or both are cardioprotective, the absolute and relative risks of cardiovascular, musculoskeletal, metabolic, and pulmonary complications appear to increase transiently during vigorous physical activity. These risks should be considered when endorsing strenuous leisure-time or exercise interventions for cardiac patients. If the current mantra "exercise is medicine" is embraced, indications and contraindications require clarification, and under- and overdosing are possible. In some patients, prolonged, excessive, or vigorous-to-near-maximal physical exertion may elicit adverse signs, symptoms, and sequelae. Thus, exercise may have a typical dose–response curve with a plateau or even toxicity at more extreme levels [140].

In summary, there are numerous physiological and clinical benefits of regular exercise for cardiac patients (Figure 83.2; Table 83.1), and in the vast majority of patients, the benefits certainly outweigh the very low risk of untoward events. Accordingly, the medical community should adopt an evidence-based risk stratification approach, while avoiding hypermedicalization that may impede patient's decisions to become more physically active. Gill et al. [141] argued that any policy (e.g., the need for routine exercise testing and extensive safety monitoring procedures) that further deters a large number of older persons from participating in an exercise program may cause more harm than good. Perhaps Professor Per-Olof Åstrand [142] summed it up best when he said: "A medical examination is more urgent for those who plan to remain inactive than for those who intend to get into good physical shape!"

ACKNOWLEDGMENT

The authors express their appreciation and gratitude to Brenda White for her assistance in preparing this chapter.

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84 Psychosocial Considerations in Coronary Heart Disease
Implications for Cardiac Rehabilitation

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CONTENTS

Psychosocial Risk Factors....1053
Type A Behavior Pattern and Hostility....1053
Depression and Anxiety: The Role of Negative Affect....1054
Acute and Chronic Stress....1055
Contextual or Environmental Factors....1056
Social Support....1056
Low Socioeconomic Status....1056
Job Strain....1056
Potential Mechanisms Linking Psychosocial Variables and CHD....1057
Cardiovascular and Neuroendocrine Reactivity....1057
Heart Rate Variability....1057
Myocardial Ischemia....1057
Inflammation and Platelet Function....1057
Interventions to Improve Psychosocial Risk Factors in Cardiac Patients....1058
Conclusions....1061
References....1062

Coronary heart disease (CHD) is the leading cause of death for American Indians and Alaska Natives, blacks, Hispanics, and whites. In 2004, 871,500 people died of heart disease, accounting for 36% of all U.S. deaths [1]. In 2005, CHD was projected to cost $393 billion, including health care services, medications, and lost productivity. We now know that the traditional risk factors, cigarette smoking, hyperlipidemia, diabetes, and hypertension, do not fully account for the timing and occurrence of CHD events, and it has been widely recognized that stress and negative emotions affect the development and course of CHD [2–4]. This chapter provides an update of our earlier chapter in which psychosocial risk factors associated with the development and clinical manifestations of CHD were reviewed, contextual factors that may moderate this risk were discussed, and potential mechanisms by which psychosocial factors increase the risk of adverse events in patients with CHD were presented. In addition, this revised chapter provides a more current review of interventions designed to modify psychosocial risk factors in patients with CHD.

PSYCHOSOCIAL RISK FACTORS

Type A Behavior Pattern and Hostility

Early observations by Friedman and Rosenman. [5] suggested that a large proportion of patients with CHD displayed a particular constellation of behaviors and personality traits, characterized by a hard-driving, competitive nature, a strong need for recognition and achievement, a sense of time urgency, and free-floating hostility. These attributes collectively were termed the *Type A behavior pattern* (TABP). Early retrospective studies supporting Friedman et al.'s initial observations found that patients with CHD were more likely to exhibit TABP than Type B behavior. A large prospective study known as the Western Collaborative Group Study (WCGS) found TABP to be predictive of CHD events in initially healthy individuals [6]. Based on a critical review of the literature, an expert panel of biomedical and behavioral scientists convened by the National Heart, Lung, and Blood Institute concluded that TABP contributed to CHD, conferring a twofold increased risk, which was of the same

order of magnitude as cigarette smoking, hypertension, and elevated serum cholesterol. Furthermore, this risk was independent of traditional risk factors [7].

In the 1980s, however, studies investigating the relationship between TABP and CHD provided inconsistent or negative findings. For example, a 22 year follow-up study of the WCGS did not support the earlier findings of a relationship between CHD and TABP [8]. Other studies also raised questions regarding the association between TABP and CHD, including the Multiple Risk Factor Intervention Trial [9] and the Aspirin Myocardial Infarction Study [10]. Subsequent reviews qualified the TABP-CHD relationship [4,11–13] and concluded that TABP is a multidimensional construct best represented by component measures [14] and that not all aspects of TABP are pathogenic.

Based on these considerations, investigators shifted their focus to examine *components* of Type A, with particular emphasis on anger and hostility [15]. Several cross-sectional studies found that ratings of hostility were associated with atherosclerosis [16,17]. Prospective studies also found that behavioral ratings of hostility predicted initial CHD events and progression of CHD [18], and Goodman et al. [19] found that patients undergoing percutaneous transluminal angioplasty (PTCA) with high hostility ratings were 2.5 times more likely to have subsequent restenosis compared to low-hostility patients. Although a follow-up of the WCGS failed to support the earlier findings of a relationship between global TABP and clinical events, analysis of these WCGS data indicated increased mortality rates among those highest in hostility [20], and further analysis of the 8½ year follow-up data showed hostility to be a significant risk factor for CHD events [21].

Self-report measures also have been used to investigate the relationship between hostility and CHD. In an early cross-sectional study of 424 patients undergoing diagnostic coronary arteriography, Williams et al. [22] found that hostility, as measured by the Cook–Medley Scale (CMHo), and TABP were both independently related to atherosclerosis. However, hostility scores were more strongly associated with atherosclerosis than was TABP. These findings have been confirmed by studies that have found similar results with other indicators of disease activity, such as frequency and severity of myocardial ischemia [23]. In addition, prospective studies also have shown CMHo scores to predict CHD morbidity and overall mortality in both medical students and law students at the University of North Carolina [24,25].

Reviews of the literature support the role of hostility in the development of CHD [26–29]. In a meta-analysis of prospective studies examining anger and hostility with future CHD events, Chida and Steptoe [29] found that higher levels of anger and hostility were associated with poorer outcomes in both healthy adults and cardiac populations. Among individuals healthy at study entry, higher levels of anger and hostility were associated with 19% greater risk of developing CHD (HR = 1.19). Cardiac patients with higher anger and hostility were also at greater risk, with greater anger and hostility associated with poor cardiac prognosis (HR = 1.24). It was suggested that anger and hostility may contribute to the development and progression of coronary atherosclerosis and also trigger acute CHD events.

Depression and Anxiety: The Role of Negative Affect

In addition to personality traits such as TABP and hostility that have been identified as risk factors for adverse cardiac events, it has been observed that myocardial infarction (MI) and sudden death may be preceded by excessive fatigue, lack of energy, hopelessness, and other symptoms of negative affect [30]. Depression in particular has been found to be a relatively common disorder among individuals with CHD and is now considered to be an important psychosocial risk factor for cardiac morbidity and mortality [31–34]. Carney et al. [33], for instance, found major depressive disorder (MDD) to be the best predictor of major cardiac events over a 12 month follow-up period of patients found to have CHD determined by cardiac catheterization. Furthermore, the relationship was independent of disease severity or smoking status.

Depression is particularly common among patients following an MI or cardiac surgery. Prevalence rates of MDD among patients with CHD have been estimated to be as high as 25%, with point prevalence rates estimated at up to 45% for patients with minor depression (mDD) or elevated depressive symptoms [31–36]. In a landmark study, Frasure-Smith et al. [31,32] found depression to be significantly related to cardiac mortality at 6 and 12 month follow-up and to be a significant predictor of mortality even after controlling for other important predictors, including previous MI, Killip class, and premature ventricular contractions of 10 or more per hour. In a meta-analysis of 20 prospective studies of CHD patients, depressive symptoms were associated with an odds ratio of 2.24 for mortality [36]. Importantly, even elevated depressive symptoms, without meeting formal DSM-IV criteria for MDD, have been shown to be associated with increased risk among CHD patients [37].

In addition to studies of post-MI patients, other studies also have shown that depression is associated with worse outcomes in other cardiac samples. Duke researchers [38], for example, found that among patients undergoing coronary artery bypass graft (CABG), moderate to severe depression before surgery and mild but persistent depression following surgery are associated with increased risk of death over extended follow-up periods. Similar findings have been reported among heart failure (HF) patients, with greater levels of depression predicting increased risk of mortality and rehospitalization [39,40]. Sherwood et al. at Duke demonstrated recently that depression was predictive of all-cause mortality and HF hospitalizations, and that persistent depression was a marker for increased mortality in HF patients [41].

Vital exhaustion is a related concept that resembles depression but occurs without feelings of sadness and other symptoms such as feelings of worthlessness or guilt. Several studies have shown that vital exhaustion is related to cardiac events and CHD severity [42–44]. Kop et al. [42] found vital exhaustion to predict new cardiac events in 127 post-PTCA

patients during 1.5 years of follow-up (odds ratio = 2.7). Multiple logistic regression showed the predictive value of vital exhaustion to be independent of traditional risk factors and initial disease severity.

Anxiety also has been studied as a possible risk factor for CHD events. In a meta-analytic review of 14 studies that investigated the relationship between anxiety and coronary disease, Friedman and Booth-Kewley [45] found anxiety to be a significant predictor of cardiac events, including both MI and angina. Subsequent studies have supported these findings and point to a relationship between anxiety and sudden cardiac death [46]. In one prospective study evaluating the association between symptoms of anxiety and risk of CHD using data from the Normative Aging Study, Kawachi et al. [47] found that, over 32 years of follow-up, the multivariate-adjusted odds ratio for men reporting two or more anxiety symptoms was 1.94 for fatal CHD and 4.46 for sudden cardiac death.

As with depression, prevalence rates of moderate to severe anxiety among MI patients in the hospital are relatively high, with estimates as high as 40% or more [51]. Moreover, about 15%–20% of patients still report anxiety 1 year after hospital discharge. Frasure-Smith [49] evaluated 461 post-MI men in the hospital and followed them for over 5 years. A high level of psychological distress in the hospital was found to confer a threefold increase in cardiac mortality over the 5 years of follow-up. In addition, highly stressed patients had 1.5 times the risk of recurrent MI over follow-up. In a related study, anxiety was associated with an adjusted odds ratio of 2.21 for a later cardiac event. Similar studies of post-MI patients also have found anxiety to have prognostic significance for future health problems, including the occurrence of cardiac arrhythmias [51].

Janszky et al. [52] recently examined the relationship between any diagnosis of anxiety and subsequent CHD events in a sample of 49,321 Swedish men, followed prospectively from age 18 to 20 over a 37 year follow-up period. Participants were initially diagnosed by a psychologist using a structured interview and the International Classification of Diseases—8th revision. Over the 37 year follow-up of the study, the presence of anxiety was associated with more than double the risk of CHD (HR = 2.17) and a similar risk for AMI (HR = 2.51). Interestingly, the authors did not find a significant association between depression and CVD outcomes in this study. In a meta-analysis of 20 studies, including 249,846 individuals followed for more than 11 years, Roest et al. [53] also found a relationship between anxiety and CHD. Anxious individuals had higher rates of CHD (HR = 1.26) and cardiac death (HR = 1.48) after controlling for other background factors and health behaviors.

There is also evidence that phobic anxiety may be associated with increased CHD risk and that this risk may be primarily for cardiac outpoints resulting from arrhythmias. Watkins et al. [54] found that the presence of phobic anxiety was associated with increased risk of CHD and sudden cardiac death, but only among women. Albert et al. [55] reported similar findings among women participating in the Nurses' Health Study. The authors prospectively followed 72,359 women for 12 years. They found that the presence of phobic anxiety, determined by self-reported symptoms on the Crisp–Crown Index, was associated with an increased risk of sudden cardiac death and fatal CHD, but not with nonfatal MI.

Although anxiety appears to be associated with increased risk of CHD, it is also often comorbid with depression. Several studies have therefore attempted to examine the unique and combined effects of these two psychosocial factors as they relate to CHD outcomes. In a study of 5073 middle-aged, healthy Dutch women, Denollet et al. [56] examined the relationship between anxiety and health outcomes while controlling for depression. At a 10 year follow-up assessment, they found that anxiety was associated with a 77% increased risk of mortality, a nearly threefold increased risk of CHD (HR = 2.77), and a tendency to be associated with an increased risk of breast cancer. Depression was not associated with increased risk of mortality or health outcomes in this study. Phillips et al. [57] found that individuals with generalized anxiety disorder and depression were at greater risk for CHD than individuals with either condition alone. Thus, there is a growing literature to suggest that both anxiety and depression are associated with increased risk and that the effects of anxiety and depression may be additive.

Acute and Chronic Stress

Acute stress has been implicated in the occurrence of cardiac events in CHD patients. For example, Kark et al. [58] examined the association between a life-threatening stressor, Iraqi missile attacks on Israel during the Gulf War in 1991, and subsequent mortality. The number of daily deaths during the 4 month period surrounding the war increased from December through January and subsequently declined through mid-March. There was an abrupt, significant increase in the number of deaths on January 18, the day of the first strike on Israeli cities, with a significant 58% increase in mortality risk on the first day of attacks. This increase was mainly due to CHD, other cardiovascular diseases, and a group of unknown causes, most probably representing sudden cardiac death.

In a naturalistic study of severe stress—a catastrophic natural disaster—Leor et al. [59] reviewed the county coroner records from the time surrounding the massive Los Angeles earthquake in January 1994. Results revealed that the number of sudden cardiac deaths rose sharply from a daily average of 4.6 in the preceding week to 24 on the day of the earthquake, only 3 of which could be attributed to physical exertion. Because the number of sudden cardiac deaths declined during the 6 days following the earthquake, to a daily average of only 2.7, the authors concluded that the earthquake itself was a significant trigger of sudden cardiac death and, based on the fact that sudden deaths due to cardiac causes declined in the week after the earthquake, that emotional stress precipitated cardiac events in predisposed individuals.

In addition to extreme emotional stress, everyday stressors have been shown to have potentially damaging health consequences. Mental stress, e.g., has been shown to provoke

myocardial ischemia in the laboratory in 50%–66% of cardiac patients with prior evidence of exercise (EX)-induced ischemia [60–63]. Moreover, stress during daily life has been associated with an increased incidence of ischemia measured by ambulatory monitoring [64–66]. Using a case-crossover design, Mittleman et al. [67] reported a relative risk of 2.3 for MI in the 2 h following an episode of anger, indicating that anger was a trigger that doubled the risk of MI.

Chronic stress also has been shown to be associated with CHD. The widely cited INTERHEART study [68,69] used a case–control design to study 15,152 individuals with their first MI and 14,820 age- and sex-matched healthy individuals without CHD. Psychosocial stress was assessed by four questions about stress at work, home, finances, and major life events. CHD patients reported higher levels of stress in all categories and also were more depressed. The composite stress index had an odds ratio of 2.67 adjusted for all other risk factors, which was comparable to the "traditional" risk factors. Taken together, data from prospective and cross-sectional studies have provided compelling evidence for the importance of stress as a risk factor, which provide the basis for developing interventions to reduce stress in vulnerable cardiac patients in order to modify the natural history of these clinical events.

CONTEXTUAL OR ENVIRONMENTAL FACTORS

Social Support

A lack of social support and social isolation have been implicated as risk factors for both cardiac morbidity and mortality. Prospective studies have found initially healthy individuals as well as post-MI patients who live alone or who lack adequate social support to be at increased risk of future cardiac events, independent of other known risk factors. Case et al. [70] observed a 6 month mortality of 15.8% among post-MI patients living alone (16.4% of total sample) versus only 8.8% among those living with others. In a follow-up study of patients with angiographically documented CAD, Williams et al. [71] observed a 5 year mortality rate of 50% among those who were most socially isolated (unmarried with no confidant) versus only 17% among those not isolated. Given the large sample size, strong effects, and ability to statistically control for known biomedical predictors, these studies provide strong evidence for the important contribution of social isolation to poor outcomes in patients with established CHD.

In a study of 194 elderly post-MI patients, Berkman et al. [72] reported that the presence of emotional support prior to the MI was the most powerful and significant predictor of survival after the MI. At 1 year follow-up, 55% of patients without support had died, compared to only 27% with two or more sources of support. In a detailed analysis of the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study, Lett et al. found that social support buffered the effects of stress; among patients with lower levels of depression, patients who reported high social support had fewer adverse events compared to patients with low social support [73]. In all of these studies, the impact of low social support on prognosis was independent of left ventricular ejection fraction and other biomedical prognostic factors. In a comprehensive review of the literature on social support and CHD, Lett et al. [74] found that low social support was associated with a 1.5- to 2.0-fold increased risk of CHD in both health and cardiac populations and concluded that perceived functional support was a more important predictor of outcomes than structural support.

Low Socioeconomic Status

It has long been known that low socioeconomic status (SES) is a significant contributor to increased CHD risk in healthy persons and to poor prognosis in CHD patients [75]. The Whitehall study was one of the first studies to demonstrate that social gradients were associated with variations in cardiac outcomes. Marmot [76] found that gradients of SES within the British Civil Service were associated with variations in cardiac outcomes and that graded increases in SES were associated with a protective effect on CVD outcomes. Ruberman et al. [77] found low education level to be a potent predictor of mortality, although not independently of social isolation. Williams et al. [71] found that the 5 year mortality rate of CAD patients with incomes less than $10,000/year was 1.9 times higher than that among patients with incomes greater than $40,000/year. This effect was independent of social isolation and disease severity. Case et al. [70] also found SES, as documented by less than a 12th-grade education, to predict increased first recurrent events, independently of social isolation or physical risk factors.

Taken altogether, these findings make a convincing case that low SES does contribute to poor prognosis in established CHD. The evidence suggests that SES has an impact over and above that conveyed by social isolation, but it is plausible that some of the adverse effects of low SES are mediated by its associations with depression and social isolation. Depressive symptoms are inversely related to SES in the general population [78], so that SES may interact with psychosocial risk factors and potentially produce an additive effect.

Job Strain

Certain job characteristics, either by themselves or in combination, also have been implicated as psychosocial risk factors for coronary disease, in particular psychological workload and decision latitude [79]. Job strain, which involves a combination of these two factors, has been the subject of intensive research in recent years. The job strain model characterizes exposure to psychosocial job stressors along the two dimensions of *demand* (psychological workload) and *control* (decision latitude). In a prospective study of CAD risk among Swedish men, Karasek et al. [80] found that high job demands were associated with disease. Low decision latitude on the job, characterized by low intellectual discretion and low personal schedule freedom, was

associated with the development of cardiac symptoms, and the job strain combination of low personal control over schedules and high job demands was associated with a four-fold increase in risk of cardiovascular-related death. These relationships remained significant after controlling for age, education, and overweight. Subsequent research has supported this relationship between the combination of high job demand and low control and increased risk of both CHD [81] and risk factors for CHD including hypertension and increased left ventricular mass [82].

POTENTIAL MECHANISMS LINKING PSYCHOSOCIAL VARIABLES AND CHD

A number of hypotheses have been proposed regarding the mechanisms whereby psychosocial variables may increase the risk for the development of CAD and the occurrence of clinical CHD events. It is widely believed that the relationship between psychosocial variables and CHD is mediated by activity of the sympathetic-adrenomedullary system, as reflected by heightened cardiovascular and neuroendocrine responses to behavioral stimuli including mental stress.

Cardiovascular and Neuroendocrine Reactivity

Exaggerated cardiovascular and neuroendocrine responses to psychosocial stressors have been proposed as one mechanism for promoting the progression of atherosclerosis and onset of clinical CHD events. Animal studies have shown a relationship between enhanced cardiovascular responses and atherosclerosis [83]. In addition, heightened responses to behavioral challenges in humans have been associated with increased cardiac mortality [84] and with the occurrence of myocardial ischemia [60], as well as with risk factors for CHD, including hypertension and dyslipidemia [85,86].

The process by which recurrent activation of the sympathetic nervous system, involving exaggerated heart rate and blood pressure responses to stress, may contribute to atherosclerosis is likely through its contribution to endothelial injury. Among the possible causes of such injury are mechanical forces, such as turbulence and sheer stress. In addition, chronic neuroendocrine hyperreactivity producing increased levels of circulating catecholamines, corticosteroids, and reproductive hormones may promote endothelial dysfunction, as well as other physiological changes. Stress may also affect clotting factors and may acutely promote plaque rupture.

Not all individuals respond to stress in the same way, however, and psychophysiological studies of humans have shown significant variability in cardiovascular and neuroendocrine reactivity to laboratory stressors. Exaggerated responsivity to stress may be considered an individual difference characteristic, and investigators have sought to associate psychosocial variables, including personality traits (e.g., TABP), mood (e.g., anger), and contextual variables (e.g., harassment or competition), that distinguish high and low reactors [87].

Heart Rate Variability

In addition to the contribution of heightened sympathetic and neuroendocrine activity, the antagonism of the parasympathetic nervous system on sympathetic activity also may influence the pathogenesis of CHD. The balance between sympathetic and parasympathetic (vagal) activity can be assessed using the analysis of heart rate variability (HRV), in which decreased variability is an independent risk factor for mortality among CHD patients. Research has shown that laboratory challenges can disrupt the sympathovagal balance, such that sympathetic nervous system activity becomes dominant under stress [88], suggesting that chronic negative arousal may be associated with decreased HRV. Indeed, research has shown decreased HRV to be associated with TABP [89], as well as with anxiety [90] and depression [91]. Alternatively, the mechanism by which such psychological traits or states impact HRV also may be behavioral, e.g., through nonadherence to regimens that affect sympathovagal balance, including regular physical activity and use of cardiac medications.

Myocardial Ischemia

Recent research has examined the relationship between stress and myocardial ischemia. Laboratory studies [60] have shown that EX produces significant increases in heart rate and blood pressure and that the double product, an indicator of myocardial oxygen demand, is significantly elevated. Although mental stress is also associated with increases in blood pressure and heart rate, it generally does not produce as great an increase in heart rate as EX but may be associated with greater diastolic blood pressure responses. The double product associated with mental stress, therefore, is considerably less than the double product associated with EX. This suggests that increased myocardial oxygen demand is not the only determinant of mental stress-induced ischemia and that myocardial oxygen supply also may be restricted during mental stress ischemia.

The possibility that a reduction in myocardial oxygen supply may be at least partially responsible for mental stress ischemia has been investigated in studies of both animals [92] and humans [93]. Such research has indicated differential vasomotor responses in stenosed versus nonstenosed coronary arteries; whereas vasodilation occurs in normal segments of coronary arteries during mental stress, paradoxical vasoconstriction leading to myocardial ischemia occurs in atherosclerotic segments. Although the precise substances responsible for such vasoconstriction have not been identified, it is known that several neurohumoral substances, such as catecholamines, are released during mental stress and may be responsible for abnormal vasoconstriction.

Inflammation and Platelet Function

Inflammatory factors, such as C-reactive protein (CRP), have been shown to play an important role in the pathogenesis and progression of CHD [94]. Higher levels of inflammation,

including interleukin (IL)-6, tumor necrosis factor (TNF) α, and CRP, have been associated with various psychosocial risk factors including lower SES, chronic work stress, caregiver strain, early life adversity, hostility, and social isolation [95]. There is also evidence that depression is associated with elevated levels of inflammation [96]. In an analysis of data from 6914 men and women between the ages of 18 and 39 years from the National Health and Nutrition Examination Survey III, a history of MDD was strongly associated with elevated CRP [94]. In a recent meta-analytic study, Steptoe et al. examined the relationship between acute psychological stress and inflammatory markers [95]. They found that acute psychological stress was associated with increased IL-6, IL-1β, and a trend for an association with higher CRP. Howren et al. [97] examined this relationship by studying the relationship between depression and several inflammatory markers, including CRP, IL-1, and IL-6 and found a dose–response relationship between depression and greater levels of inflammation across both clinical and community samples. In addition, Howren et al. found evidence to suggest that depression may predispose to greater inflammation and that inflammation may increase depressive symptoms.

Increased platelet activation also has been shown to play an important role in the pathogenesis of CHD [98,99]. Although platelet activation has been most closely related to depression [100], recent evidence suggests that other "negative" psychosocial factors, such as anxiety and mental stress, are also associated with higher platelet levels. Zafar et al. [101] found that depressed adults with comorbid anxiety had the highest platelet levels compared with either condition alone. Aschbacher et al. [102] observed elevated platelet activity following acute public speaking tasks that responsivity was stable over time. Increased platelet activity has been associated with higher levels of depression among both healthy populations and individuals with CHD [103]. In addition, severity of depression has been shown to correlate with platelet levels, and reduced depressive symptoms have been shown to be associated with lower platelet levels [104].

INTERVENTIONS TO IMPROVE PSYCHOSOCIAL RISK FACTORS IN CARDIAC PATIENTS

Despite the considerable epidemiological evidence for a stress–CHD relationship, as reviewed earlier, the health benefits of reducing stress in cardiac patients are not well established because of limited data from randomized clinical trials (RCTs) and a lack of hard evidence that improving psychosocial risk factors improves clinical outcomes.

Intervention programs specifically targeting psychosocial factors shown to play a role in CHD have been implemented as part of more comprehensive and longer-term rehabilitation programs, both to improve quality of life during rehabilitation and potentially to reduce cardiac morbidity and mortality.

In one of the earliest psychosocial interventional studies, Adsett and Bruhn [105] observed that coronary patients lacking close family relationships and the support of friends had more difficulty adjusting after an MI. Their study assessed the efficacy of short-term group psychotherapy for six male post-MI patients having trouble adjusting to their situation, with treatment including their spouses. Results showed improved psychosocial adaptation for both patients and their spouses, although there was no control group. Trzcieniecka-Green and Steptoe [106] studied the effects of a 12 week relaxation-based stress management program on a variety of psychosocial variables in 78 patients following MI, CABG, or PTCA. After treatment and at follow-up, subjects showed significant improvements in anxiety, depression, general psychological well-being, activities or daily living, social activity, quality of interactions, and satisfaction with sexual relationships. Because there was no control group, however, conclusive statements about the results are not possible.

There have been a number of RCTs assessing improvements in psychosocial factors in CHD patients. These studies have used a variety of therapeutic techniques, from relaxation training and cognitive-behavioral treatment to group counseling. Stern et al. [107] evaluated the effects of group counseling versus EX therapy in 160 MI patients who exhibited a low functional capacity on treadmill testing, were anxious and/or depressed, or both. Subjects were randomly assigned to 12 weeks of an EX program, group counseling, or a control group. Both active groups showed improvements in psychological functioning as compared to the control group. Subjects who underwent group counseling substantially reduced their level of depression and interpersonal friction and increased their sense of friendliness, independence, and sociability, whereas the control group showed no changes.

Van Dixhoorn et al. [108] evaluated the impact of adding relaxation training to a traditional physical conditioning program in 69 MI patients who were randomly assigned to an EX and relaxation group or an EX-only control group. Patients in the relaxation training group showed significant improvements in well-being, whereas those in the EX-only group did not show psychological improvements. Additionally, patients displaying the TABP showed the greatest improvements resulting from relaxation training. Lewin et al. [109] implemented a home-based psychosocial self-help program for post-MI patients. They found that psychological adjustment, as assessed by the Hospital Anxiety and Depression Scale, was better in the treatment group compared to the control group. Moreover, those in the treatment group had significantly fewer hospital readmissions during the first 6 months, and they had significantly less contact with their doctors over the next year. As in many of these studies, the greatest improvements were seen in those patients who were clinically anxious or depressed at baseline.

A limited number of studies have used "hard" clinical endpoints such as cardiac morbidity and mortality as clinical outcomes. In a controlled trial of brief group psychotherapy for post-MI patients, Rahe et al. [110] randomly assigned 44 patients to either a control condition or a supportive, educational group therapy condition with a modest emphasis on modification of coronary-prone behaviors. All patients

were followed for 3 years. Patients in the treatment condition showed significantly less coronary morbidity, including arrhythmias, mild to moderate congestive HF, and angina pectoris, as well as lower mortality at follow-up compared to control patients, and this was not explained by changes in conventional coronary risk factors. Therapy patients, however, did show changes in certain coronary-prone behaviors. Because educational information presented in the therapy sessions was largely forgotten over follow-up, the authors concluded that it was primarily the general support provided by the therapy that explained the outcome differences.

In the Ischemic Heart Disease (IHD) Life Stress Monitoring program [111,112], 461 post-MI men patients were assigned to either a usual care (UC) condition or an experimental intervention in which a monitor would call once a month and administer Goldberg's General Health Questionnaire (GHQ). Whenever a patient's responses generated a GHQ score of 5 or more, the monitor informed the nurse assigned to that patient, who would then schedule a home visit to work with the patient until the patient's problems were resolved or he or she was able to deal with them alone and the GHQ score had returned to normal. Nurses were instructed to lower the stress levels of their patients using whatever strategies seemed appropriate for each patient. This intervention provided patients with social support, both instrumental in terms of dealing with problems and emotional in terms of providing a caring human being to listen to the patient describe his or her problems.

The monitoring group exhibited reduced mortality relative to the UC group after 4 months. By the end of the first 12 months of follow-up, the monitoring group experienced a 47% reduction in cardiac mortality relative to the UC group. Interestingly, of the patients on beta-blockers, 11% of the controls died compared to only 3% of the treated group, suggesting that stress management might further complement medical therapy. Long-term follow-up revealed that the group with high distress (GHQ $\geq$ 5) assigned to stress monitoring/nurse intervention experienced significant reductions in both recurrent MI and cardiac mortality over 5 years. Whether in UC or monitoring intervention groups, the low-distress group (GHQ < 5) experienced lower mortality than the high-distress group assigned to UC. Thus, it was only in those with high distress that the psychosocial intervention in this study led to improved prognosis.

More recently, Frasure-Smith et al. [113] attempted to replicate their earlier findings in a new sample of 1376 post-MI men and women. Patients completed a baseline interview that included assessment of anxiety and depression. Patients were then randomized to either an intervention condition or to a UC control group. As in the earlier study, patients randomly assigned to the intervention were telephoned 1 week after discharge and then every month for 1 year. If a patient scored 5 or more on the 20-item GHQ scale or he or she was readmitted to the hospital, the research assistant contacted the study nurse who then arranged for an initial 1 h visit at the patient's home or at another convenient location. The intervention had no overall survival impact (the overall odds ratios were 1.44 and 1.41 for cardiac and all-cause mortality, respectively). Moreover, there was a higher cardiac (9.4% vs. 5.0%) and all-cause mortality (10.3% vs. 5.4%) among women in the intervention group. There was no evidence of either benefit or harm among men. However, there was no evidence that the intervention successfully reduced the patients' distress levels. Because the intervention failed to significantly reduce distress, it is not surprising that the intervention had no beneficial impact on clinical outcomes.

In a large-scale study of post-MI patients, the Recurrent Coronary Prevention Project (RCPP) [114] randomized 1035 Type A men and women who had suffered an MI within the past 6 months to cardiologic counseling (n = 270) or to an intervention that included not only cardiac counseling but also a behavioral program designed to reduce their Type A behavior (n = 592). A third group, who refused randomization, formed an additional UC control group. The intervention consisted of weekly group meetings in which cognitive behavior therapy and behavior therapy principles were applied to train patients in skills and strategies to reduce Type A behavior, including both the time urgency and hostility components. Subjects were given "drills" to practice as homework between group meetings, and the results of their efforts were shared with other group members at the meetings. The intervention was successful in reducing both time urgency and hostility, using behavioral observation to assess these components. At 3 year follow-up, statistically significant reductions in Type A behaviors were observed in those assigned to the Type A counseling treatment group. In addition, CHD recurrence rates were significantly lower (7.2%) among the treatment group compared with the control group (13%). This pattern continued at the 4½ year assessment, marking the end of treatment, with 35.1% of treatment-group participants showing a marked reduction in Type A behaviors compared to 9.8% in the control group, and a cardiac recurrence rate of 12.9% in the treatment group versus 21.1% in the control group and 28.2% in the nonrandom comparison group.

Mendes de Leon et al. [115] reported specific behavioral and psychosocial changes that occurred as a result of the Type A treatment program in the RCCP. Patients in the treatment group showed significant reductions not only in global TABP but also in the components of hostility, time urgency, and impatience. Furthermore, they had reduced depression and anger and improvements in self-efficacy, social support, and well-being. As with the initial IHD life Stress Monitoring study, the RCPP enrolled mostly men and too few minority group members to evaluate its impact upon them. Another omission was the absence of any reports of process variables that might be mediators of the treatment benefits.

Ornish et al. [116] assigned 48 patients with angiographically documented CHD to UC (n = 20) or to a comprehensive lifestyle change program (n = 28) incorporating EX, low-fat vegetarian diet, stopping smoking, and stress management training (SMT), with twice-weekly group support meetings. Compared to the UC group, patients in the intervention group were more likely to show regression of angiographically

documented lesions after 1 year in the program. The patients who were most adherent to the overall program showed the most pronounced regression of their coronary stenoses.

Given the comprehensive and extensive nature of the intervention in this study, it is not possible to identify which aspects of the program were responsible for the regression of arterial lesions. Certainly social support was provided by the twice-weekly group meetings and may have played an important part, but in the absence of a controlled design that permits evaluation of the impact of the various components, it is possible to say only that the "package" was responsible for whatever benefits were observed. The observation that those most adherent to the overall program experienced the greatest decrease in arterial stenoses is useful in guiding future trials to assess adherence to the intervention regimen. The Ornish et al. study also obtained consent after patients were informed of their group assignment, so that strict randomization procedures were not followed. Moreover, the sample size was too small to determine if changes in the extent of CAD were associated with reductions in clinical CHD events.

Other clinical studies also have examined the effect of behavioral interventions on morbidity and mortality but lacked adequate power to detect group differences [117,118]. In one of the largest studies to date, Jones and West [119] failed to show significant benefits for the psychosocially treated group. In this large-scale clinical trial conducted in Great Britain, 2328 patients discharged from the hospital within 28 days from a confirmed MI participated in an RCT comparing UC to a comprehensive rehabilitation program comprising psychological therapy, counseling, relaxation training, and SMT over seven weekly group outpatient sessions for patients and their spouses. At 6 months' follow-up, there were no significant differences between rehabilitation patients and controls in reported anxiety and depression. At 12 months there were no differences in clinical complications, clinical sequelae, health service use, return to work, or mortality. It was concluded that rehabilitation programs offered little objective benefit to post-MI patients. However, the short duration of the intervention and the failure to document treatment effectiveness were major limitations of the study. Because the intervention failed to effectively modify those relevant psychosocial risk factors that are thought to affect clinical prognosis, it is not surprising that no effects on clinical outcomes were observed.

Several recent studies have targeted patients at increased risk of CHD events because of high levels of psychosocial stress. One of the largest trials to examine the effects of a psychosocial intervention on mortality and morbidity was the ENRICHD randomized trial [120]. In this study, post-MI patients who were depressed or who had low social support were randomized to receive either UC or a cognitive-behavioral therapy (CBT) intervention. CBT was initiated soon after hospital discharge for up to 6 months of individual CBT. When possible participants were offered group therapy, psychiatrists were encouraged to prescribe medication for participants with Hamilton Rating Scale for Depression scores >24 or with BDI scores with less than a 50% reduction at 5 weeks. After 3 years, results revealed that the special CBT intervention group achieved significant reductions in depression and improvements in social support. However, there were no differences between the special intervention and education controls in event-free survival [121].

Other trials have examined the effects of antidepressant pharmacotherapy on CHD outcomes among individuals with depression. The SADHART trial was a randomized, double-blind, placebo-controlled, 24 week trial of sertraline for MDD among patients hospitalized for acute MI [122]. Results showed improvement in depressive symptoms among participants with more severe depression who were treated with sertraline but not in the overall sample. Although the study was considered a safety and efficacy trial, and was not powered to examine clinical outcomes, clinical data suggested that the sertraline group tended to have fewer adverse events. A second study of HF patients with depression, known as SADHART-CHF, found that sertraline did not reduce depressive symptoms any better than placebo and that patients treated with sertraline had no better clinical outcomes compared to those receiving placebo [123].

The MIND-IT study of antidepressant therapy for MI [124] showed similar results. In this multicenter randomized trial, 320 post-MI patients were randomized to either antidepressant treatment with mirtazapine or placebo, or received treatment as usual. If participants refused or did not respond to initial treatment, citalopram was offered as a second-line intervention. Results showed no differences between intervention and control participants in either depressive symptoms or cardiac outcomes.

Lesperance et al. [125] compared the benefits of antidepressant medication and psychotherapy in the CREATE study. In this randomized 2 × 2 design, cardiac patients with MDD were randomized to receive either citalopram plus clinical management, interpersonal therapy plus clinical management, clinical management only, or placebo plus clinical management for 12 weeks. Results showed that depressive symptoms were reduced more in the citalopram group compared to placebo, whereas there were no differences between the interpersonal therapy and clinical management groups.

The COPES study [126] was a recent RCT in which 237 patients, including 157 persistently depressed patients, were randomized to a special intervention depending on patients' preferences (problem-solving therapy and/or antidepressant medication) or UC. At the end of the trial, 3 intervention patients and 10 UC patients experienced a major adverse cardiac event. While the results were very preliminary, and the study was obviously underpowered for "hard" clinical events, results were encouraging.

Several recent comprehensive reviews have summarized the value of psychosocial interventions in cardiac patients. Linden et al. [127,128] noted that patients who received psychosocial interventions were over 40% less likely to die and

were 65% less likely to have a recurrent coronary event than controls over a 2 year follow-up period. Van Dixhoorn and White [129] also conducted a meta-analytic review on the effects of relaxation therapy in cardiac patients and reported that relaxation therapy was associated with improvement in a wide range of physiological outcomes such as resting heart rate, HRV, EX tolerance, HDL cholesterol, angina, arrhythmias, and EX-induced ischemia. Moreover, subsequent cardiac events and cardiac death were reduced in patients undergoing relaxation training. Notably, relaxation remained superior when EX-based CR programs were directly compared. Finally, Rees et al. [130] aggregated findings from 18 studies in which 5242 patients were randomized. Although there was limited support for the benefits of stress management on total mortality in the 10 trials that reported death as an outcome (OR = 0.9; 95% CI = 0.7–1.2) and on cardiac mortality in four studies (OR = 0.6; 95% CI = 0.4–0.99), there was evidence of a significant reduction in nonfatal MI compared to controls (OR = 0.7; 95% CI = 0.5–0.9) in eight studies. Thus, there is encouraging evidence that stress management is associated with improved health outcomes, although key methodological elements of RCTs (e.g., blinding of assessors and lack of allocation concealment) detracted from the overall quality of the studies. Moreover, the RCTs described earlier focused on "hard" clinical endpoints such as death and MI.

Another approach that has been recently adopted is to study intermediate markers of risk in CHD patients. Examination of changes in intermediate endpoints can provide important insights into the mechanisms and potential value of psychosocial interventions and has a number of important advantages over "hard endpoints" in that (1) fewer patients are required to detect treatment effects; (2) changes in cardiac risk can be reliably and objectively measured over short follow-up intervals; and (3) these studies can be performed relatively inexpensively at a single site. Blumenthal et al. [131] at Duke University Medical Center conducted a study of patients with mental stress-induced myocardial ischemia in which CHD patients were randomly assigned to EX or SMT; a third group of participants who lived too far from Duke to participate in the trial served as a control group. Results revealed that patients who underwent 16 weeks of SMT exhibited a relative risk of further cardiac events of only 0.26 compared to UC controls. Although the Duke study was not fully randomized, the findings demonstrated that stress management was effective in reducing stress-induced ischemia and ambulatory ischemia. Moreover, the 74% reduction in clinical events including MI, death, and revascularization procedures because of progressive angina was highly significant. EX training also was associated with a 32% reduction in risk for cardiac events, although this reduction did not achieve statistical significance. Moreover, a follow-up of study participants revealed that the benefits of stress management were maintained over time, with participants who received SMT experiencing fewer cardiac events and having less medical expenditures compared to UC or EX over 5 years of follow-up [132].

In an attempt to address the methodological shortcoming of their initial study, a subsequent, fully randomized trial of 134 patients with stable CHD examined the impact of SMT on biomarkers of CHD [133]. Patients were fully randomized to SMT, EX, or UC. Patients in both active treatment groups exhibited reductions in depression (and distress compared to UC controls) and exhibited smaller reductions in left ventricular ejection fraction during mental stress testing. In addition, there was a reduction in ischemia following SMT in the subset of patients who presented with significant ischemia at baseline, and patients in both active treatment groups exhibited greater improvements in a variety of cardiovascular "biomarkers" including flow mediated dilation (FMD) and baroreflex sensitivity (BRS). Interestingly, SMT patients also exhibited greater improvements in HRV compared to exercisers and UC controls, suggesting the potential added value of combining SMT with EX training in CHD patients.

The intervention trials reviewed earlier have several features in common. All included some aspects—whether regular group meetings or nurse home visits—that *directly* provided patients with added social support, over and above whatever support systems they had access to on their own. This suggests that providing social support has considerable promise as an intervention that will improve prognosis in patients with established CHD. The Ornish et al. study [117], the RCPP [115], and the Duke studies [131–133] also included instruction in what can be broadly characterized as stress management techniques—relaxation skills, cognitive strategies to decrease anger and hurrying, communication and assertion skills, time management, and the like. In addition to whatever direct benefits these components of the intervention provided (e.g., decreased sympathetic activation caused by relaxation and anger management), they also have the potential to increase social support *indirectly* (i.e., if one is not hostile toward one's family and friends, they may be more likely to provide social support).

CONCLUSIONS

Psychosocial factors play an important role in the development and clinical manifestations of CHD and contribute to adjustment and quality of life in a variety of cardiac populations including post-MI, cardiac surgery, stable and unstable angina, and HF. Despite the strong epidemiologic evidence for stress as a risk factor for patients with CHD, evidence that reducing stress improves prognosis is limited [134]. Future research is needed to determine the value of stress reduction in improving clinical outcomes and to identify individuals who could potentially benefit most from such interventions. For example, the NIH-sponsored ENHANCED study is currently under way to determine the added value of stress management when included in a traditional EX-based cardiac rehabilitation program [135]. Additional multicenter trials are needed to evaluate the impact of stress reduction on clinical outcomes.

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85 Evaluation and Treatment of the Patient with Peripheral Arterial Disease

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CONTENTS

Peripheral Arterial Disease 1067
Evaluation of Claudication 1067
Diagnosing Peripheral Arterial Disease 1068
Test Modalities 1068
Evaluation of Functional Status 1068
Assessing Cardiac Status in the PAD Patient 1068
Cardiovascular Risk 1068
Walking Capacity 1068
Cardiovascular Disease Risk Factors 1069
Skin and Foot Assessment 1069
Exercise Training 1069
Evidence Base for Exercise Training 1069
Mechanisms for an Exercise Training Effect in Claudication 1070
Exercise Prescription 1070
Alternative Modes of Exercise 1071
Postrevascularization Considerations 1071
Program Considerations 1071
References 1072

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease (PAD) results from systemic atherosclerosis. The disease process that affects the blood vessels is the same for patients with coronary artery disease (CAD) and stroke, and the risk factors for these atherosclerotic conditions are essentially the same. Among cardiovascular disease risk factors, diabetes is perhaps the strongest risk factor for PAD. The clinical presentation of PAD varies widely. Some individuals with PAD may be asymptomatic or experience exertional leg discomfort. Some present with the classic symptom of intermittent claudication (IC), which is characterized as leg pain during walking. IC limits exercise tolerance and presents a unique challenge to care providers in that it will require modification to the rehabilitative process and exercise prescription that is typically used for many other health conditions. This chapter will be primarily focused on individuals with IC.

EVALUATION OF CLAUDICATION

Because leg discomfort is a common complaint, particularly among older patients, it is important to recognize the characteristics of claudication that differentiate it from other causes of leg pain. IC is pain or profound fatigue in a muscle brought on by exertion and relieved by a few minutes of rest. Most commonly, a patient with PAD will develop pain in the calf, thigh, or buttocks that is worsened by walking. The pain subsides after a variable period of rest and the patient may resume walking, often for the same distance. The distance to onset of claudication depends on the severity of the disease. Claudication pain is consistent and reproducible and should not be confused with severe sudden onset pain due to an acute occlusion or thrombosis of an artery in the lower extremity. An acute occlusion of an artery will more likely result in pain that is severe and constant, even at rest, and associated with other signs of obstructed blood flow such as a cold, pale, or bluish extremity and the absence of pulses below the area of obstruction. Patients with PAD may have some of these same signs, but they will occur progressively as the disease worsens over time.

Claudication should also be differentiated from leg aches and pains such as arthritis and chronic venous insufficiency. Arthritis causes pain in the joints, may vary from day to day or with changes in the weather, and may occur with or without activity. Chronic venous insufficiency in the lower extremities results in blood pooling in the extremities and is associated with leg or ankle edema. The symptom is aggravated

by standing or sitting for long periods. It is described as an ache or full sensation in the legs that becomes progressively worse during the day and is relieved by resting with the legs elevated.

Specific findings on physical assessment help confirm the diagnosis of PAD and claudication. Peripheral pulses are diminished or absent by palpation. Color changes include pallor of the extremity, especially if elevated above heart level, or dependent rubor, a bright reddish color occurring in the affected limb when it is placed in a dangling (dependent) position. Diminished blood flow results in a cooler extremity when compared to the unaffected leg. Mild to moderate claudication is not a limb-threatening condition. The goal of treatment is the relief of symptoms with exercise training and risk-factor modification.

When PAD becomes severe, it is referred to as critical limb ischemia, and patients may develop rest pain. The patient experiences this symptom as a burning pain in the toes, and it occurs most often when the patient is in bed or has the affected limb elevated. Patients may get some relief by hanging the foot over the side of the bed or by sitting up in a chair. Even narcotics provide only minimal relief. Ischemic pain may progress to paresthesia and paralysis of the toes and foot. Rest pain is a limb-threatening symptom and must be referred immediately for further evaluation and revascularization.

DIAGNOSING PERIPHERAL ARTERIAL DISEASE

Test Modalities

Lower extremity PAD can be diagnosed using the ankle brachial index (ABI), which is a ratio of systolic blood pressure measured in the ankle and brachial arteries. The ABI is measured using blood pressure cuffs and a pencil-size Doppler probe. A stethoscope is not used because the structure of the foot makes it difficult to place the head of the scope on a flat area to detect the pulse. Normal ABI values are between 0.91 and 1.30, mild impairment from 0.70 to 0.89, moderate impairment from 0.40 to 0.69, and severe impairment $\leq$0.40. This procedure is easy to perform and can be followed by other testing such as Doppler and duplex ultrasound imaging, computed tomographic angiography, magnetic resonance angiography, or angiography if additional testing is needed prior to intervention or treatment.

Postexercise ABIs, measured immediately after walking on the treadmill, can also be used to confirm the diagnosis. A common initial procedure after the diagnosis is established by the ABI in noninvasive Doppler arterial testing of the lower extremities. A complete study begins with segmental systolic arterial pressures. These are obtained using BP cuffs placed in four locations: the upper thigh, above the knee, below the knee, and at the ankle. A Doppler ultrasound stethoscope is used to measure systolic pressures at each level. Generally, these pressures should be equal to, or slightly higher than, the brachial systolic pressure. Leg pressures that are lower than brachial pressures by 20 mmHg or more indicate arterial insufficiency.

Evaluation of Functional Status

The evaluation of the PAD patient includes an assessment of the impact of claudication on activities of daily living. Improving the functional capacity of the patient is an essential goal of exercise training for PAD. An initial assessment of functional disability can then be used to measure progress during treatment. Disease-specific questionnaires, such as the Walking Impairment Questionnaire and the PAD Physical Activity Recall Questionnaire, are useful in documenting the functional status of patients before and after participation in an exercise program [1].

ASSESSING CARDIAC STATUS IN THE PAD PATIENT

Cardiovascular Risk

The risk of CVD is markedly increased in patients with PAD [2]. More than 95% of persons with PAD have one or more CVD risk factors [1]. Because claudication limits physical activity, many patients may not experience any cardiac symptoms. Before beginning any exercise program, these patients should undergo appropriate cardiac stress evaluation. A bicycle rather than a treadmill test may permit increased myocardial work before leg symptoms occur and therefore allow more accurate assessment of cardiac risk. Though pharmacological stress testing with cardiac imaging may be considered for the patient with claudication, an exercise study is preferred before starting an exercise program.

Walking Capacity

Once cardiac risk status has been determined, as per ACC/AHA guidelines, standardized treadmill testing should ideally be performed prior to initiating exercise training to establish the magnitude of the functional limitation due to claudication and to provide a baseline to measure the response to therapy [3]. Exercise testing may also reveal nonvascular factors contributing to the impaired walking ability such as degenerative joint disease and assist in individualizing the exercise prescription. Continuous ECG monitoring is useful, particularly given the high prevalence of concomitant CVD. A treadmill test can be used to determine the extent of claudication and to evaluate the effectiveness of subsequent treatment. The two graded protocols are widely used with claudication patients. The same speed, 2 mph, is used in both protocols. The Gardner–Skinner protocol increases the grade by 2% every 2 min [4]. The Hiatt protocol increases the grade by 3.5% every 3 min [5]. Both protocols have been proven effective and accurate in evaluating the onset of claudication and the maximum walking distance.

During the test, the patient is asked to walk on a treadmill until the claudication forces the test to be terminated. Data including the time of onset of claudication symptoms and the maximum walking time should be recorded. Immediately after stopping, ankle pressures are also recorded again. In the absence of PAD, ankle pressures will not decrease with exercise. A postexercise drop in ankle systolic pressure confirms the diagnosis of arterial disease. Subsequent ankle pressures are recorded at 1 min intervals for 10 min or until the return to baseline levels. In addition to estimating the location and severity of the disease, this testing provides baseline information for subsequent progress evaluations. Follow-up testing should be performed upon completion of an exercise training program and should include a resting ABI calculation, a treadmill walk at the same settings as the baseline evaluation, and postexercise ankle pressures with recovery time. Though the ABI may actually change very little in response to exercise training, improvement is noted by a delayed onset of claudication, increased maximum walking distance, and shorter recovery time of ankle pressures.

If formal exercise testing is not performed, a 6 min walk test may be used as an alternative to treadmill testing [3].

Cardiovascular Disease Risk Factors

As stated earlier, the same risk factors that contribute to CVD are also associated with PAD and should be treated aggressively. Overall, smoking is the most significant controllable risk factor for PAD. Aside from its contribution to the development and progression of atherosclerosis, cigarette smoking increases claudication pain severity, reduces peripheral circulation, and negatively affects cardiac and pulmonary responses to exercise [6], thereby further reducing exercise capacity. The benefits derived from participation in an exercise program will be attenuated if patients, particularly those who have undergone revascularization procedures, continue to smoke.

SKIN AND FOOT ASSESSMENT

Limited blood flow to the extremities contributes to poor skin perfusion, making skin more fragile and susceptible to injury and infection. Many patients with PAD also have diabetes and suffer from neuropathy, which decreases their ability to feel pain or irritations to the feet until damage is severe. Patients with PAD should be encouraged to see a podiatrist for evaluation to assure that proper shoes are used. When the skin is broken, and thus susceptible to infection, the arterial system is unable to meet the increased demands needed for healing. If healing is not progressing adequately, a referral for specialized wound care treatment or revascularization may be required. In more severe cases, if infections cannot be controlled, amputation may be required. If ulcers are present on the extremity, boots or casts that keep pressure off of the ulcer or alterations in the exercise regimen such arm exercise will be required until the ulcers are healed.

EXERCISE TRAINING

Evidence Base for Exercise Training

Supervised exercise training is considered a primary treatment for many individuals with PAD and IC. The American College of Cardiology/American Heart Association clinical practice guideline for treatment of PAD rated exercise therapy for IC as a Class I, level of evidence A, recommendation, which compares very favorably to similar or lower levels of recommendation for medications or revascularization procedures [7].

Because of the evidence-based efficacy of exercise training, the American College of Cardiology and American Heart Association Task Force on Performance Measures in 2010 recommended that health care providers either refer a patient to a program or discuss exercise training as a treatment option for appropriate patients with PAD [8].

A meta-analysis of both nonrandomized and randomized studies reported a 179% increase in pain-free walking distance and a 122% increase in maximum walking distance [9]. A Cochrane review of 22 randomized controlled trials for claudication reported an overall improvement in walking ability of approximately 50%–200% [10].

Most patients experience a near doubling of their pain-free and maximum walking distances with exercise training, with the most consistent results occurring in supervised programs versus home-based training. Another Cochrane review found a significant improvement in maximum treadmill walking distance in supervised compared to unsupervised programs, with a difference of approximately 150 m [11].

Only a few studies have compared exercise training to lower extremity revascularization for claudication. A prospective randomized trial compared supervised exercise to angioplasty and found that mean maximum walking distances progressively increased in the exercise group at 6, 9, and 12 months but did not increase in the angioplasty group despite an increase in ABIs with angioplasty [12]. In a follow-up at a median of 70 months, the functional outcome was the same between the exercise and angioplasty groups [13]. Among patients randomized to angioplasty or medical treatment [14] at 2 years, there were no group differences in treadmill walking distances or quality of life; the medical group was given “advice” to walk on their own but did not participate in a supervised program.

A randomized trial of 151 patients with claudication received either angioplasty with conditional stenting or 24 weeks of twice-weekly 30 min supervised exercise sessions [15]. Though revascularization provided more immediate clinical success, after 6 and 12 months, the treatment groups were equivalent for functional capacity and quality-of-life scores. The CLEVER (Claudication versus Endoluminal Revascularization) trial is an ongoing NIH/NHLBI-funded multicenter randomized clinical trial [16]. The treatment

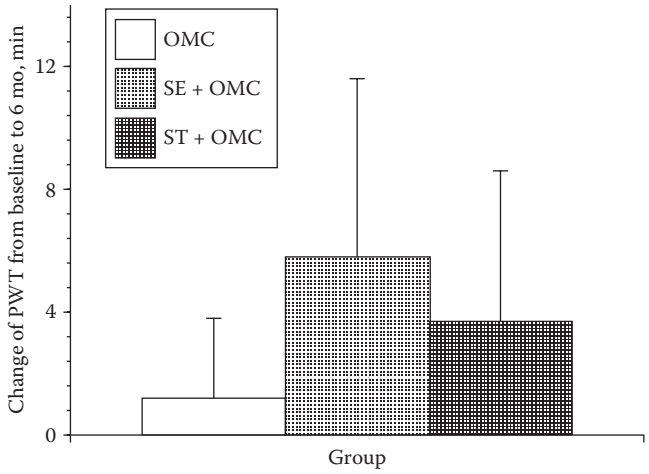


FIGURE 85.1 CLEVER 6 month change in peak walking time in superior treadmill walking performance compared with stent placement and medical care only, even for those with aortoiliac PAD.

arms are as follows: (1) medical care (claudication pharmacotherapy), (2) primary stent placement plus medical care, and (3) supervised exercise rehabilitation plus medical. The outcomes will be evaluated at 6 and 18 months [16]. The 6 month outcomes were recently reported [17], and as shown in Figure 85.1, supervised exercise resulted in superior treadmill walking compared with the stent and medical-care-only groups. Conversely, secondary measures of treatment efficacy favored primary stenting, with greater improvements in self-reported physical function. At the very least, these 6 month results suggest that supervised exercise is a reasonable option for patients compared with stenting and that efforts should be made to encourage exercise and to develop supervised programs that are available and affordable.

Disease-specific quality-of-life measures also improved with both exercise and stenting compared to medical care, with a trend toward greater improvements in self-reported physical function in the stent group. Nevertheless, the CLEVER 6 month results suggest that supervised exercise is a reasonable strategy compared with stenting and that efforts should be made to develop supervised exercise programs that are more readily available and affordable to patients.

Mechanisms for an Exercise Training Effect in Claudication

The specific mechanisms to explain why exercise reduces claudication symptoms is not known but is likely multifactorial. Initial theories proposed that exercise increases collateral vessels via angiogenesis or leads to increased blood flow, but subsequent data on these hypotheses are inconsistent [18–20]. Probable mechanisms for the benefit of exercise training include metabolic adaptations with improved oxygen extraction by the muscle, better walking efficiency from a biomechanical standpoint, and enhanced endothelial function [19–21]. Calf skeletal muscle may increase its oxidative capacity; improvements in exercise have correlated with changes in carnitine metabolism [18].

In addition, the benefits of exercise may not be fully explained by local effects on the lower extremities, as evidenced by a randomized trial in which patients with PAD were assigned to either upper-limb aerobic exercise, lower-limb aerobic exercise, or no exercise for 24 weeks [22]. Similar gains in claudication distance and maximum walking distance were seen in both exercise groups but not among controls, suggesting a systemic benefit of exercise. Furthermore, an increase in exercise pain tolerance was also observed in the exercise groups. A more recent study [23] randomized 41 patients with claudication to 12 weeks of 3 h/week of supervised training using arm ergometry, treadmill walking, or a combination, versus control. The results showed that arm exercise training improved walking capacity compared to controls, and improvement was not different from that seen in response to treadmill walking. Of interest, the combination of arm and treadmill exercise had similar improvements to either modality alone. These data also support a systemic benefit of exercise. Confirmation of these studies in larger studies is needed to provide support for the novel approach of arm exercise as a therapeutic option for PAD patients whose disease severity and claudication limit their ability to perform walking exercise, or who have an aversion to exercise-induced ischemic leg pain that occurs during treadmill exercise training.

Exercise may also attenuate inflammatory responses over the long term and has well-established beneficial effects on cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and obesity [19,20,24]. A 2009 nonrandomized trial from Japan showed that completion of a 12 week supervised exercise training program reduced both CV morbidity and mortality in patients with PAD [25] though the long-term impact of exercise on these outcomes in PAD patients needs further investigation.

Exercise Prescription

Based on current guidelines, for patients with PAD, supervised exercise is performed three times per week, generally in a cardiovascular rehabilitation or wellness program setting, usually for 12–24 weeks, for 1 h per session. The 60 min exercise session includes a 5 min warm-up and 5 min cooldown period. The initial exercise training intensity is established using a graded treadmill test or a functional evaluation during the initial exercise session and is defined as the treadmill grade (% inclination) that brings on the onset of claudication pain, with the initial speed set at 2.0 mph. The initial pain target should be set at level 2 of 5 on the claudication pain scale (Table 85.1). Some patients may not be able to walk at 2 mph and may need to start at a slower speed and progress as tolerated. Participants are asked to walk to a mild to moderate pain level (3–4 of on a scale of 5), stop and sit down and rest until the claudication pain has completely resolved, and then resume walking.

TABLE 85.1
Claudication Pain Scale

No pain	1
Onset of pain	2
Mild pain	3
Moderate pain	4
Severe pain	5

The initial goal of the early training sessions is to have the participants accumulate 15 min or more of total treadmill time, excluding warm-up and cooldown, with the eventual goal to progress the participant to a cumulative exercise session of 50 min of exercise including warm-up and cooldown periods of 5 min.

Participants walk at a constant work-speed throughout each session without change. The use of the claudication pain scale is an important tool for monitoring symptomatic improvements in exercise performance and resulting increases in exercise intensity. If the participant is able to walk at a workload for 8 min or more before experiencing moderate claudication pain (3–4/5), then the grade is increased by a 1%–2% increment for the following training session. Once a participant is able to walk at a 10% grade for 8 min or more, the speed is increased by 0.1–0.2 mph increments for the following session, up to 3.0 mph. If a participant is able to walk for 8 min or more at 3.0 mph/10% grade, the grade is once more increased by 1%–2% increments for the following training session up to 15% grade (i.e., last increase is 1% increment). This is followed by increases in speed by 0.1–0.2 mph increments for the following training session as tolerated.

It should be noted that in contrast to guidelines for people with coronary disease who experience angina, where cessation of exercise is recommended when pain occurs, patients with PAD should walk to the point of experiencing mild to moderate pain though severe pain should be avoided. Ischemic chest pain is not safe due to the risk of ischemic-induced cardiac arrhythmias whereas this is obviously not a concern when experiencing mild to moderate leg pain. For the IC patient, this level of pain serves as stimulus for the physiological adaptive responses that produces a beneficial training effect [19,20,26]. Table 85.2 shows several other key features of exercise rehabilitation for PAD versus CAD.

TABLE 85.2
PAD versus CAD Exercise Rehabilitation

PAD	CAD
Patients with PAD often remain at the same level of walking impairment for several years	There is often spontaneous recovery after a major cardiac event
Because symptoms remain stable, exercise goals are to relieve symptoms, improve functional capacity, and increase walking ability	Phase II (early) cardiac rehabilitation is more focused on recovery from an acute event and preventing deconditioning
Patients walk to leg pain to stimulate adaptive processes that lead to a training effect	Chest pain during exercise is a contraindication requiring the patient to slow down or stop, or use nitroglycerin

Alternative Modes of Exercise

Treadmill walking is the cornerstone of rehabilitation exercise for patients with IC. There is some evidence that other modalities of aerobic training may also be beneficial in improving symptoms. These modes of exercise may be useful if the patient cannot or will not tolerate walking. Additionally, because these exercises largely avoid leg pain, they may be useful to achieve higher exercise intensity in the presence of IC that markedly limits exercise capacity. These include pole striding [27], pain-free treadmill walking [28], and arm exercise [22,23,29,30]. However, the studies are relatively few and need further study with larger samples to warrant changes in PAD exercise rehabilitation guidelines. Though resistance training has been shown to provide some benefits in terms of functional capacity, the existing data are too limited to support a recommendation that resistance training be considered a primary mode of exercise rehabilitation for reducing claudication symptoms [21]. Thus, as tolerated, resistance training can be done as supplement but not as a substitute for walking minutes each for a total of 60 min per session.

POSTREVASCULARIZATION CONSIDERATIONS

The length of time after surgery until rehabilitation may begin will depend on the procedure and the overall condition of the patient. Generally, patients who have a minimally invasive procedure, such as peripheral angioplasty, will be ready for a rehabilitation program relatively quickly, within a week or 2. Conversely, abdominal aortic surgery carries a much longer recovery period (generally 6–8 weeks). Lower extremity bypass procedure patients may recover more quickly but are limited more by groin and knee incision soreness. Any graft placement that crosses the knee joint requires the avoidance of any prolonged, sharp flexion of the knee joint, which could cause a kink in the graft. The use of a cycle is usually permissible with proper seat height adjustment, but such patients should probably avoid rowing machines.

PROGRAM CONSIDERATIONS

In spite of the numerous studies demonstrating the efficacy of exercise training, several barriers prevent its widespread use. Most notably, supervised exercise rehabilitation is not generally a covered benefit under most health insurance plans including Centers for Medicare and Medicaid Services (CMS), though PAD rehabilitation has had a Current Procedural Terminology code (CPT 93668) since 2001. Of note, the lack of insurance coverage is not due to a lack of efficacy of the rehabilitation but because the exercise workout sessions are typically supervised by exercise physiologists or

nurses, who are not recognized providers by Medicare and other insurance carriers. Though these health care professionals may work directly under the supervision of a physician, Medicare has decided that there is not a sufficient amount of physician work involved to warrant payment. Other barriers to participation include a time commitment and lack of broad availability of PAD exercise rehabilitation centers.

Barriers also exist at the provider level as many clinicians hesitate to refer a high-risk patient with multiple comorbidities to an exercise program. However, that same patient may in fact derive the greatest benefit from exercise. Due to the systemic nature of PAD and the high prevalence of CVD in this population, in many cases, patients with PAD may qualify for cardiac rehabilitation by meeting one of the qualifying criteria for cardiac rehabilitation such as recent myocardial infarction, coronary revascularization, or angina [31]. The decision to refer a patient with PAD to an exercise training program should be individualized and may be affected by medical comorbidities that limit walking ability such as pulmonary or degenerative joint disease. Treadmill exercise is not recommended in patients with foot ulcers or critical limb ischemia.

To address some of the barriers to participation, there have been recent efforts for the development of dedicated exercise rehabilitation programs for PAD and the incorporation of PAD care within existing CR programs to accommodate the patient with both cardiac disease and PAD [32]. In 2010, the American Association of Cardiovascular and Pulmonary Rehabilitation in conjunction with the Vascular Disease Foundation published the P.A.D. Exercise Training Toolkit, A Guide for Health Care Professionals. This toolkit was developed to allow cardiovascular rehabilitation and other health care professionals to work within their communities to improve access to supervised exercise programs for people with IC. The toolkit includes information to implement appropriate and safe supervised exercise programs. It also includes practical tools such as sample brochures plus participant and staff education materials. This toolkit can be found at www.aacvpr.org or www.vdf.org. The toolkit is published in an electronic format (PDF) and will be updated regularly to incorporate the last clinical and scientific updates.

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86 Impact of Medical Therapy on Cardiovascular Secondary Prevention

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CONTENTS

Introduction ... 1076
Pathophysiology of Acute Coronary Syndromes ... 1077
Antiplatelet Agents ... 1077
Aspirin ... 1077
Background ... 1077
Pharmacology ... 1077
Indications for CVD ... 1077
Safety ... 1077
Summary ... 1078
Thienopyridines ... 1078
Background ... 1078
Pharmacology ... 1078
Indication in CVD ... 1078
Non-Thienopyridine P2Y12 Receptor Antagonists (Ticagrelor) ... 1080
Pharmacology ... 1080
Indications in Coronary Artery Disease and ACS ... 1080
Summary ... 1080
Lipid-Lowering Therapy ... 1080
HMG-CoA Reductase Inhibitors (Statins) ... 1080
Background ... 1080
Pharmacology ... 1080
Indications for Secondary Prevention of Coronary Artery Disease ... 1081
Summary ... 1085
Omega-3 PUFA ... 1085
Pharmacology ... 1085
Indications in Optimizing Lipid Profile ... 1085
Indications in CVD ... 1085
Summary ... 1086
Niacin ... 1086
Background ... 1086
Pharmacology ... 1086
Indications in CVD ... 1086
Summary ... 1087
Fibrates ... 1087
Background ... 1087
Pharmacology ... 1087
Indications in CVD ... 1088
Summary ... 1088
β-Blockers ... 1088
Background ... 1088
Pharmacology ... 1088
Indications for Coronary Artery Disease ... 1089

Angiotensin-Converting Enzyme Inhibitors 1091
Background and Pharmacology 1091
Indications for Secondary Prevention of Coronary Artery Disease 1091
Ineffective Therapies 1093
B Vitamins 1093
Antioxidants 1093
Estrogens 1093
Conclusion 1093
References 1094

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in both men and women in the United States. According to the most recent Center For Disease Control and Prevention's National Vital Statistics Report, every year approximately 785,000 Americans experience their first myocardial infarct while 470,000 Americans who have already had their first cardiac event will suffer another episode.[1,2] The economic burden and predicted costs of CVD continue to increase with estimates of $444 billion in 2009 to greater than $500 billion in 2010.[2] However, recent trends show an overall decline in death due to CVD (between 1997 and 2007, death due to CVD among men and women ≥65 years of age decreased by 52% in men and 49% in women). This improvement in mortality, while at a significant cost, is due to both aggressive acute reperfusion strategies and intervention for primary and secondary prevention.

Patients who present with acute coronary syndromes (ACSs) face significant CVD risks (including death, heart failure, arrhythmia, stroke, or recurrent ACS) after hospital discharge. According to the Global Registry of Acute Coronary Events (GRACE) study, conducted between 1999 and 2002, those that experienced ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina had 4.8%, 6.2%, and 3.6% ($p < 0.001$) risk of death, respectively, from discharge to 6 month follow-up, while up to 25% experienced a recurrent CVD event.[3] In this large multinational registry, an increase in 6 month post-discharge mortality was predicted by multiple factors[4] including age, history of heart failure, positive cardiac markers, elevated heart rate, systolic blood pressure, and ST depression at initial presentation. In addition, elevated serum creatinine and need for percutaneous intervention (PCI) during hospitalization were also risk factors for post-discharge mortality. Patients who presented with ACS continued to have an increased risk of mortality in subsequent years after initial ACS event with 14.8% dying at 1 year and 39.2% at 4 years.[5] Furthermore, those that presented with recurrent myocardial infarction (MI) experienced even higher rates of mortality or major CVD event at 1 year.[6] In addition, at age 40 or older, 5 year mortality for patients who have experienced an MI is 33% for men and 43% for women.[2]

Goals for secondary prevention include prevention of death, recurrent MI, revascularization, left-ventricular (LV) dysfunction, and anginal symptoms. The American Heart Association (AHA) and the American College of Cardiology (ACC) have recommended strategies for secondary prevention that target principles of lifestyle and behavior modifications, control of comorbid conditions, appropriate vaccinations, and evidence-based pharmacotherapy.[7] Over the last two decades, significant advances in lipid management, prevention of heart failure, myocardial remodeling, and sudden cardiac death (SCD) have significantly reduced mortality in patients following a CVD event. Blood pressure control, increase in physical activity, weight management, and smoking cessation are also important in secondary prevention.

Despite strong evidence and availability of reasonably priced pharmacologic intervention in secondary prevention, underprescribing and suboptimal adherence continue to be problematic.[8] In a study investigating long-term adherence of the use of medications for secondary prevention, only 71%, 46%, and 43% of patients consistently took aspirin, β-blockers, and lipid-lowering therapy, respectively, and only 21% of patients took the combination of the three drugs.[9] To bridge the gap between evidence-based practice guidelines and physician and patient behavior, the AHA along with other organizations initiated a campaign to address barriers to adherence.[10] Many hospitals have since emphasized quality control measures and guideline adherence in patients admitted for ACS and heart failure. In addition to the public health benefit of implementing such guidelines, economic benefits are also evident. The 2011 Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial found that enhanced prescription coverage improved medication adherence by 4%–6% compared to usual prescription coverage ($p < 0.001$) and decreased rates of first major vascular events (11.0 vs. 12.8; HR, 0.86; 95% CI, 0.74–0.99; $p = 0.03$).[11] Furthermore, enhanced prescription coverage decreased patient spending without increasing overall health care costs (relative spending, 0.74; 95% CI, 0.68–0.80; $p < 0.001$).

This chapter will focus on the impact of medical therapy on cardiovascular secondary prevention and corresponding supportive evidence. Antiplatelet and lipid therapies are highlighted. Appropriate use of β-blockers and angiotensin-converting enzyme (ACE) inhibitors are emphasized. Specific pharmacology and clinical indications are reviewed. Lastly, ineffective therapies are briefly covered.

PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

ACS is composed of three clinical syndromes:

1. *Unstable angina*: Angina or an angina-equivalent lasting more than 30 min with no evidence of myocardial injury, onset of new angina, or change in stable angina pattern.
2. *NSTEMI*: Prolonged symptoms with no ST-segment elevation on an electrocardiogram in the setting of positive cardiac biomarkers.
3. *STEMI*: Prolonged symptoms with ST elevation ≥1 mm in two contiguous leads (≥2 mm in V_1–V_3 leads), or new left bundle branch block in the setting of positive cardiac biomarkers.

The majority of acute coronary events occur when the surface of an atherosclerotic plaque erodes or ruptures. The process leading up to plaque erosion or rupture begins years earlier with hypertension, hyperlipidemia, tobacco-related toxins, advanced glycosylated end-products, and inflammatory cytokines, all potential factors resulting in endothelial injury. Endothelial injury then permits atherosclerotic plaque formation due to subendothelial low-density lipoprotein accumulation, oxidation, and inflammatory cell accumulation. Atherosclerotic plaques that are vulnerable to rupture or erosion usually have thin fibrous caps and have a higher percentage of inflammatory cells such as monocytes, macrophages, and T-lymphocytes. Plaques that are prone to rupture also usually have a large lipid-rich necrotic core and are found more often in males. Plaques that are prone to erosion often have a missing endothelial cap lining, have less calcification and inflammation, and are more common in women.[12] Rupture or erosion of the fibrous cap then exposes subendothelial contents to the blood, causing a cascade that leads to platelet adherence, aggregation, fibrin deposition, and thrombus formation, with the potential for coronary artery luminal obstruction, resulting in myocardial ischemia or obstruction.

Secondary prevention emphasizes clinical risk stratification, atherothrombosis prevention, plaque stabilization with the potential for reversal, arrhythmia prevention, myocardial oxygen demand reduction, and prevention of adverse myocardial remodeling.

ANTIPLATELET AGENTS

Aspirin

Background

Coronary atherothrombosis occurs when a plaque is disrupted and circulating platelets are exposed to, and activated by, subendothelial plaque contents. Platelet activation then results in an intracellular process that releases thromboxane A_2, serotonin, and adenosine diphosphate (ADP),[13] which induces more platelet activation, aggregation, and thrombosis formation. By stimulating coronary atherothrombosis, platelets play a major role in the development of recurrent ACS. Therefore, preventing platelet activation and aggregation has been a mainstay in secondary CVD prevention, with several pathways in the activation cascade serving as targets.

Pharmacology

Aspirin (acetylsalicylic acid) was first isolated from the bark of the willow tree and has been used for many centuries for its analgesic, anti-inflammatory, and antipyretic effects. It was not until the latter half of the twentieth century that its anti-inflammatory and antiplatelet effects in coronary artery disease (CAD) were discovered. Aspirin works by irreversibly inhibiting cyclooxygenase-1 (COX-1), preventing thromboxane A_2 formation, and thereby reducing platelet activation and aggregation.

Indications for CVD

Aspirin has been shown to decrease CVD events and mortality in those with known CVD. In a randomized trial comparing aspirin to placebo, the administration of 324 mg of aspirin to 1266 men with unstable angina within 48 h of hospital admission reduced rates of death and MI by 51%.[13] A trial conducted in Canada in 555 men and women with unstable angina showed that treatment with 325 mg of aspirin four times daily markedly decreased cardiac death and nonfatal MI over a 2 year follow-up.[14] Another landmark trial comparing aspirin, heparin, or both in patients admitted with unstable angina showed that the use of 325 mg of aspirin twice daily significantly reduced the rate of fatal and nonfatal MI.[15] With increasing evidence in support of the use of aspirin for secondary CVD prevention, a meta-analysis of 16 randomized controlled trials in patients with previous MI, stroke, or transient ischemic attack comparing aspirin to placebo showed an 18% relative risk reduction (RRR) in both serious vascular events* ($p < 0.0001$) and coronary events† ($p < 0.0001$).[16]

Safety

In addition to inhibiting COX-1 intravascularly, aspirin also inhibits COX-1 production of gastric mucosal prostaglandins, increasing the risk of major gastrointestinal bleeding.[17] In a post hoc analysis of the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial, patients undergoing PCI taking low (≤100 mg), moderate (101–199 mg), and high (≥200 mg) doses of aspirin were followed and risk of major bleeding was evaluated.[18] Comparing the three dose categories, there were no differences in rates of CVD death, MI, or stroke. Risk of bleeding, however, was positively correlated with increasing doses of aspirin (1.9%, 2.8%, and 3.7%, respectively, $p = 0.0001$).[18] In the Clopidogrel and Aspirin Optimal Dose Usage to Reduce

* Myocardial infarction, stroke, or vascular death (coronary heart disease death, stroke death, death from pulmonary embolism and death from any hemorrhage).

† Myocardial infarction, coronary death or sudden death.

Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial, patients who were randomized to either high-dose (300–325 mg) or low-dose (75–100 mg) aspirin also did not differ in the primary outcome of CVD death, MI, or stroke at 30 days.[19] Although there was no significant risk in major bleeding, minor bleeding was increased in the high-dose aspirin group.[19] Thus, in patients who have had ACS, low-dose aspirin is better tolerated than high-dose aspirin, with similar efficacy in preventing major CVD events.

Aspirin use can be associated with aspirin-exacerbated respiratory disease (AERD), a clinical syndrome that results in upper and/or lower respiratory reactions, such as rhinitis, laryngospasm, and bronchospasm.[20] COX-1 inhibition results in shunting arachidonic metabolism to leukotriene synthesis and subsequent release of histamine from mast cells.[21] AERD may occur in 0.3%–0.9% of the general population but up to 10%–20% of patients with asthma.[22] In those with adverse reaction to aspirin, monotherapy with a thienopyridine is an acceptable alternate therapy.

Summary

Due to strong evidence supporting the use of aspirin in secondary prevention, the ACC and AHA have placed a class I recommendation with level A evidence for daily use of aspirin to be continued indefinitely for patients with a history of ACS.[23] Higher-dose aspirin (>162 mg) has not been shown to be more efficacious than lower-dose aspirin in preventing recurrent CVD events and may be associated with increased risk of bleeding.

Thienopyridines

Background

Though aspirin is an effective antiplatelet drug, it is not sufficient to completely prevent all coronary atherothrombosis, as there are other pathways of platelet activation. Furthermore, it has been reported that aspirin "resistance," defined as the lack of an expected decrease in platelet activity with aspirin therapy, can be as high as 65% in the general population, and that 39% of these patients can experience a CVD event despite appropriate therapy.[24] Additional therapy with a thienopyridine (ticlopidine, clopidogrel, or prasugrel), a class of antiplatelet agents that inhibit ADP-mediated platelet activation, results in additional atherothrombosis prevention.

Pharmacology

ADP activates platelets via the P2Y12 receptors, inducing several intra-platelet pathways that increase glycoprotein IIb–IIIa complex and fibrinogen binding, amplifying platelet aggregation.[25] Thienopyridines such as ticlopidine, clopidogrel, and prasugrel irreversibly bind to the P2Y12 receptor, inhibiting ADP-related platelet activation.

Clopidogrel and prasugrel are prodrugs that require hepatic activation. Clopidogrel is initially hydrolyzed to an inactive form by esterases, leaving only 15% to undergo oxidative activation by a two-step cytochrome P-450 enzyme (CYP)-dependent processes using CYP3A4, CYP1A2, CYP2B6, and CYP2C19.[26] Prasugrel is activated in a single-step cytochrome P-450-dependent process, using CYP2B6 and CYP3A4, with less CYP2C19 involvement.[27,28] Prasugrel's simpler cytochrome P-450-dependent activation process results in more potent and predictable antiplatelet response with lower loading and maintenance doses required (60 mg loading dose vs. 300 or 600 mg of clopidogrel).[27] In one study, a prasugrel loading dose of 60 mg and maintenance dose of 10 mg caused greater platelet inhibition than a clopidogrel loading dose of 600 mg and maintenance dose of 150 mg.[29]

Indication in CVD

Clopidogrel as Monotherapy

In the Clopidogrel and Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, clopidogrel as monotherapy was found to be more effective than aspirin as monotherapy for secondary prevention in patients presenting with recent ischemic stroke or MI (RRR of 8.7%, $p = 0.043$).[30] It was also shown that severe bleeding, particularly gastrointestinal bleeding, was more common in patients treated with aspirin than in those taking clopidogrel, suggesting a safer bleeding profile for clopidogrel.[30]

Clopidogrel in ACS

While effective as monotherapy, clopidogrel's main role has been in combination with aspirin therapy, a strategy known as dual antiplatelet therapy (DAPT). In CURE trial, 12,562 patients who presented with non-STEMI or unstable angina were randomized to either clopidogrel or placebo, with all patients receiving aspirin.[31] The addition of clopidogrel to aspirin therapy was notable for a significant decrease in all endpoints (cardiovascular death, MI, stroke) as compared to aspirin alone.[31] The same decrease in major endpoints was found irrespective of whether patients with ACS were treated with PCI, coronary artery bypass grafting (CABG), or medical therapy alone.[32] The efficacy of clopidogrel was also confirmed in patients presenting with STEMI in the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) study.[33] The addition of clopidogrel to aspirin in patients presenting with STEMI resulted in a 36% ($p = 0.03$) RRR in the odds of death or recurrent MI as compared to aspirin alone.[33] This strong evidence supports the premise that patients who present with ACS should be treated with DAPT as compared to aspirin alone. However, despite this strong evidence, DAPT is underused, particularly in those who receive medical therapy without PCI or surgical revascularization.[34]

Clopidogrel in Patients without ACS

While strong evidence for the benefit of DAPT has been shown in patients with ACS and in those undergoing percutaneous revascularization, the broader population of patients with stable CVD or who are at high risk for CVD (i.e., those with multiple CVD risk factors, such as diabetes (type I or II), diabetic nephropathy, ankle-brachial index <0.9,

asymptomatic carotid artery stenosis, age, tobacco use, hypertension, and hyperlipidemia) have not been shown to have the same benefit with the use of DAPT.[35] In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, 15,603 patients with multiple CVD risk factors (asymptomatic) or established stable CVD (symptomatic) were enrolled and randomized to treatment with clopidogrel or placebo, in combination with aspirin. It was found that DAPT was not significantly more effective than aspirin alone in reducing the rate of MI, stroke, or death. In subgroup analysis, DAPT was found to possibly be associated with increased risk of mortality in patients who are "asymptomatic."[35] However, there was a slight but significant reduction in ischemic events in patients who were "symptomatic."[35]

Dosing and Length of Treatment with Clopidogrel

To achieve maximal platelet inhibition in patients with ACS without increasing the risk of bleeding, adequate dosing and optimal length of treatment are necessary. In CURRENT-OASIS 7, while there was no difference in the primary outcome of CVD death, MI, or stroke (4.2% in patients taking 150 mg vs. 4.4% in those taking 75 mg, HR, 0.94; CI, 0.83–1.06; p = 0.3), there was an increased risk of minor bleeding in the patients taking the higher dose (HR 1.13, p = 0.04).[19] Furthermore, the CURE trial, which showed benefit of DAPT in NSTE-ACS, evaluated up to a year of clopidogrel treatment. Therefore, current AHA/ACC recommendations are for continued DAPT with clopidogrel at doses of 75 mg daily for 1 year post-ACS. A more recent trial investigating a longer duration of DAPT in patients who had received drug-eluting stents, many for ACS, did not show any additional benefit to longer durations of clopidogrel plus aspirin versus aspirin alone.[36]

Clopidogrel and Proton Pump Inhibitors

Treatment with DAPT incurs a significant risk of gastrointestinal bleeding.[37] Clinical decision to continue antiplatelet agents is often difficult in patients who have CVD and an increased risk of gastrointestinal bleeding. In a small retrospective study, approximately 4.5% and 9.2% of patients on DAPT experienced a gastrointestinal bleeding complication in 1 and 2 years, respectively.[38] Therefore, prophylactic use of proton pump inhibitors (PPIs) has been used to prevent gastrointestinal bleeding. However, PPIs are prodrugs that also require cytochrome P450 metabolism, potentially causing competitive inhibition of clopidogrel activation.[39]

Omeprazole, one of the most commonly used PPIs, has been shown to have a higher degree of affinity for the CYP2C19 system.[39] A randomized trial, Omeprazole Clopidogrel and Aspirin (OCLA) Study, showed that patients undergoing PCI followed by treatment with DAPT plus omeprazole had significantly decreased platelet inhibition compared to those receiving DAPT plus placebo.[40] A post hoc analysis of a randomized controlled trial evaluation of different DAPT regimens demonstrated a lower inhibition of platelet aggregation in the group taking clopidogrel plus a PPI (predominantly omeprazole).[29] A large retrospective study of patients with ACS found that use of clopidogrel with a PPI (predominantly omeprazole) at discharge or at any time during a 3 year follow-up was associated with a higher risk of death or rehospitalization for ACS.[41] Therefore, these data suggested that, due to the biochemical pathway of omeprazole metabolism, its use can potentially attenuate clopidogrel antiplatelet activity, resulting in an increased risk of adverse ischemic clinical events.

However, the only randomized controlled trial comparing DAPT with and without omeprazole, the Clopidogrel and Optimization of Gastrointestinal Events (COGENT) trial, did not support these other findings. In COGENT, 3873 patients taking DAPT were randomized to omeprazole or placebo.[42] The rates of upper GI bleeding were less in subjects using PPI and DAPT (1.1% with omeprazole vs. 2.9% with placebo, $p < 0.001$) with no observed increase in CVD events. Furthermore, other PPIs may have different cytochrome P450 interaction profiles, with it being suggested that omeprazole is more likely associated with competitive and attenuating effects on clopidogrel metabolism as compared to pantoprazole or esomeprazole.[43] In a cross-sectional observational study, platelet activity was significantly higher in patients taking clopidogrel with omeprazole compared to patients taking clopidogrel with pantoprazole or esomeprazole.[43] In a head-to-head comparison of omeprazole and pantoprazole, the use of pantoprazole was associated with significantly better clopidogrel-induced platelet inhibition.[44] In another study, patients who were taking clopidogrel without PPIs had the same amount of platelet activity as those taking clopidogrel with pantoprazole or esomeprazole.[45] Therefore, concurrent use of a PPI, particularly one other than omeprazole, may be reasonable in patients taking clopidogrel when gastrointestinal bleeding risk is high or when PPIs are indicated for other conditions.

Genetic Polymorphisms and Clopidogrel Hyporesponsiveness

The genes encoding these cytochrome P450 enzymes have several polymorphisms, resulting in significant variability in enzyme activity.[46] CYP2C19 is one of these enzymes that has a relatively high prevalence of reduced-function alleles.[46] The presence of these reduced-function CYP2C19 variants in patients have been shown to result in slowed clopidogrel activation and more inactivation by esterases, reduced platelet inhibition in vivo, and an increase in the risk of CVD death, MI, stroke, and stent thrombosis.[47,48] In addition, platelet hyporesponsiveness to clopidogrel in general (whatever the cause) as measured by platelet function assays (such as light transmission aggregometry, vasodilator-stimulated phosphoprotein (VASP), and point-of-care assays such as VerifyNow and Plateletworks) have been shown to be associated with increased risk of adverse CVD events.

Unfortunately, effective strategies to overcome such clopidogrel hyporesponsiveness have not yet been demonstrated. In the Gauging Responsiveness with A VerifyNow

Assay—Impact on Thrombosis And Safety (GRAVITAS) trial, treatment with high-dose (150 mg) clopidogrel versus standard-dose (75 mg) therapy in patients with high on-treatment platelet reactivity did not show a significant difference in reduction in the rate of death, MI, or stent thrombosis.[49] Currently, other randomized trials using CYP2C19 genetic polymorphism assays and various platelet function assays to determine clopidogrel resistance are under way.[50]

Prasugrel

DAPT using clopidogrel has been established as the standard of care in ACS patients. Prasugrel was compared to clopidogrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) study, in which 13,608 patients presenting with ACS and undergoing PCI on aspirin were randomized to prasugrel or clopidogrel. Those treated with prasugrel showed a 19% RRR in death from CVD causes, nonfatal MI, or nonfatal stroke (2.1% vs. 2.4%; HR, 0.81; CI, 0.73–0.9, $p < 0.001$) compared to patients treated with clopidogrel.[29] Similar clinical benefit was seen in urgent revascularization and stent thrombosis.[29] In addition, the use of prasugrel showed significant superior efficacy in certain subgroups, such as in those with diabetes and past MI.[29] However, patients taking prasugrel had a 32% relative risk increase in bleeding events compared with clopidogrel (2.4% vs. 1.8%; HR, 1.32; CI, 1.03–1.68; $p = 0.03$).[29] Post hoc analysis demonstrated that patients >75 years of age, patients weighing <60 kg, and those with a history of transient ischemic attack or stroke incurred particularly unfavorable risk versus benefit balances.[29] Though no difference in all-cause mortality was seen between prasugrel and clopidogrel treatment groups, this trial was not powered for mortality.

Currently, prasugrel is approved for use in patients presenting with ACS and undergoing PCI. However, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) trial is currently evaluating the efficacy of DAPT with prasugrel in comparison to clopidogrel in patients undergoing medical management of their ACS.[51]

Non-Thienopyridine P2Y12 Receptor Antagonists (Ticagrelor)

Pharmacology

Like the thienopyridines, ticagrelor inhibits the P2Y12 platelet receptor. However, unlike the thienopyridines, ticagrelor does not require hepatic metabolism to be activated.[52] In addition, ticagrelor binds reversibly to P2Y12 receptors, allowing for possible faster reversal of platelet inhibition in patients at risk for bleeding complications.[52]

Indications in Coronary Artery Disease and ACS

In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor or clopidogrel in combination with aspirin was compared in 18,624 ACS patients. Ticagrelor use significantly decreased the relative risk of the primary endpoint, a composite of all-cause death from CVD causes, MI, and stroke, by 16% (9.8% vs. 11.7%; HR, 0.84; CI, 0.77–0.92; $p < 0.001$) and was associated with a decrease in other secondary endpoints, such as death from any cause, death from CVD cause, MI, and stent thrombosis.[53] Ticagrelor was not associated with higher risk of major bleeding, overall; however, it was associated with higher risk of non-procedure-related bleeding and some adverse reactions, such as dyspnea and asymptomatic ventricular pauses. With recent approval by the FDA, ticagrelor shows promise as an alternative reversible therapeutic option to the thienopyridines.

Summary

DAPT, using aspirin and a P2Y12 receptor antagonist for 1 year after ACS, is the standard of care for patients. Clopidogrel has been the most thoroughly studied of the P2Y12 receptor antagonists and has the most clinical experience behind it. The relatively recent introduction of other P2Y12 receptor antagonists (prasugrel and ticagrelor) with superior CVD event reduction and different risk and side effect profiles than clopidogrel has highlighted the need for careful consideration of their use in place of clopidogrel and continued investigation into the selection of the most appropriate agent.

LIPID-LOWERING THERAPY

HMG-CoA Reductase Inhibitors (Statins)

Background

Elevated serum cholesterol has been established as one of the most important risk factors for the development of coronary atherosclerosis and has become a crucial treatment target of both primary and secondary prevention of cardiovascular events.[54] Secondary prevention trials had demonstrated the importance of cholesterol lowering, even prior to the routine use of HMG-CoA reductase inhibitors.

Data from both the Framingham Heart Study and the cohort in The Multiple Risk Factor Intervention Trial (MRFIT) indicate a direct relationship between total cholesterol levels and rates of CAD, beginning with total serum cholesterol levels as low as 180 mg/dL and indicating a nearly fourfold increase in the top 10% versus the bottom 10% of observed values. The observations of the Framingham study and the Lipid Research Clinics Coronary Primary Prevention Trial (CPPT) indicate an approximate 2% reduction in coronary events for every 1% reduction in serum cholesterol.[54–56]

Pharmacology

The first statin, mevastatin (compactin), was isolated in 1972 from the bacterium *Penicillium citrinum,* along with other similar but less active compounds. Lovastatin was later isolated from *Aspergillus terreus*, representing the first statin to demonstrate reduction of LDL in human subjects.[57–59] Subsequently, multiple other agents with varying potencies

and pharmacokinetic/pharmacodynamic properties have been developed, including pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin.

HMG-CoA reductase inhibitors (statins) target the rate-limiting step of in vivo cholesterol synthesis, dependent on the enzyme HMG-CoA reductase, the majority of which takes place in the liver and to a lesser extent in the intestine. Statins reduce serum LDL by reducing hepatic LDL synthesis and increasing the expression of LDL receptors via promotion of mRNA formation.[59]

Conventional doses of statins reduce LDL by 18%–41%, varying widely with an individual's metabolic idiosyncrasies and variable CYP3A4-mediated first-pass metabolism of some agents. This feature of drug metabolism becomes important in considering drug interactions of various agents, notably simvastatin and lovastatin. Fluvastatin and pravastatin are not significantly metabolized by the CYP3A4 system, although fluvastatin undergoes extensive CYP2C9 biotransformation.[60] The dose–response curves of these agents are flat, and doubling doses of these medications has been reported to offer an additional reduction in LDL of approximately 6% over initial reductions.[61] A recent meta-analysis of 32,258 pooled subjects confirmed this magnitude of reduction with increasing doses, reporting an additional reduction of 4%–7% with doubling baseline doses of atorvastatin, simvastatin, or rosuvastatin. A majority of patients were able to meet NCEP goals for risk-based LDL cholesterol reduction when doses were escalated as indicated over a wide range of initial LDL levels.[62]

Indications for Secondary Prevention of Coronary Artery Disease

In addition to the establishment of LDL cholesterol as a marker of CAD, multiple large randomized controlled secondary prevention trials have demonstrated a reduction in cardiovascular events and total mortality with statins.

Reduction of Cardiovascular Events and Mortality

Several large trials have shown the benefit of HMG-CoA reductase inhibitors in secondary prevention during both long- and short-term follow-up. While most studies included patients less than 70 years of age, one study focused on patients 70–82 years of age, implicating the importance of HMG-CoA reductase inhibitors in all groups with CAD or significant risk factors (Table 86.1).

The Cholesterol and Recurrent Events Trial (CARE) enrolled 4159 subjects with acute myocardial infarction (AMI) in the previous 3–20 months, ages 21–75, plasma total cholesterol levels of <240 mg/dL, or LDL cholesterol levels of 115–174 mg/dL. Subjects were randomized to pravastatin 40 mg daily versus placebo with a median follow-up of 5.0 years. The pravastatin group experienced a 24% RRR in fatal coronary events or nonfatal MI, a 26% relative reduction in need for coronary artery bypass surgery, and 23% RRR in need for coronary angioplasty. The frequency of stroke was reduced by 31%. This study did not detect any significant difference in overall mortality or mortality from noncardiovascular causes. There was a greater decrease in the rate of coronary events among women compared to men, who comprised 13.8% of the study population, and individuals with the highest baseline LDL levels experienced the greatest benefit.[63]

In the Scandinavian Simvastatin Survival Study (4S), 4444 subjects (both male and female, ages 35–70) with a history of angina or AMI who were on a lipid-lowering diet were randomized to simvastatin versus placebo over a median 5.4 year follow-up period. Doses were initiated at 20 mg daily and titrated to achieve goal serum total cholesterol of 5.5–8.0 mmol/L over a range of 10–40 mg of simvastatin daily. In the simvastatin group, the relative risk of death was 0.7 ($p = 0.0003$), relative risk of coronary death was 0.58, and the relative risk of major cardiovascular events was 0.66. In addition, there was an observed 37% risk reduction in need for revascularization procedures. This benefit was shown consistently in subgroup analyses based on gender and age greater than 60.[64]

Another large double-blind randomized trial, the Long-Term Intervention with Pravastatin Ischaemic Disease (LIPID) Study, compared the effects of pravastatin 40 mg daily with placebo in 9014 individuals 31–75 years of age with a history of AMI or unstable angina and plasma total cholesterol of 155–271 mg/dL. All subjects were on lipid-lowering diets at baseline. During the 6.1 year follow-up period, there was a 24% RRR in death from coronary disease in the pravastatin group versus placebo (6.4% vs. 8.3% respectively, $p < 0.001$). A 22% reduction in overall mortality was observed in the pravastatin group versus placebo, as well as all other cardiovascular outcomes, including MI (29% RRR), stroke (19% RRR), and need for coronary revascularization (20% RRR).[65] These outcomes were consistent with the results of the 4S and CARE trials, confirming the long-term benefit of lipid reduction with HMG-CoA reductase inhibitors in the secondary prevention of coronary events.

The shorter term effects of HMG-CoA reductase inhibitors were investigated in the Lescol in Severe Atherosclerosis (LiSA) trial. In the trial, 365 subjects, ages 40–70 years, with stable, symptomatic CAD were enrolled with a follow-up period of 1 year. Subjects were randomized to receive fluvastatin 40 mg twice daily versus placebo. The fluvastatin group had a cardiac event rate of 1.6% vs. 5.6% in the placebo group, a statistically significant difference ($p < 0.05$). Subjects in the fluvastatin group also experienced improved exercise tolerance, greater reduction in the incidence of angina pectoris episodes (although not statistically significant), and decrease in exercise-ECG discontinuation due to angina pectoris and ST-segment depression (also not statistically significant). A subgroup of 76 patients with mean carotid intima–media thickness (CIMT) value of 0.73 mm remained unchanged over this 1 year study period.[66] The results of this study suggested that the HMG-CoA reductase inhibitors provide benefit soon after initiation with regard to altering the natural history of stable CAD.

Given the efficacy and tolerability demonstrated in the earlier studies in patients <70 years of age, the question

TABLE 86.1
Key Trials of HMG-CoA Reductase Inhibitors in Secondary Prevention of Cardiovascular Disease

Title	Study Drugs	Number of Subjects	Subjects' Characteristics	Follow-Up	Findings and Comments
Cholesterol and Recurrent Events (CARE)	Pravastatin 40 mg daily vs. placebo	4159	21–75 years of age AMI in prior 3–20 months TC <240 mg/dL LDL-C: 115–174 mg/dL	5.0 years	24% RRR in fatal coronary events or nonfatal myocardial infarction 26% RRR in need for coronary artery bypass 23% RRR in percutaneous coronary intervention 31% reduction in frequency of stroke
Scandinavian Simvastatin Survival Study (4S)	Simvastatin 10–40 mg vs. placebo	4444	35–70 years of age History of angina or AMI Lipid-lowering diet	5.4 years	RR of death was 0.7 (p = 0.0003) RR of coronary death was 0.58 RR of major cardiovascular events was 0.66 37% RRR in need for revascularization
Long Term Intervention with Pravastatin Ischaemic Disease (LIPID)	Pravastatin 40 mg daily vs. placebo	9014	31–75 years of age History of AMI or unstable angina TC: 155–271 mg/dL Lipid-lowering diet	6.1 years	24% RRR in death from CAD (p < 0.001) 22% RRR in overall Reduction in death from: myocardial infarction (29% RRR) Stroke (19% RRR) 20% RRR in need for coronary revascularization
Lescol in Severe Atherosclerosis (LiSA)	Fluvastatin 40 mg twice daily vs. placebo	365	Ages 40–70 years, with stable, symptomatic CAD	1.0 years	ARR in cardiac event rate of 4% (p < 0.05) Improved exercise tolerance
Pravastatin in elderly individuals at risk of vascular disease (PROSPER):	Pravastatin 40 mg daily vs. placebo	5804	70–82 years of age Smoking, hypertension, or diabetes mellitus	3.2 years	24% reduction in cardiovascular mortality No difference in adverse outcomes Statins safe and effective in elderly patients with CAD or significant risk factors
Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes (PROVE-IT)	Pravastatin 40 mg daily vs. Atorvastatin 80 mg daily	4162	AMI within the preceding 10 days	24 months	Greater magnitude of LDL-C reduction with intensive therapy 16% reduction in combined endpoint of all-cause mortality, AMI, unstable angina, revascularization, and stroke (p = 0.005) Benefit in intensive lipid-lowering therapy to a goal LDL of less than 70 mg/dL post-ACS
Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis (ASTEROID)	Rosuvastatin 40 mg daily	507	Baseline IVUS performed	24 months	Statistically significant plaque reduction Limited by lack of control group High rate of drug discontinuation (63 subjects) due to adverse effects

ARR, absolute risk reduction; RRR, relative risk reduction; RR, relative risk.

of benefit and safety in older patients was examined in the pravastatin treatment in elderly individuals, 70–82 years of age, at risk of vascular disease (PROSPER trial). This study enrolled 5804 subjects, both male and female with CVD or risk factors, defined as the presence of smoking, hypertension, or diabetes mellitus, who were randomized to treatment with pravastatin 40 mg daily versus placebo. Over the 3.2 year follow-up period, there was a 24% reduction in cardiovascular mortality in the pravastatin group, consistent with reductions seen in previous trials with younger subjects. In addition, there was no difference between the pravastatin in adverse outcomes, including myalgia and rhabdomyolysis, indicative of both safety and efficacy in elderly patients with CAD or significant risk factors.[67]

The hypothesis that additional benefit is seen with more intensive reduction in LDL post-MI was evaluated in the PROVE-IT trial. A total of 4162 patients hospitalized with AMI within the preceding 10 days were randomized to standard treatment with pravastatin 40 mg daily or intensive treatment with atorvastatin 80 mg daily with a median follow-up of 24 months. The composite primary endpoint in this trial included death from any cause, MI, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. The median LDL cholesterol level was 95 mg/dL in the standard-dose pravastatin group and 62 mg/dL in the high-dose atorvastatin group ($p < 0.001$). Over the 18–36 month follow-up period, the rates of the primary endpoint at 2 years were 26.3% in the pravastatin group and 22.4% in the atorvastatin group, indicating a 16% reduction in the hazard ratio (HR) for the composite primary endpoint ($p = 0.005$; 95% CI, 5%–26%). These findings support intensive lipid-lowering therapy to a goal LDL of less than 70 mg/dL post-ACS. This is reflected in the most recent NCEP guideline update for lipid management.[181,82]

Regression of Atherosclerotic Plaque

Clinically, intensive reduction in serum cholesterol levels with HMG-CoA reductase inhibitors may promote regression of atherosclerosis as assessed by coronary intravascular ultrasound (IVUS). The Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis (ASTEROID) Trial enrolled 507 patients who underwent baseline IVUS studies, 349 of which had evaluable follow-up studies performed at 24 months. All patients were treated with rosuvastatin 40 mg daily, although 63 patients withdrew during the study period due to adverse events. The majority of lesions assessed demonstrated statistically significant regression of percent atheroma volume (PAV) for the entire vessel of −0.98% (97.5% CI, −1.21% to −0.53%). The mean change in atheroma volume in the most diseased 10 mm subsegment of coronary arteries was −6.1 mm^3 (97.5% CI, −6.8 to −4.0 mm^3). The major limitation of this study was the lack of a placebo group due to the ethical concerns of assigning high-risk patients to placebo. However, knowing the pathophysiology and natural history of CAD, it is unlikely that spontaneous plaque regression would have occurred without intensive lipid-lowering therapy.[68]

Pleiotropic Effects

The observation that patients treated with statins have less cardiovascular events than placebo-controlled individuals with similar serum lipid levels, as well as the early benefit of these agents, raises the possibility of beneficial effects mediated via mechanisms other than lipid reduction.[63,69] These include inhibition of vascular smooth muscle proliferation, improvement of vascular endothelial function, and perhaps antioxidant and anti-inflammatory effects.[70–72]

A recent small study demonstrated improvement of endothelial function in 41 hypercholesterolemic subjects with LDL >130 mg/dL and mean age 52 years who were randomized to treatment with atorvastatin or cerivastatin. Endothelium-dependent vasodilatation was assessed by upper extremity plethysmography after infusion of acetylcholine at 3 and 14 days of treatment. There was an observed 46% improvement in endothelium-dependent vasodilatation after 3 days of statin treatment with no further benefit at 14 days. This was in contrast to reduction of LDL by 11.9% at 3 days and 29.6% at 14 days, indicating a mechanism of this observed improvement of vascular function independent of lipid-lowering effects.[73]

The anti-inflammatory effects of HMG-CoA reductase inhibitors have been evaluated in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial of 17,802 healthy men and women with LDL less than 130 mg/dL and C-reactive protein (CRP) levels of 2 mg/L or higher. Patients were randomized to rosuvastatin 20 mg daily or placebo for a median 1.9 year follow-up (5 years maximum) and followed for the occurrence of the combined vascular endpoint inclusive of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. The rosuvastatin group experienced a reduction in LDL cholesterol levels of 50% and CRP levels of 37%. The HR for the primary endpoint in the rosuvastatin group was 0.56 (95% CI, 0.46–0.69; $p < 0.00001$); 0.46 for acute MI (95% CI, 0.30–0.70; $p = 0.0002$); 0.52 for stroke (95% CI, 0.34–0.79; $p = 0.002$); 0.52 for revascularization or unstable angina (95% CI, 0.40–0.70; $p < 0.000010$); 0.53 for the combined endpoint of MI, stroke, or death from cardiovascular causes (95% CI, 0.40–0.69; $p < 0.00001$); and 0.80 for death from any cause (95% CI, 0.67–0.97; $p = 0.02$). Importantly, the rosuvastatin group did not have a significant increase in myopathy or cancer.[74]

Statin-Associated Myopathy and Management of Intolerant Patients

Consideration of the individual pharmacokinetic properties of various HMG-CoA reductase inhibitors are of importance when initiating, titrating, or otherwise altering therapy (Table 86.2). This is particularly true of CYP3A4-mediated interactions with other medications the patient may be concurrently receiving. Coadministration of commonly prescribed antibiotics including macrolides, cardiovascular drugs including diltiazem and verapamil, and azole antifungals among many others can significantly increase serum levels of HMG-CoA reductase inhibitors with resulting dose-related adverse effects, particularly myopathy (Table 86.2).[60]

When statins are used as monotherapy, the most significant limiting side effect is the development of myalgias. In most cases, this occurs in the absence of clinically detectable myositis or elevation in serum markers of muscle injury. Rhabdomyolysis, defined as serum CPK >10 times the upper limit of normal, is a rare but serious adverse event. The incidence of clinically significant myalgias has been reported to be as high as 10% in observational studies, although the incidence in clinical trials has been

TABLE 86.2
Common Drug–Drug Interactions Resulting in Changes in Statin Serum Concentration

	Statin					
	Simvastatin	**Lovastatin**	**Atorvastatin**	**Fluvastatin**	**Pravastatin**	**Rosuvastatin**
Antifungals						
Itraconazole	↑	↑	↑			
Ketoconazole	↑	↑	↑			
Posaconazole	↑	↑	↑			
Voriconazole	↑	↑	↑			
Macrolides						
Clarithromycin	↑	↑	↑		↑	
Erythromycin	↑	↑	↑			
CCB						
Diltiazem	↑	↑	↑			
Verapamil	↑	↑	↑			
Protease inhibitors						
Ritonavir	↑	↑	↑		↓	
Lopinavir	↑	↑	↑			↑
Other drugs						
Amiodarone	↑	↑	↑			
Carbamazepine	↓	↓	↓	↓	↓	
Cyclosporine	↑	↑	↑	↑	↑	↑
Digoxin			↑			
Efavirenz	↓		↓		↓	
Rifampin	↓		↓	↓	↓	
Gemfibrozil	↑	↑	↑		↑	↑

Source: Adapted from Garcia-Sabina, A. et al., *Farm. Hosp*., 36 (2), 97, 2011.
↑ or ↓ indicates increase or decrease in serum concentration of statin, respectively.

exceedingly low, likely because of bias against enrollment of individuals with a history of myalgias in such trials. Subclinical myalgias remain a common reason for discontinuation of HMG-CoA reductase inhibitors in patients who may derive important benefit from their use. The mechanism of development of myopathy remains unclear, but proposed mechanisms include depletion of cellular cholesterol resulting in membrane instability, coenzyme Q10 (CoQ10) depletion, isoprenoid depletion, and mitochondrial dysfunction. However, none of these mechanisms have been consistently linked to development of myopathy in symptomatic or asymptomatic patients.[75] Coadministration of other drugs is another common reason for alterations in serum levels of statins that may increase the risk for statin-induced myopathy (Table 86.3).

Strategies for management of statin-intolerant patients remain a significant challenge in current practice, particularly since non-statin agents or combinations of non-statin agents have not shown comparable efficacy in reduction of serum lipid levels and corresponding cardiovascular events. Individual patients may tolerate some statins better than others for unclear reasons, and switching to another HMG-CoA reductase inhibitor is an appropriate initial step, particularly for patients who have no biochemical evidence of myositis.[76]

TABLE 86.3
Commonly Used Medications That May Increase the Risk of Statin-Induced Myopathy

Non-lipid related
Cyclosporine
Macrolide antibacterials (erythromycin, clarithromycin)
Azole antifungals (itraconazole, ketoconazole, fluconazole)
Calcium channel antagonists (diltiazem, verapamil)
Nefazodone
HIV protease inhibitors (ritonavir, nelfinavir, indinavir)
Warfarin
Histamine H_2 receptor antagonists (cimetidine, ranitidine)
Omeprazole
Amiodarone

Lipid related
Fibrates (gemfibrozil, clofibrate, fenofibrate)
Niacin

Other substances
Grapefruit juice
Over-the-counter medications (Chinese red rice fungus)

Source: Adapted from Chatzizisis, Y.S. et al., *Drug Saf*., 33 (3), 171, 2010.

Alternate-day dosing of HMG-CoA reductase inhibitors has also demonstrated efficacy and tolerability in small studies, particularly with atorvastatin and rosuvastatin, although thus far available data have focused only on the effect on lipid levels and not on the incidence of cardiovascular outcomes.[77–79]

Summary

HMG-CoA reductase inhibitors are among the most important interventions in patients with known CVD regardless of age or gender. Benefits have been seen over a wide range of baseline serum lipids with cardiovascular and survival benefits related to LDL reduction. In addition, these agents may have vascular and systemic benefits that are distinct from their ability to reduce atherogenic serum lipid levels.

The AHA/ACC Guidelines recommend treatment of all post-ACS patients with LDL-C of 100 mg/dL or above (class I/LOE A) and LDL-C levels of less than 100 mg/dL or unknown lipid levels (class I/LOA B) with statins as primary agents for lipid therapy.[23] Treatment goals generally target LDL-C less than 100 mg/dL, but in patients with high cardiovascular risk, an LDL-C target of less than 70 mg/dL may be considered.[80,81]

Omega-3 PUFA

The Mediterranean region, along with Japan and Greenland, has a lower prevalence of atherosclerotic heart disease than other Western countries.[82,83] One proposed mechanism for this finding is the high intake of omega-3 polyunsaturated fatty acids (PUFAs) in these regions. There have been multiple epidemiologic studies showing a correlation between the intake of omega-3 PUFAs and the decreased incidence of CVD. The exact mechanism by which this occurs is unclear, but available evidence has demonstrated a reduction in risk of MI and SCD.

Pharmacology

The majority of studies involving omega-3 PUFA have focused on eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These two types of omega-3 PUFA play different roles in improving the lipid profile and decreasing inflammation and oxidative stress.[84] Benefits seen in the incidence of SCD, arrhythmia, hypertension, and heart failure all likely involve very different mechanisms. These potential mechanisms include the following[85]:

1. Effects related to the metabolism of omega-3 PUFA on cellular mediators
2. Direct effects on ion channels
3. Effects on genetic expression of proteins important for lipid metabolism
4. Effects related to incorporation of omega-3 PUFA into cellular membranes

EPA has been shown to compete with arachidonic acid for COX-1 conversion to eicosanoids having anti-inflammatory, vasodilatory, and antiplatelet actions.[84] Alternatively, DHA is converted to cellular mediators that have known anti-inflammatory and antioxidant effects.[84,85] Omega-3 PUFAs also may have direct effects on ion channels in addition to being incorporated into cellular membranes of the heart, vessel walls, and the nervous system, which may modify responses to extracellular signaling.[85,86]

Indications in Optimizing Lipid Profile

Omega-3 PUFAs have been shown to decrease serum triglyceride levels through regulation of genetic expression of proteins controlling hepatic triglyceride metabolism.[87] High doses of at least 3 g and often greater than 6 g of DHA and EPA per day are necessary to achieve significant triglyceride-lowering effects. To date, there have been no large outcome-based randomized trials using omega-3 PUFA in patients with hypertriglyceridemia; therefore, it is not known whether using omega-3 PUFA in this manner has any benefit on clinical event reduction. While the triglyceride-lowering effects of omega-3 PUFA therapy can be potent, the effects on other lipid parameters are more modest with only a slight increase in both LDL-C and high-density cholesterol (HDL-C). There are both prescription and nonprescription omega-3 PUFAs available with the prescription formulation being the most highly concentrated.

Indications in CVD

The consumption of omega-3 PUFA has been shown in prospective and retrospective cohort and case–control studies to decrease major cardiovascular events, such as MI, SCD, atrial fibrillation, and death in individuals with chronic heart failure.[88–91] Several RCTs have demonstrated cardiovascular benefits with omega-3 PUFAs. In the Diet and Reinfarction Trial (DART), dietary advice to increase fatty fish demonstrated a 29% reduction in all-cause mortality over a 2 year follow-up, as well as a nonsignificant difference in nonfatal CVD events.[92] The GISSI Prevenzione trial was notable for a reduction in the risk of death, nonfatal MI, and nonfatal stroke by 15% (12.3% vs. 14.6%; RR, 0.85; 95% CI, 0.74–0.98; p = 0.023) in patients treated with 850 mg daily of omega-3 PUFA.[93] Significant reductions in CVD mortality, coronary mortality, and coronary events were also seen. The Japan EPA Lipid Intervention Study (JELIS) randomized patients with hyperlipidemia to receive either 1800 mg of EPA plus statin or statin alone. This trial demonstrated a significant 19% risk reduction of the cumulative rate of major CVD events, including SCD, fatal, and nonfatal MI compared to patients taking statin alone (2.8% vs. 3.5%; p = 0.011). There were also significant reductions in nonfatal events, such as unstable angina, angioplasty, or CABG.[94] In the GISSI-Prevenzione Heart Failure trial, there was a modest reduction in all-cause mortality in patients with heart failure who had been randomized to 1 g of omega-3 PUFA daily (HR, 0.9; CI, 0.833–0.998; p = 0.41) and CVD death (HR, 0.9; CI, 0.81–0.99; p = 0.045).[95] The exact mechanism for this benefit was unclear but is thought to be primarily due to reduction in arrhythmias as opposed to MI.

Although many trials have shown reduction in CVD risk with omega-3 PUFA use, not all have shown clinical benefit. In one large multicenter RCT, supplementing with 600 mg of EPA and DHA daily was not associated with any significant effects on major vascular events and all-cause mortality.[96] In another study designed to change dietary habits in 3114 male patients with stable angina, those advised to eat at least two portions of fatty fish a week or 3 g of fish oil supplement had no significant improvement in mortality and had a significantly higher mortality from cardiac and sudden death than those not advised.[97] EPA levels were measured in a portion of the patients studied, and a follow-up survey was issued to ensure compliance. Subgroup analysis of these patients showed a higher HR for mortality in the fish oil supplement group, which may be attributed to medication interactions and modification of risk-taking behavior. More recently, the Alpha Omega trial showed that supplementation with 400 mg of EPA and DHA daily did not significantly reduce the rate of major CVD events among patients who had recently experienced an MI.[88] Though this trial showed a nonsignificant reduction of 10% in ventricular arrhythmia-related events, patients with diabetes did have a significant decrease in fatal coronary events and arrhythmia-related events (HR, 0.51; CI, 0.27–0.97).[88] Another major RCT, the Omega trial, also reported negative results with the use of omega-3 PUFA in patients with CVD. It demonstrated that in patients with a history of acute MI, supplementation with highly purified 1 g a day of omega-3 PUFA did not show any differences in major vascular events and mortality from all causes in the background of standard therapy.[98]

Summary

Omega-3 PUFAs in high doses (3–4 g) have been shown to significantly decrease serum triglyceride levels. Although not all trials have demonstrated clinical benefit, overall there seems to be a modest protective effect of omega-3 PUFAs on CVD, such that the AHA has recommended daily use of 1 g of omega-3 PUFA in the form of DHA and EPA for secondary prevention of CVD.[99]

Niacin

Background

In contrast to LDL-C, HDL-C has an anti-atherosclerotic effect through a different mechanism called reverse cholesterol transport. HDL is involved in cholesterol uptake from atherosclerotic plaques (and excess cholesterol in peripheral cells) and its transportation to the liver for bile synthesis or free cholesterol hepatic excretion.[100] Additional studies have shown other beneficial effects of HDL-C, including antioxidant, anti-inflammatory, and anticoagulation effects.[101] HDL-C may also play a role in stimulating endothelial regeneration by promoting endothelial progenitor cell-mediated endothelial repair[102] and accepting hydroperoxidases.[101] In addition, HDL-C may protect against thrombosis by inhibiting procoagulant activity.[103,104] Thus, there has been great interest in finding ways to increase HDL-C in patients with known CAD.

As early as 1955, it was shown that the use of nicotinic acid reduced total cholesterol levels.[105] Subsequent clinical trials utilized niacin to lower total cholesterol levels.[106,107] The Coronary Drug Project was the first randomized trial to assess the effect of niacin on CVD events.[108] It was a secondary prevention trial that randomized 1119 patients with CVD to niacin or placebo. In the initial trial, there was a modest reduction in nonfatal MI, but no difference was seen in overall mortality. However, subsequent studies at a follow-up of 15 years, nearly 9 years after the trial termination, demonstrated an 11% reduction in mortality in the niacin group compared to placebo.[109]

Pharmacology

Niacin, more specifically nicotinic acid, inhibits the hepatic synthesis of VLDL and LDL by decreasing triglyceride synthesis[110] and inducing apolipoprotein B (main lipoprotein found on LDL) degradation in the hepatocytes.[111,112] Decreasing VLDL directly decreases LDL, a VLDL catabolic by-product. Niacin also plays a direct role in increasing HDL levels by decreasing its hepatic clearance.[112,113] In addition, niacin also acts to induce enzymes that facilitate cholesterol transfer from monocytes and macrophages to HDL, thereby reversing the atherosclerotic process.[114] Niacin may increase HDL by as much as 15%–35%, while lowering triglyceride level by 20%–35% and LDL by 5%–25%. In combination with statins, niacin has been shown to improve lipid profiles with potential regression of atherosclerotic disease.[115–117] It has also been suggested that niacin may have antioxidant and anti-inflammatory properties through its ability to increase intracellular nicotinamide adenine dinucleotide phosphate, subsequently reducing reactive oxygen species, LDL oxidation, and TNF-α release.[110]

Three types of niacin formulations are available: immediate release (IR), sustained release (SR), and extended release (ER). Niacin IR is absorbed and metabolized quickly, requiring three times daily dosing. Niacin SR has a slower absorption and metabolism rate, but this is highly variable (12–24 h). Niacin ER has an absorption and metabolism rate intermediate of IR and SR formulations (8–12 h) and thus has a more predictable rate of action with improved tolerability.[118] It is important to note that nicotinamide, which is the amide form of nicotinic acid, has no lipid-altering effects. This is important because many, if not all, of the "no-flush" niacin formulations contain nicotinamide (not nicotinic acid). If clinicians recommend over-the-counter niacin preparations, they must educate patients about this crucial difference.

Indications in CVD

Despite achieving an LDL-C goal with statins, patients with a history of a CVD often have residual cardiac risk that may be attributable to low HDL-C and elevated triglyceride levels. Niacin, with its known HDL-C-raising properties, could potentially reduce this residual risk. In the HDL-Atherosclerosis Treatment Study (HATS), patients

were randomized to receive simvastatin plus either niacin or placebo. It was shown that patients treated with simvastatin and niacin had regression of coronary artery stenosis ($p < 0.001$) compared to placebo as measured by quantitative coronary angiography.[115] Furthermore, there was a 90% RRR ($p = 0.03$) in the combined primary endpoint of death from CVD causes, MI, stroke, and revascularization in favor of simvastatin and niacin. Niacin also has been shown to have a more pronounced regression than ezetimibe in the CIMT, a surrogate measure for atherosclerosis. In the ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) trial, patients treated with statins randomly assigned to ER niacin had a significant amount of CIMT regression compared to ezetimibe.[119]

However, more recent evidence from the Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial demonstrated no significant added benefit from niacin for patients with adequate LDL therapy but low HDL. This was the largest trial looking at niacin in the modern era and examined patients with a prior history of CVD and low HDL-C randomized to simvastatin or simvastatin plus niacin with the goal of having equivalent LDL-Cs in the groups. AIM-HIGH was terminated early because of a lack of benefit in the simvastatin plus niacin arm of the trial despite this group having an equivalent LDL-C and higher HDL-C. The reasons for the lack of benefit seen with niacin in this trial are unknown; however, it is important to note that these patients were very aggressively treated with LDL-C in both groups approaching 60 mg/dL and had received state-of-the-art modern CVD therapies. The study also may have been underpowered to demonstrate a statistical difference. Since the early termination of the AIM-HIGH trial, the role of niacin in the secondary prevention of CVD has become less clear. Future studies such as the Heart Protection Study 2: Treatment of HDL to reduce the Incidence of Vascular Events (HPS2-THRIVE) that are currently under way may further define the role niacin will play in the secondary prevention of CVD. Niacin may have a role in patients with CVD who cannot achieve target LDL-C goal with statin therapy alone.

Although niacin may have beneficial effects on LDL and HDL levels, many patients are not able to tolerate the side effect profile of niacin. Up to 88% of patients taking the ER formulation experience a vasocutaneous flushing reaction.[120] It has been proposed that niacin induces skin Langerhans cells to release prostaglandin chemokines responsible for flushing symptoms.[121] These symptoms are better tolerated in patients using niacin ER, and continued use over weeks may further decrease this reaction. Patients may also empirically take aspirin 1 h prior to taking niacin to decrease prostaglandin synthesis and attenuate the flushing reaction. In addition to vasocutaneous flushing, patients with diabetes may experience worsening of glycemic control with niacin when used in doses greater than 2000 mg/day.[122] This effect has been associated more with the niacin IR formulation and has been attributed to an increase in insulin resistance. Combination therapy of niacin and a statin may increase the risk of hepatotoxicity. This effect has been observed in patients taking the niacin SR formulation at higher doses (>1500 mg).[56] Monitoring liver enzymes in patients using this combination therapy is necessary to avoid potential hepatotoxic effects. Niacin may also cause hyperuricemia and induce gout flares in patients who are predisposed to gout. Milder side effects include gastric irritation, an eczema-like reaction, and worsening of acanthosis nigricans.[106]

Summary

Though niacin has been shown to significantly improve lipid parameters, its clinical benefit when added to comprehensive medical therapy with well-controlled LDL-C is less clear. Niacin continues to have a role in patients who cannot achieve target LDL-C goal with statin therapy alone or who have significantly elevated triglycerides despite lifestyle modification. Niacin ER is usually better tolerated with less risk for hepatotoxicity. Patients should be discouraged from taking over-the-counter "no-flush" preparations as they do not release nicotinic acid and have no known clinical benefit.

Fibrates

Background

Hypertriglyceridemia is a common lipid abnormality that has a strong epidemiologic association with CVD. However, this association is significantly attenuated when studies adjust for LDL-C and HDL-C. This has created a great deal of controversy over the independent effect of triglycerides on CVD risk with some arguing that these findings are merely associations and that elevated triglyceride levels are only a marker for other processes that may play a more causal role in CVD risk. Regardless of this controversy, elevated triglycerides are at the very least a marker of a patient at potentially high risk for the development of CVD events, necessitating careful assessment of their risk factors, and more specifically their lipid profile.

Pharmacology

Indirect metabolic pathways of triglyceride catabolism have been implicated in the pathogenesis of atherosclerosis. It has been proposed that elevation of triglycerides promotes elevation of triglyceride-rich VLDL particles and a sequential increase in LDL serum levels. In addition, some have proposed that chylomicrons containing high amounts of triglyceride particles are metabolized to remnants that directly invade the subendothelial space, depositing cholesterol and activating foam cell formation.

Fibrates are synthetic ligands for PPAR $\propto$ receptors that act intracellularly to induce genetic expression of lipoprotein lipase, decrease the production of apolipoprotein C in the liver, and regulate the catabolism of free fatty acids. Additionally, fibrates also increase HDL levels by inducing the expression apolipoprotein A through the same PPAR

genetic regulation. In summary, fibrates affect the lipid profile through various mechanisms:

1. Increases LPL concentration and activity
2. Induces liver fatty acid uptake and decreases liver triglyceride production
3. Decreases LDL levels by increasing LDL affinity for removal from circulation
4. Decreases lipid exchange between VLDL and HDL
5. Increases HDL production by increasing ApoA production in the liver

Indications in CVD

It has been shown that fibrates are effective in decreasing triglyceride level by 35%–50%, while increasing HDL by 20%. Although highly effective in decreasing triglycerides and increasing HDL levels, clinical trials have been inconsistent in demonstrating reduction in CVD risk and mortality. In the Bezafibrate Infarction Prevention (BIP) Study, the use of bezafibrate in 3090 patients with a previous MI or unstable angina increased HDL by 18% and decreased triglycerides by 21%.[123] Despite significant changes in the patients' lipid profile, the use of bezafibrate did not decrease the primary endpoint of MI or SCD. However, in a subgroup analysis of patients with triglyceride ≥200 mg/dL, treatment with bezafibrate significantly decreased the cumulative probability of the primary endpoint by 39.5% ($p = 0.02$).[123] This finding was consistent with the Veteran Affairs High Density Lipoprotein Intervention Trial (VA-HIT). This study reported that treatment with gemfibrozil in 2531 men with a history of CVD reduced CVD events by 11% for every 5 mg/dL increase in HDL ($p = 0.02$).[124] In patients with diabetes, there have been mixed findings on the effects of fibrate therapy and reduction in CVD events. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9795 type 2 diabetics not taking statins were randomized to fenofibrate or placebo.[125] Treatment with fenofibrate was associated with a nonsignificant 11% decrease (HR, 0.89; CI, 0.75–1.05; $p = 0.16$) in the primary endpoint of first MI or coronary heart disease death. However, this study did find a significant 11% reduction ($p = 0.035$) in total CVD events, which included a significant reduction in nonfatal MI (HR, 0.76; CI, 0.62–0.94; $p = 0.01$) and coronary revascularization (HR, 0.79; CI 0.68–0.93; $p = 0.003$). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial also evaluated the effects of fibrate therapy in patients with diabetes. In this large RCT, 5518 patients were randomized to fenofibrate and statin or statin alone. It was found that there was no significant reduction in the primary endpoint of first occurrence of MI, stroke, or death from CVD causes.[126] However, in subgroup analysis, patients with triglyceride levels ≥204 mg/dL and an HDL ≤34 mg/dL had a 31% risk reduction of the primary endpoint.[126] As observed in both BIP and ACCORD studies, fibrate therapy may play a greater role when targeting patients with higher baseline triglycerides (≥200 mg/dL).

Caution must be taken when using fibrates concomitantly with statins as there is an increased risk of myopathic adverse reactions (myopathy and rhabdomyolysis) and liver toxicity, particularly in elderly patients and those with diabetes. These adverse reactions may be less common with the use of fenofibrate compared to gemfibrozil. In addition, fibrates may interact with medications such as warfarin, and dose adjustment for these medications is necessary to avoid adverse events.

Summary

Hypertriglyceridemia is associated with increased CVD risk. It is less clear, however, that elevated triglycerides play a causal role in CVD. Patients with elevated triglycerides should have a thorough evaluation of their overall CVD risk, and consideration of medical therapy to help achieve target LDL-C and non-HDL-C goals should be undertaken. Fibrates are one of the most effective triglyceride-lowering agents, and although studies have been somewhat mixed in demonstrating clear benefits of fibrates, it must be noted that no large clinical trial has been performed in patients with significantly elevated triglycerides (≥200 mg/dL) and that subgroup analysis of the current trials has suggested benefits in those patients with very elevated triglyceride (≥180–200 mg/dL) and low HDL levels (≤32–34 mg/dL). Fibrates are also indicated in those patients who have not reached their LDL-C goal despite optimal statin therapy.

β-Blockers

Background

Robust evidence exists for the use of beta-adrenergic antagonists, both in the setting of AMI and long-term post-MI. There are several other indications for β-blocker therapy, many of which occur concomitantly with atherosclerotic coronary disease. These include anti-anginal therapy, cardiac dysrhythmias, systolic heart failure, glaucoma, hyperthyroidism, portal hypertension, and systemic arterial hypertension.

Over the past 30 years, beta-adrenergic antagonists have become a mainstay of treatment for secondary prevention of MI. As a class, these agents have been shown to reduce the rate of recurrent MI, the incidence of SCD from ventricular arrhythmias, and both cardiovascular and all-cause mortality in individuals with prior STEMI. Recently, beta-adrenergic antagonists have demonstrated benefits in slowing the progression of atherosclerosis as measured by IVUS and may help in the stabilization of potentially vulnerable coronary artery plaques.

Pharmacology

Pharmacologically relevant β-receptor subtypes include β_1-, β_2-, and β_3-adrenoreceptors. Currently available β-blockers possess a wide range of adrenoreceptor subtype selectivity, although most have very little β_3-affinity. These compounds exert variable actions at their target sites, including competitive antagonism, local membrane stabilizing/anesthetic properties, K^+-channel blockade, intrinsic sympathomimetic/partial agonist activity, and potential antioxidative effects.[127]

The administration of β-blockers leads to several net cardiovascular effects in humans, based on their actions at receptor subtypes. These include reduction in heart rate (negative chronotropy), reduction of velocity and force of contraction (negative inotropy), and reduction in blood pressure regulated a by decrease in renin release from the renal juxtaglomerular apparatus. In addition, some currently prescribed formulations (e.g., labetalol and carvedilol) have α_1-antagonist properties, which lower systemic arterial resistance primarily via reduction in splanchnic smooth muscle tone.

The effects of β-blockers both within the cardiovascular system and in other tissues often limit their use and maximally tolerated dosages. β-Blocker use is often limited by low blood pressure or bradycardia. Both sinus and associated nodal inhibition can cause heart block, which represents an extreme of intended treatment effects. In patients with acutely decompensated heart failure, administration of β-blockers has the potential for worsening pump failure due to negative inotropy. In bronchial tissue, β_2 stimulation leads to smooth muscle relaxation and bronchoconstriction. Administration of β-blockers to patients with active asthma or chronic bronchitis can worsen bronchospasm, although this effect is less clinically significant with the so-called cardioselective β-blockers.

Indications for Coronary Artery Disease

β-Blockers have proven beneficial in many aspects of secondary prevention of CAD. The goals of treatment include reduction in anginal symptoms with a resulting improvement in quality of life, prevention of LV dysfunction, prophylaxis of ventricular arrhythmias, slowing the progression of atherosclerosis, and reducing the risk of recurrent ACS, SCD, and all-cause mortality. β-Blockers are also useful in the management of comorbidities, including hypertension, dysrhythmias, and systolic heart failure.

Chronic Stable Angina and Exercise Tolerance

β-blockers were initially developed to reduce angina associated with myocardial oxygen deprivation and MI. At rest, myocardial oxygen extraction is substantial, approximately 70%–80% of precapillary levels. Exercise is the most important stimulus for increased coronary oxygen extraction, and a substantial portion (50%–70%) of this is due to increase in heart rate to augment cardiac output in response to systemic demands. Increases in myocardial oxygen demand in the face of exercise are consequently largely met by increases in blood flow mediated by reduction in coronary vascular tone, augmenting flow rates by three to five times baseline levels in proportion to increases in heart rate.[128]

This vasodilatation becomes impaired in atherosclerotic coronary disease due to luminal narrowing from plaque formation and endothelial dysfunction due to impaired cell signaling pathways involved in nitric oxide (NO)-mediated vasodilatation. The result is impaired myocardial oxygen delivery, particularly when demand is higher, clinically manifested as exertional angina. β-Blockers mitigate oxygen supply/demand mismatch by reducing heart rate, contractility, and ventricular wall tension (the major determinants of oxygen demand).[129] β-blockers thus reduce myocardial oxygen consumption in the face of dynamic or fixed flow limitation, reducing symptoms of chronic stable angina.

Initial studies of healthy subjects given the prototypical beta-adrenergic antagonist, propranolol, found an adverse effect on exercise tolerance.[130] In later years, two randomized placebo-controlled trials of 23 individuals each with chronic stable angina given timolol at 10–30 mg twice daily versus placebo demonstrated significant reduction in anginal frequency and increase in exercise capacity.[131,132] In a subsequent randomized controlled trial of 77 individuals post-MI who were given either metoprolol succinate (target dose 200 mg daily) or placebo, there was a significant increase in maximal exercise capacity.[133]

Although there is no proven mortality benefit in patients with isolated chronic stable angina, β-blockers are frequently used for this indication over other agents (if only one agent is to be chosen) because of their impact on mortality and recurrent MI in patients with previous MI or systolic heart failure.

Prevention of Recurrent Cardiac Events, Reduction in Mortality

The most compelling evidence for β-blocker therapy post-MI lies in the effect on the rate of recurrent cardiac events and both cardiovascular and overall mortality. In the acute MI setting, β-blockers have been shown to reduce in-hospital mortality as well as long-term risk of cardiovascular death. In the randomized, placebo-controlled, double-blind Goteborg Metoprolol Trial, 1395 subjects with suspected AMI were randomly assigned to metoprolol (15 mg i.v. + 200 mg/day) or placebo for 90 days. The metoprolol group experienced a mortality reduction of 36%. All individuals were assigned open treatment with metoprolol at 3 months, but the group treated with metoprolol in the first 3 months maintained this survival benefit at 1 year. There was a reduction of infarct size in the subset who received metoprolol in the first 12 h of presentation and a 35% reduction of both fatal and nonfatal infarction during the next 90 days.[134]

The BHAT study (β-Blocker Heart Attack Trial), a randomized controlled trial of 3837 individuals given either propranolol (a nonselective β-blocker) or placebo post-MI at a dose of 180–240 mg/day, demonstrated a reduction in cardiovascular death and a relative reduction in all-cause mortality of 26%. Additionally, the propranolol group demonstrated a 28% relative reduction in SCD versus placebo, an important subset of cardiovascular mortality. Owing largely to rapid introduction and titration, side effects such as hypotension and symptomatic heart failure were more common in the treatment arm.[135]

The Norwegian study of timolol (another nonselective β-blocker) demonstrated similar benefits. This was a randomized, placebo-controlled trial of 1884 AMI survivors who were given timolol 10 mg twice daily or placebo. The treatment group demonstrated a 39.3% relative reduction in all-cause mortality, a 44.6% reduction in cardiovascular

mortality, and a relative reduction of 28% in the rate of recurrent cardiovascular events. As with the BHAT trial, the rate of clinically decompensated heart failure was higher in the timolol group.[136]

Multiple smaller randomized controlled trials have been performed with various agents in post-MI subjects. A meta-analysis of 23 of these heterogeneous trials indicated a 20% reduction in the risk of death post-MI with long-term oral beta-blockade.[137] This was corroborated by more recent large randomized controlled trials, specifically in individuals with depressed left-ventricular ejection fraction (LVEF) in addition to recent MI.

In the CAPRICORN trial (Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction), a multicenter, randomized, placebo-controlled trial of 1959 post-MI individuals with an LVEF of <40% who received carvedilol at a dose titrated to 25 mg twice daily or placebo, the carvedilol group demonstrated a 23% reduction in all-cause mortality versus placebo. There was no significant difference in the two groups in certain relevant secondary endpoints, including rates of subsequent hospitalization or sudden death.[138]

Another similar study, the MERIT-HF trial, investigated the effect of beta-adrenergic blockade in patients with known CAD post-MI. MERIT-HF was a double-blind, randomized trial of 1926 individuals with a history of hospitalization for AMI with New York Heart Association class II–IV systolic heart failure and an LVEF <40%. Subjects were treated with metoprolol succinate controlled release/extended release versus placebo. Administration of metoprolol succinate at a goal dose of 200 mg daily reduced total mortality by 40% and SCD by 50%. The combined endpoint of all-cause mortality/hospitalization for worsening congestive heart failure was reduced by 31% and cardiac death/nonfatal acute MI by 45%. A subsequent subgroup analysis of individuals with more severe heart failure, LVEF <20%, showed similar benefits.[139] In contrast to earlier studies indicating significant survival benefit in post-MI treated with β-blockers (Norwegian study of timolol and the BHAT trial of propranolol), the CAPRICORN and MERIT-HF trials indicate no increase and likely benefit in subsequent clinical heart failure and cardiovascular hospitalizations, respectively.

In addition, β-blockers have shown significant benefits in euvolemic patients with NYHA class III–IV symptoms and LVEF <25% whether due to ischemic or nonischemic cardiomyopathy. In the COPERNICUS trial, a randomized controlled trial of 2289 such individuals given oral carvedilol at a goal dose of 25 mg twice daily or placebo in addition to standard therapy, carvedilol reduced the combined risk of death or hospitalization for a cardiovascular reason by 27% and the combined risk of death or hospitalization for heart failure by 31%. In addition, the subjects given carvedilol spent 27% fewer days in the hospital for any reason and 40% fewer days in the hospital for heart failure. Importantly, these individuals were also less likely than those given placebo to experience worsening heart failure, SCD, cardiogenic shock, or ventricular tachycardia (VT).[140]

Ventricular Tachyarrhythmia Prophylaxis

Roughly 50% of all deaths after AMI are due to SCD. Sustained VT or ventricular fibrillation (VF) leading to SCD occurs in up to 7% of AMI survivors within 180 days, with the highest risk being within the first 30 days. The majority of these patients (83%) experience SCD after hospital discharge, underscoring the importance and challenge of effective prophylactic management of such devastating events.[141]

The VF threshold is pathologically reduced in ischemic myocardium, both acutely and long term. β-blockers have been shown, in animal models in which myocardial ischemia was induced, to increase VF threshold in a dose-dependent fashion, leading to myocardial electrochemical stabilization.[142] β-blockers attenuate the lowered VF threshold, increased metabolic demand, and ischemic supply/demand mismatch provoked by B1-adernergic stimulation. The most effective agents in reducing SCD have been metoprolol, timolol, carvedilol, and propranolol, all of which are also highly lipophilic agents.[143] This benefit is attributed to the ability of these agents to cross the blood–brain barrier and reduce central sympathetic outflow. In rabbit models, metoprolol was superior to the hydrophilic atenolol in the reduction of VF in subjects with pharmacologically induced hyperadrenergic states and coronary artery ligation despite having similar effects on the degree of myocardial ischemia.[182]

There is a survival benefit in AMI patients treated with β-blockers in both the immediate post-MI period and long term. The overall impact of the effect is a 30%–50% reduction in mortality,[134–140] much of which is due to a reduction in SCD. Despite this, β-blockers remain underprescribed, particularly acutely in AMI patients who develop sustained VT/VF in hospital. In data from the Valsartan in Acute Myocardial Infarction Trial (VALIANT) registry, 5391 patients were evaluated for the incidence of sustained VT/VF and treatment rate/outcomes with β-blocker administration. Sustained VT/VF occurred in 5.7% of patients, with an in-hospital mortality rate of 20.3%. Only 55.2% of individuals were administered beta-blockade within the first 24 h, but those patients had an absolute risk reduction of 5.8% for in-hospital death, indicating an important immediate treatment benefit. It should be noted that AMI patients with sustained VT/VF were significantly less likely to receive β-blocker therapy than those without.[144]

Summary

Given the cumulative benefits in patients with known CAD, the ACC/AHA guidelines recommend indefinite use of a beta-adrenergic antagonist in all patients (except low risk) without contraindications post-STEMI (class I/LOE A); they should be strongly considered in low-risk patients post-STEMI (class IIa/LOE A).[23]

The most commonly prescribed agents for the secondary prevention of CAD include metoprolol tartrate, metoprolol succinate (which has added benefit in patients with comorbid systolic heart failure), and carvedilol. The dosage of the β-blocker chosen should be adjusted to attempt to achieve a

resting heart rate of 55–60 beats/min.[145] This goal is sometimes unachievable due to hypotension that is often more pronounced in agents with significant α_1-antagonist properties. Administration should begin with low doses titrating upward with a goal of reaching the doses found efficacious in recent randomized controlled trials: 200 mg daily for metoprolol succinate,[134,139] and 25 mg twice daily for carvedilol.[138,140]

Angiotensin-Converting Enzyme Inhibitors

Background and Pharmacology

The renin–angiotensin–aldosterone system (RAAS) mediates several important short- and long-term physiologic processes. Renin is released by the renal juxtaglomerular apparatus (as well as extrarenal tissues) in response to low glomerular perfusion, sympathetic autonomic stimulus, or decreased tubular delivery of chloride at the level of the juxtaglomerular apparatus.[146] Renin cleaves angiotensinogen to yield angiotensin I, which is in turn converted to the active angiotensin II by ACE.

There are two components of the RAAS in humans: circulating and tissue. Physiologically, in the setting of hypotension or hypovolemia, the circulating RAAS acts to preserve organ perfusion and prevent hemodynamic collapse. RAAS activation causes peripheral vasoconstriction, release of aldosterone with resulting renal sodium and water conservation, and increase in sympathetic tone and release of vasopressin from the posterior pituitary resulting in further peripheral vasoconstriction and antidiuresis. These actions are mediated in vivo by angiotensin II stimulating AT1 receptors found in cardiovascular, adrenal, and renal tissues. In contrast, AT2 receptors are found in many other tissues, including fetal tissues, vascular endothelium, and interstitial fibroblasts of adult myocardium. The tissue component of the RAAS is chronically operative at the local tissue level, notably within myocardium.[147] The expression of myocardial AT2 receptors is up-regulated in the setting of atherosclerosis, ischemia, infarction, and heart failure.[148] Long-term stimulation of AT2 receptors may play a role in myocardial remodeling and fibrosis, as well as physiologic antagonism of AT1 receptors, impairing normal circulatory and hemodynamic physiology.[149]

ACE is also responsible for degradation of bradykinin, a product of the kallikrein–kinin system that causes vasodilatation through the synthesis of NO and vasodilatory prostaglandins. The inhibition of bradykinin degradation leads to the ACE inhibitor-associated cough seen in many patients who are prescribed these agents.

The development of ACE inhibitors followed the isolation of a family of peptides named bradykinin-potentiating factors from the venom of the Brazilian viper, *Bothrops jararaca*, by Ferreira and Green in 1970 after the observation that human plasma incubated with viper venom yielded a substance capable of producing hypotension.[150,151] The chemical structure and synthesis were published in 1971[152] when it was noted that these peptides also blocked conversion of angiotensin I to angiotensin II.[8] The first ACE inhibitor that is still in use today, captopril, entered clinical trials in 1977.[150]

As expected, inhibition of ACE leads to decreased systolic and diastolic blood pressures, reduction of preload and afterload, and decrease in bradykinin degradation. There is negligible effect on cardiac output if any. The effects of various agents within this class depend on their ability to distribute into extravascular tissues and various other pharmacokinetic properties. Some agents may demonstrate additional benefits such as plaque stabilization, potentiation of NO and prostaglandin-mediated vasodilatation, mitigation of LV hypertrophy and smooth muscle proliferation, decreased coronary vasoconstriction, and antimacrophage function.[147]

Indications for Secondary Prevention of Coronary Artery Disease

Post-MI with LV Dysfunction

There is a large body of evidence that underscores the benefit of ACE inhibitors in AMI, which is outside the scope of this discussion. Survivors of MI with signs of cardiac damage, particularly LV systolic dysfunction, comprise the other major subgroup of CAD patients who derive benefit from ACE inhibitor therapy in both short- and long-term studies.

The RAAS and sympathetic nervous system (SNS) are activated within hours of AMI,[136] leading to increased systemic vascular resistance, increased heart rate, myocardial wall stress, and coronary vasoconstriction. This is particularly true in patients with complicated clinical courses when compared to uncomplicated MI.[153] This can result in increased risk of ventricular dysrhythmia, infarct expansion, adverse LV remodeling, progressive LV dilatation, and increased risk for myocardial rupture in the immediate post-AMI period. In particular, LV dysfunction and persistent SNS and RAAS activation have been shown to be major determinants of mortality after AMI.[154–157] Small studies also suggest that RAAS blockade improves coronary flow reserve and ability to meet increased oxygen demand.[158]

Several small early trials showed benefit in the use of ACE inhibitors to target RAAS-mediated LV remodeling and dilatation in the hope of reducing heart failure and mortality in AMI survivors. These trials focused on echocardiographic and hemodynamic parameters of LV function, such as end systolic and diastolic volumes as well as ejection fraction. Benefit with early initiation of ACE inhibitors in survivors of MI was noted, particularly in patients with depressed ejection fraction.[159–161]

ACE inhibitor therapy in AMI survivors with LV dysfunction was studied longitudinally in the Survival and Ventricular Enlargement (SAVE) trial. In this double-blind, placebo-controlled study, 2231 subjects with prior AMI and LVEF <40% without clinical heart failure were randomly assigned to treatment with captopril titrated to target dose of 25 mg three times daily or placebo in addition to standard therapy. The average follow-up was 42 months. Individuals treated with captopril experienced a 19% relative reduction

in all-cause mortality (p = 0.019), as well as significant reductions in both fatal and nonfatal vascular events including recurrent MI (RRR, 25%; p = 0.015) and heart failure (RRR, 37%; p = <0.001).[162] These results indicated significant additional benefit in patients already on standard treatment, including β-blockers and aspirin. The Acute Infarction Ramipril Efficacy (AIRE) trial evaluated the effect of RAAS blockade with ACE inhibitors in 2006 individuals with a history of AMI and clinical heart failure (regardless of LVEF) followed for an average of 15 months. Subjects were randomly assigned ramipril with a goal dose of 5 mg twice daily or placebo in addition to standard therapy. Mortality from all causes was significantly reduced in the ramipril group with an RRR of 27% (p = 0.002). Secondary outcomes including MI, heart failure, and stroke were reduced by 19% (p = 0.008), further supporting the role of ACE inhibitor therapy in post-MI patients with either symptomatic heart failure or LV dysfunction.[20,163]

These studies were followed by much larger multicenter trials. The GISSI-3 trial evaluated the benefit of ACE inhibitor therapy added to standard therapy in 19,394 AMI survivors randomized to lisinopril alone, nitrates alone, lisinopril plus nitrates or placebo. At 6 weeks, there was an 11% relative reduction in mortality, as well as reduction in rates of LV dysfunction (defined as EF <35%) in the lisinopril group.[164] Similarly, the Fourth International Study of Infarct Survival (ISIS-4) followed 58,050 AMI survivors randomized to captopril at a goal dose of 50 mg three times daily, mononitrate therapy, or placebo initiated within 24 h of AMI and continued for 1 month. The captopril group not only demonstrated a 7% relative reduction in mortality at 5 weeks but also showed mortality benefit at 12 months despite cessation of therapy after 28 days.[164] These studies confirmed the benefit of early initiation of ACE inhibitor treatment in all AMI survivors, with particular benefit in high-risk patients, including those with prior history of MI or LV dysfunction.

Coronary Atherosclerosis with No History of AMI or LV Dysfunction

Given the clear benefit in AMI, LV dysfunction, and post-MI survival and morbidity, several subsequent trials sought to evaluate the role of ACE inhibitor therapy in patients with known coronary disease without a history of MI or LV dysfunction. The Heart Outcomes Prevention Evaluation Study (HOPE), European trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease (EUROPA), and Prevention of Events with ACE inhibition (PEACE) trials examined the benefit of ACE inhibitors in patients with stable coronary disease or high risk for future cardiovascular events.[165–167] Although there were conflicting results with regard to cardiovascular benefit in these studies, a meta-analysis of the pooled 29,805 subjects indicated that ACE inhibitors significantly reduced all-cause mortality (7.8% vs. 8.9%, p = 0.0004), cardiovascular mortality (4.3% vs. 5.2%, p = 0.0002), nonfatal MI (5.3% vs. 6.4%, p = 0.0001), all stroke (2.2% vs. 2.8%, p = 0.0004), heart failure (2.1% vs. 2.7%, p = 0·0007), and need for coronary artery bypass surgery (6.0 vs. 6.9%, p = 0.0036), confirming their role in both the primary and the secondary prevention of CVD.[168]

Adverse Reactions

Possible adverse drug effects of ACE inhibitors include hypotension, hyperkalemia, increase in serum creatinine, and ACE inhibitor-associated cough, a common reason for discontinuation of therapy. The development of cough in association with ACE inhibitors occurs in 5%–20% of subjects, most commonly occurring within the first 6 months of treatment and recurring with rechallenge with any ACE inhibitor. Proposed mechanisms include inhibition of ACE-mediated bradykinin degradation and accumulation of substance P and prostaglandin E2. Bradykinin can cause bronchial irritation and histamine release from mast cells, although the variable incidence in patients, the lack of detectable rise in serum bradykinin levels, and preponderance in women cast some doubt on the feasibility of this mechanism.

Clinically, patients taking ACE inhibitors may have many potential causes of new-onset cough, but discontinuation of ACE inhibitors or change to an angiotensin receptor blocker (ARB) is an appropriate first step due to the frequency of this side effect and the usually prompt cessation of symptoms (usually 1–4 days, although as long as 4 weeks) to obviate the need for extensive diagnostic workup.[169]

Although uncommon, one of the most serious adverse reactions related to ACE inhibitor therapy is angioedema. Most commonly, this includes symmetric swelling of the tongue, lips, face, and/or proximal aerodigestive mucous membranes, but can sometimes present as isolated laryngeal or gastrointestinal edema. This phenomenon has been described in patients on long-term therapy with ACE inhibitors, although it more commonly occurs soon after treatment initiation. Patients with hereditary or other acquired forms of angioedema are more likely to develop this problem. Patients who develop angioedema while taking ACE inhibitors should not be rechallenged with other ACE inhibitors. The association between ARBs and angioedema has been described, and although infrequent, this risk should be taken into consideration when contemplating change to ARB therapy in patients with ACE inhibitor-associated angioedema.[170]

Summary

Inhibition of the RAAS in patients with coronary disease with ACE inhibitors has been shown to be effective in patients with atherosclerosis with or without MI, survivors of AMI regardless of LV function, and patients with echocardiographic or symptomatic LV dysfunction. In the secondary prevention of CAD, the ACC/AHA guidelines state that an ACE inhibitor should be prescribed at discharge for all patients without contraindications after STEMI (class 1/LOE A). ARBs are an acceptable alternative in patients intolerant of ACE inhibitors with either clinical or radiological signs of heart failure and LVEF <0.40. Valsartan and candesartan have established efficacy for this recommendation, but with less robust evidence (class I/Level of Evidence: B).[23]

INEFFECTIVE THERAPIES

B Vitamins

Homocysteine has been implicated in many observational studies as an independent risk factor for CVD.[171,172] Homocystenemia leads to production of abnormal proteoglycans in the elastic fibers of arterial walls and the deposition of lipid droplets. In addition, calcium ions and excess sulfate groups of proteoglycan molecules facilitate calcification on arterial walls.[173] Homocysteine is an essential amino acid that is metabolized and converted to either cysteine or methionine. B vitamins, such as folic acid, B_{12}, and B_6, are essential cofactors in these metabolic pathways. It was hypothesized that supplementing with B vitamins may enhance metabolism of homocysteine to cysteine or methionine, thereby decreasing serum homocysteine concentrations and cardiovascular risk. Intervention trials and subsequent meta-analysis did confirm that supplementing with folic acid and B_{12} was associated with significant homocysteine-level reduction of 25% and 5%, respectively, while B_6 did not.[174] However, RCTs have not demonstrated a decrease in MI, coronary revascularization, or CVD mortality, despite a decrease in homocysteine levels.[174,175]

Though B vitamin supplementation is well tolerated in low doses of 1 mg/day, larger doses of 5 mg/day or more can cause abdominal cramps. Doses of >15 mg/day can cause disturbed sleep patterns, irritability, confusion, nausea, flatulence, and increase in seizure frequency.[122] Some RCTs may even suggest an increase in cardiovascular events, incidence of prostate cancer, breast cancer in women, or mental decline in patients greater than 65 years of age.[122,176] The routine use of B vitamins for secondary prevention is currently not recommended.

Antioxidants

According to the "oxidative-modification theory" of atherosclerosis, a central mechanism in the development of atherosclerotic plaque involves oxidation of LDL and accumulation of modified LDL in the subendothelial space.[177] Furthermore, oxidized LDL causes a direct increase in chemotactic activity of endothelial cells by inducing the production of chemokines, attracting monocytes and macrophages. In addition, complete lipid peroxidation of LDL by monocytes and macrophages further induces scavenger receptors on macrophages to internalize LDL forming foam cells. Several vitamins, mainly vitamin E, C, and beta-carotene, have been reported to reduce LDL oxidation. However, supplementing with vitamin E, C, and beta-carotene has not reduced CVD morbidity and mortality in primary and secondary prevention and may increase all-cause mortality and CVD mortality in postmenopausal women.[178,179] Furthermore, combining antioxidant supplements with statin and niacin blunted the lipid-modifying benefits of statin–niacin.[115] Thus, routine use of antioxidant supplementation for CVD prevention is not recommended.

Estrogens

The use of estrogen in the prevention of CVD has changed over the last three decades with the emergence of data from large placebo-controlled clinical trials centering on its use. Practice guidelines in the early 1980s and 1990s relied largely on observational studies that noted reduced all-cause mortality[180] and CHD risk[181–183] in women that reported to have used estrogen hormone therapy. However, two landmark trials, the Women's Health Initiative (WHI)[184,185] and the Heart and Estrogen-Progestin Replacement Study (HERS)[186] were pivotal in reversing these guidelines.

The use of estrogens in the secondary prevention of CHD was addressed in HERS. It analyzed conjugated equine estrogen (CEE) (0.625 mg/day) combined with daily medroxyprogesterone acetate (MPA) (2.5 mg/day) versus placebo in 2763 women aged less than 80 years (mean age, 67 years) with an intact uterus and prior diagnosis of CHD. Results demonstrated no significant differences between groups in the primary outcome (MI or CHD death) (HR, 0.99; 95% CI, 0.80–1.22) or in any of the secondary cardiovascular outcomes. A 3 year extension of HERS showed no evidence of later protection (relative hazard after 6.8 years of follow-up 1.00; 95% CI, 0.77–1.29).[187] The Estrogen Replacement and Atherosclerosis (ERA) trial demonstrated no benefit of CEE (0.625 mg/day), alone or combined with 2.5 mg/day MPA, on angiographic progression of disease in 309 women with angiographically verified coronary disease (mean age 65.8 years).[188,189]

Based on results largely centered around WHI and HERS, the 2011 AHA update on the Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women recommend that hormone therapy and selective estrogen-receptor modulators (SERMs) should not be used for the primary or secondary prevention of CVD (*class III, Level of Evidence A)*.[190]

CONCLUSION

The treatment of atherosclerotic CVD has long been focused on mechanical interventions (Table 86.4). These mechanical interventions began with the advent of coronary artery surgery in 1967 and the first coronary intervention in 1977. The past 40 or so years have been dominated by these two approaches to coronary revascularization. These techniques have been a major focus of treatment despite limited randomized clinical trial data to demonstrate their efficacy. Recently published studies such as the COURAGE and BARI 2-D trials have cast doubts on the ability of these techniques to significantly reduce mortality in most populations beyond optimal medical and lifestyle therapy. Importantly, pharmacologic therapy for clinically stable atherosclerotic coronary disease has significantly advanced. This chapter highlights a number of these medications including aspirin and other antiplatelet drugs, β-blockers, and a variety of non-statin lipid-lowering agents such as omega-3 fatty acids, niacin, and fibrates. No class of drugs, however, has had more

TABLE 86.4
Optimal Medical Therapy in Secondary Prevention of Cardiovascular Disease

ACC/AHA Goals for Secondary Prevention in Patients with CVD

	Target Goals and Level 1 Therapeutic Recommendations
Smoking	Complete cessation. No exposure to environmental tobacco smoke
Blood pressure	<140/90 or <130/80 if patient has diabetes or chronic kidney disease
Lipids	LDL-C < 100 mg/dL if TG ≥ 200 mg/dL; non-HDL-C should be <130 mg/dL
Physical activity	30 min, 7 days/week (minimum 5 days/week)
Weight	Body mass index: 18.5–24.9 kg/m^2; waist circumference: men < 40 in.; women < 35 in.
Diabetes	HbA1c < 7%
Antiplatelet agents	*Aspirin*: 75–162 mg/day and continue indefinitely in all patients unless contraindicated
	Clopidogrel or prasugrel or ticagrelor: in combination with aspirin for up to 12 months in patients with acute coronary syndrome or percutaneous stent placement
Anticoagulation	*Warfarin*: for paroxysmal or chronic atrial fibrillation or flutter, and in post-myocardial infarction when clinically indicated (e.g., atrial fibrillation, left ventricular thrombus)
Renin–angiotensin–aldosterone system blockers	*ACE inhibitors*: start and continue indefinitely for all patients with left ventricular ejection fraction ≤40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated
	Angiotensin receptor blockers: those intolerant to ACE inhibitors and who have heart failure or in those with previous myocardial infarct and left ventricular ejection fraction ≤40%
	Aldosterone blockade: use in post-myocardial infarction patients, without significant renal dysfunction[a] or hyperkalemia,[b] who are already receiving therapeutic doses of an ACE inhibitor and β-blocker, have a left ventricular ejection fraction ≤40%, and have either diabetes or heart failure
β-Blockers	Start and continue indefinitely in all patients who have had myocardial infarction, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated
Influenza vaccination	Patients with cardiovascular disease should have an influenza vaccination

Source: Adapted from Smith, S.C., Jr. et al., *Circulation*, 113(19), 2363, 2006.

[a] Creatinine should be 2.5 mg/dL in men and 2.0 mg/dL in women.

[b] Potassium should be 5.0 mEq/L.

dramatic an effect on the history of coronary disease than has statins. Unfortunately, these potentially lifesaving medications remain suboptimally prescribed and used. It is our hope that education of physicians and patients will achieve a more complete implementation of these life-prolonging pharmacologic therapies.[180,181]

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87 Exercise-Based Cardiac Rehabilitation
Outcomes and Expectations

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CONTENTS

Potential Benefits of CRET....1101
Exercise Capacity....1101
Lipids and Inflammation....1102
Obesity Indices....1103
Psychological Risk Factors....1103
Major Morbidity and Mortality....1105
Benefits of CRET in HF....1105
Conclusions....1105
References....1106

Considerable data from both observational studies as well as randomized controlled trials (RCTs) have demonstrated the significant benefits of physical activity, exercise training (ET), and overall cardiorespiratory fitness (CRF) in both the primary and secondary prevention of coronary heart disease (CHD).[1,2] We and others have published on the marked benefits obtained from formal cardiac rehabilitation and ET (CRET) programs in patients with established CHD, especially after CHD events.[1–6] However, despite the very clear benefits of formal, supervised outpatient CRET programs, as well as intense efforts to improve referrals to these programs, current statistics continue to demonstrate poor overall referral and participation rates for eligible patients, with dismal participation in rural areas and in patients with lower socioeconomic status, limited levels of higher education, as well as females and elderly patients.[1,2,7]

In this chapter, we discuss the proven benefits of formal CRET programs in the secondary prevention of CHD, including the impact on various CHD risk factors, psychological benefits, as well as the effectiveness of this therapy in reducing major CHD events.

POTENTIAL BENEFITS OF CRET

A broad range of patients, with differing clinical characteristics, benefit from formal CRET programs, which are summarized in Table 87.1. Although occasionally CRET programs are altered due to the individual needs of patients, the majority of documented benefits are from programs that last for 12 weeks, consisting of 3 educational and exercise sessions weekly, for a total of 36 outpatient education and exercise sessions.[2,8] Although most of the attention in CRET programs is directed at the exercise, especially aerobic exercise, it must be emphasized that formal CRET programs also involve resistance training, which is important to maintain strength with aging and improve insulin sensitivity and quality of life,[8] as well as dietary therapy and other behavioral interventions directed at multiple CHD risk factors, thus enabling both the patient and their family members to exert more control over the disease process and its management.[2,8] Finally, considerable focus in CRET programs is also directed at psychological aspects of CHD.[9] Therefore, the benefits obtained from formal outpatient CRET programs is likely the result of the combined impact of all of these components of the program.

EXERCISE CAPACITY

Perhaps one of the most important benefits of formal CRET programs are improvements in aerobic exercise capacity and major parameters of CRF.[1–3] Although there is variability in the improvements in CRF following CRET, on average a 35% improvement in estimated aerobic exercise capacity (defined as estimated metabolic equivalents or METs) has been observed. Our studies, however, have noted a considerable discrepancy between estimated METs and CRF that is precisely and directly measured by cardiopulmonary gas exchange, including peak oxygen consumption (peak VO_2 or peak measured METs).[10–12] Since this terminology can be confusing, we prefer to define CRF as either estimated METs (when estimated based on incline and speed on the treadmill by validated equations) or measured peak VO_2. Typically, studies have demonstrated that estimated METs significantly overestimate true CRF both before but, particularly, after ET. Nevertheless, despite these discrepancies, both studies that have estimated METs as well as those precisely measuring peak VO_2 have demonstrated that

TABLE 87.1
Benefits of CRET Programs

- Improvement in exercise capacity
  - Estimated METs, +35%
  - Peak VO_2, +15%
  - Peak anaerobic threshold, +11%
- Improvement in lipids
  - Total cholesterol, −5%
  - Triglycerides, −15%
  - HDL-C, +6% (+13% to +16% increase in subgroups with low HDL-C levels)
  - LDL-C, −2%
  - LDL-C/HDL-C, −5% (higher in some subgroups)
- Reduction in inflammation (hs-CRP, 40%)
- Reduction in obesity indices
  - Body mass index, −1.5%
  - Percent fat, −5%
  - Metabolic syndrome, −37%
- Improvements in behavioral characteristics (depression, anxiety, somatization, and hostility)
- Improvement in autonomic tone
- Improvement in blood rheology and viscosity
- Reduction in homocysteine levels
- Improvements in overall quality of life and its components
- Reduction in hospitalization costs
- Reduction in psychological distress (total, depression, anxiety, and hostility)
- Reduction in overall morbidity and mortality after MI and PCI, as well as HF

measures of CRF potently predict major clinical prognosis and mortality.[1–3,12] In fact, in studies of CRET of nearly 15,000 men and women, every 1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ increase in directly measured peak VO_2 was associated with a 10% reduction in major cardiovascular (CV) mortality.[13,14] In one major study, mortality fell by 2% for every 1% increase in peak VO_2 that occurred as a result of ET.[15] Numerous studies and meta-analyses have demonstrated a very powerful relationship between estimated exercise capacity and major CV events and all-cause mortality.[16] Although patients with low baseline exercise capacity generally obtain considerably greater improvement in exercise capacity following formal CRET programs, we have demonstrated that even patients with relatively high baseline exercise capacity still obtain marked improvements following CRET.[17]

LIPIDS AND INFLAMMATION

In order to obtain goal levels of low-density lipoprotein cholesterol (LDL-C), most current patients with CHD are taking statin medications,[18–20] and, therefore, improvements in LDL-C with CRET are fairly minimal. However, many CHD patients also do not have optimal levels of high-density lipoprotein cholesterol (HDL-C) and/or triglycerides (TGs) that can significantly improve with CRET. Although improvements may average +6% for HDL-C and −15% for TGs, respectively, after CRET, considerably greater improvements have been noted in subgroups of patients who have more abnormal baseline lipid values.[21–24] Many patients with CHD have "isolated" low levels of HDL-C with relatively normal or borderline-elevated LDL-C and/or TGs, and these patients are often thought to be relatively resistant to nonpharmacological and pharmacological regimens. In these patients, however, we have reported fairly marked improvements in HDL-C (+17%) and LDL-C/HDL-C (−11%) following formal CRET.[22]

Many studies have demonstrated the significance of systemic inflammation, especially assessed by levels of C-reactive protein (CRP).[25,26] We have recently reviewed the potential improvements of CRP in both primary and secondary CHD prevention, as well as the potential roles of physical activity, ET, and overall CRF on inflammation, especially levels of CRP.[27] In a study of 277 patients with CHD, evaluating 235 CRET completers and 42 "controls" with CHD, we demonstrated that CRET was associated with a nearly 40% reduction in CRP (Figure 87.1).[28] We also demonstrated that CHD patients with the metabolic syndrome (MS) had a nearly twofold higher level of CRP compared with CHD patients without MS, and both groups of patients had nearly a 40% reduction in CRP following CRET.[29] This reduction in CRP, however, was 43% following CRET in 73 obese patients with CHD, whereas there was a nonsignificant 19% reduction noted in 72 lean CHD patients, indicating an interaction between CRET-induced reductions in systemic inflammation and body habitus.[30] To further support this hypothesized interaction, in a more recent study of 529 patients with CHD who completed CRET, 393 overweight/obese subjects were assessed for the relationship between weight loss and change in CRP. In the 196 overweight/obese who had more than the

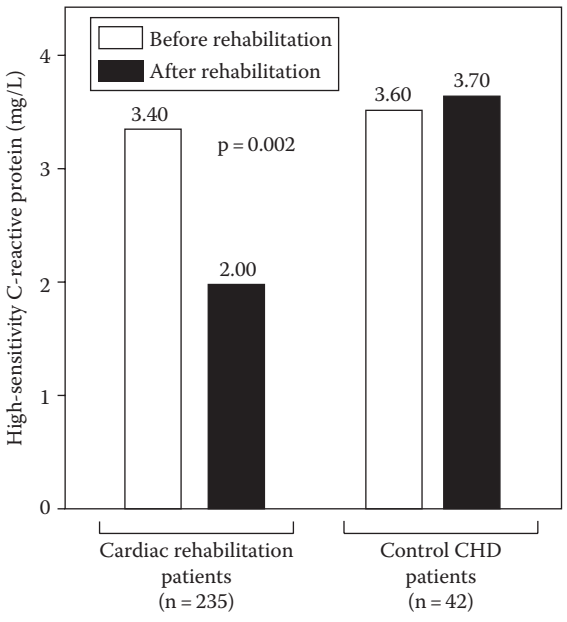


FIGURE 87.1 Median changes in high-sensitivity CRP in cardiac rehabilitation and in control patients with CHD. (From Milani, R.V. et al., *J. Am. Coll. Cardiol.*, 43, 1056, 2004. With permission.)

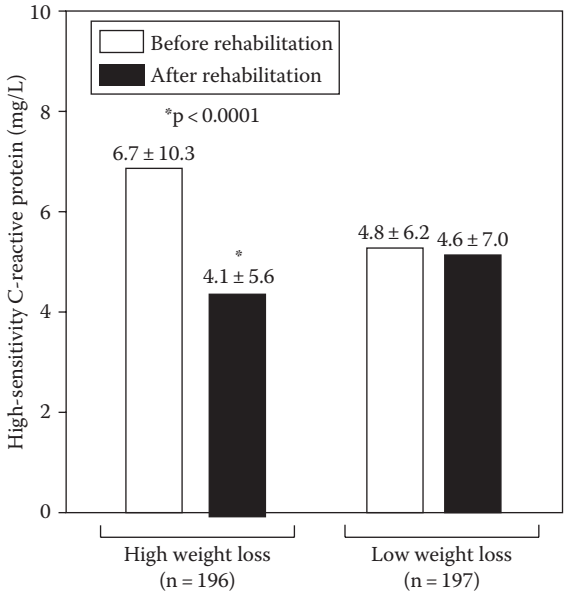


FIGURE 87.2 Mean levels of high-sensitivity CRP before and after CRET in 393 overweight and obese patients with CHD divided by median weight loss. (From Lavie, C.J. et al., *Am. J. Med.*, 122, 1106, 2009. With permission)

median weight loss (average reduction in weight 5%) during CRET, a 40% reduction in CRP was noted; on the other hand, the 197 overweight/obese without significant weight loss during CRET had only a nonsignificant 6% reduction in CRP (Figure 87.2).[31] Moreover, in a study by Caulin-Glaser et al.,[32] patients with CHD who participated in formal CRET programs have significant improvements in CRP that were independent of gender, age, or presence of MS. Ades et al.[33] also showed a significant 16% reduction in CRP in patients with CHD following CRET, but they failed to demonstrate any differences between high and lower exercise intensity and CRP reductions, despite the fact that higher intensity (or high-caloric-expenditure) exercise promoted greater weight loss. Collectively, these results suggest that CRET significantly reduces levels of CRP. Although generally CRP reductions appear to be more marked when accompanied by significant weight loss, there does not appear to be a significant direct impact on exercise intensity and reduction in overall inflammation.

OBESITY INDICES

Clearly, overweightness and obesity are increasing at alarming and epidemic proportions in the United States as well as most other Westernized/industrialized societies.[34] A potential benefit of formal CRET programs is the promotion of weight reduction in the large number of CHD patients who are overweight or obese, as well as those patients who meet criteria for MS. Despite the obesity paradox that our group has published extensively on,[31,34–45] we believe that many studies, including from our CRET programs, have established the efficacy and safety of purposeful weight reduction for patients with CHD.[46] In the large number of CHD patients who are at risk for MS, we have demonstrated that following formal CRET programs, there was a 37% reduction in the prevalence of definite MS.[29]

Several studies from cohorts of patients with CHD have supported the benefits of weight reduction in secondary prevention. In a small group of 45 obese patients from our CRET program who achieved 5% or greater weight loss during CRET (for an average of 10%), we noted greater improvements in exercise capacity and plasma lipids compared with 81 obese who did not lose weight.[47] In a more recent larger study from our CRET center, we noted that overweight/obese patients who lost weight showed significantly greater improvements in most of their CHD risk factors, including plasma lipids, fasting glucose, and inflammation (as discussed previously).[31] Although consistent with the obesity paradox, the overweight and obese CHD patients in secondary prevention have lower mortality compared to their lean counterparts; nevertheless, the lowest mortality appears to be present in the overweight/obese who successfully lose weight during CRET. A recent study of 377 consecutive CHD patients from the Mayo Clinic's CRET program demonstrated that weight reduction was associated with benefits on total mortality plus major CV events, even among those with a body mass index of less than 25 kg m^{-2}, as well as in those who are overweight or obese.[48] In a study by Ades et al.[33] of 74 overweight CHD patients enrolled in a high-intensity, high-caloric-expenditure ET program, as opposed to standard CRET, the authors demonstrated that those in the high-energy-expenditure group had twofold greater reductions in weight loss that was associated with reduced insulin resistance (including decreases in measures of insulin), improved lipids (increases in HDL-C and reductions in TGs and total cholesterol/HDL-C), as well as reduced blood pressure and plasminogen activator inhibitor I, which promotes systemic fibrinolysis.

Although collectively these studies and other recent reports,[31,34,46–49] support the efficacy and safety of purposeful weight loss in patients with CHD, there are limited data from large studies assessing weight loss in CHD. However, a study of over 1500 CHD patients demonstrated that intentional weight loss from a 6 month dietary program without specific ET produced a lower incidence of CHD events over a 3 year follow-up.[49]

PSYCHOLOGICAL RISK FACTORS

Although the lay public has generally been extremely interested in the impact of psychological stress (PS) on both general and, in particular, CV health, this topic has been greatly under-emphasized by clinicians, especially among those involved in the prevention and treatment of patients with CV diseases.[9,50] Clearly PS is an important risk factor for CHD and impacts prognosis following major CHD events.

Perhaps the most impressive data to date on the role of PS and CHD come from the INTERHEART study,[51] which evaluated CHD risk factors and PS among a diverse group of

over 11,000 MI patients and nearly 14,000 age and gender-matched controls from 52 countries in 262 centers. This landmark study demonstrated that among nine major modifiable CV disease risk factors, PS was ranked only below lipids and smoking in overall importance, accounting for almost one-third of the total attributable risk.

We have demonstrated a high prevalence of PS risk factor in CHD patients,[52–64] with marked benefits following CRET (Figure 87.3).[53] However, those patients who remained depressed following CRET had a fourfold higher mortality (20% vs. 5%; $p < 0.001$) during 3 year follow-up.[61] Among the group of patients with baseline depression who completed CRET, mortality was 73% lower (8% vs. 30%; $p < 0.001$) compared with a control group of depressed patients who did not participate in formal CRET. Perhaps more importantly, we demonstrated that patients who did not improve CRF, as determined by peak VO_2, after CRET have a high prevalence of depression and a high mortality risk, whereas those who either slightly improved CRF (<10% improvement in peak VO_2 following CRET) or who markedly improved CRF (≥10% improvement in peak VO_2 after CRET) had marked reductions in both depression and mortality during follow-up (Figure 87.4).[61] We believe that these results suggested only mild improvements in CRF are needed to reduce both depression and depression-related increased mortality. Although our results are obtained in CHD patients in CRET (secondary prevention), we believe that these results may also be applicable to the large number of patients with depression in primary prevention who also are at increased risk of major CV events.

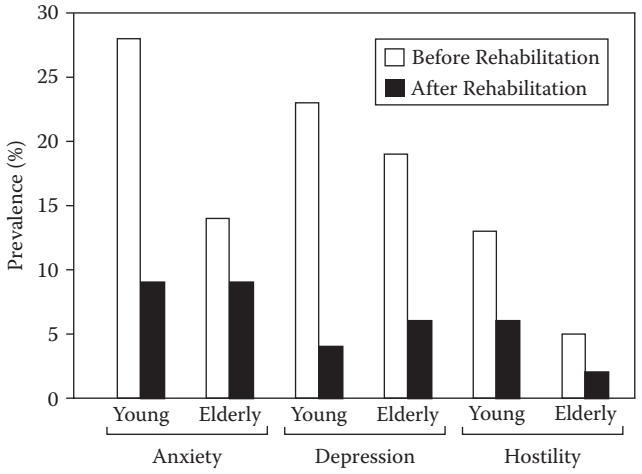


FIGURE 87.3 Impact of formal cardiac rehabilitation and ET programs on prevalence of adverse PS parameters (anxiety, depression and hostility) in older and younger patients with CHD. (Data adapted from Lavie, C.J. and Milani, R.V., *Arch. Intern. Med.*, 166, 1878, 2006.)

Very recently, we assessed the impact of ET and depression on survival in patients with CHD and significantly reduced left ventricular ejection fraction.[62] Similar to non-heart failure (HF) patients, depression symptoms fell by 40% after CRET. Among those HF patients who remained depressed following CRET, the mortality was fourfold higher (43% vs. 11%; $p < 0.001$) compared to those whose depression resolved with CRET. Depressed HF patients who completed CRET had nearly 60% lower mortality compared with depressed HF patients who did not complete CRET (18% vs. 44%; $p < 0.05$).

Our data have also demonstrated the benefits of formal CRET in patients with high levels of total PS.[63,64] Not only do CHD risk factors markedly improve following CRET in patients with high PS,[63] but there are also marked benefits on survival.[64] In fact, almost all of the mortality during follow-up in our CRET patients was noted in those with high PS who did not significantly improve CRF following CRET. Patients with low PS had lower mortality during 3 year follow-up, as did those with high PS who improved their level of CRF during CRET.[64]

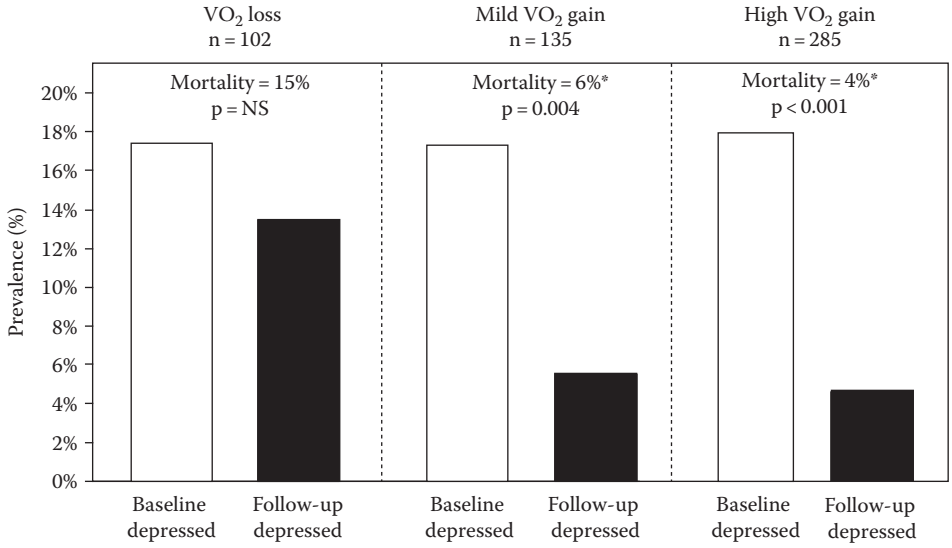


FIGURE 87.4 Prevalence of depression and subsequent mortality based on changes in peak VO_2 during cardiac rehabilitation and ET. *$p < 0.001$ compared with VO_2 loss. (From Milani, R.V. and Lavie, C.J., *Am. J. Med.*, 120, 799, 2007. With permission.)

MAJOR MORBIDITY AND MORTALITY

Perhaps one of the most important benefits of formal outpatient CRET programs is on major CV morbidity and mortality. Many individual trials of CRET have not been large enough or long enough to adequately determine major CV end-points, but several large meta-analyses have attempted to address these issues. O'Connor et al.[65] in 1989 performed a meta-analysis of 22 RCTs of CRET in 4554 post-MI patients followed for an average of 3 years following CRET. Compared with controls, those randomized to formal CRET programs had significant reductions in total mortality, CV mortality, and future MI of between 20% and 25%. Additionally, there was a statistically significant 37% reduction in the risk of sudden cardiac death after 1 year, with trends in favor of CRET at 2 and 3 years, which were not statistically significant. A more recent meta-analysis of 32 RCTs in 8440 participants demonstrated a 31% reduction in CV mortality in those randomized to CRET.[66] An analysis of 1821 post-MI patients from the Mayo Clinic Olmsted County, Minnesota, database demonstrated better 3 year survival (95% vs. 64%; $p < 0.001$) in those participating in formal CRET, even after adjusting for baseline variables.[67] Although one would expect that with the advances in other medical management, the benefits of CRET theoretically may be attenuated in more recent years, however, these Mayo Clinic investigators noted the benefits of CRET were actually more marked in 1998, when other medical interventions were more vigorous, than in 1982, when medical interventions and revascularization procedures were less aggressive.[67]

Suaya et al.[68] recently assessed the effects of CRET on survival in a large elderly cohort. Among those who attended CRET, there was a 34% reduction in 5 year mortality. Moreover, in those who attended 25 or more CRET sessions, (the average CRET program is 36 exercise and educational sessions), mortality was 19% lower ($p < 0.001$) than in those who attended fewer sessions. Hammill et al.[69] studied a natural 5% sample of Medicare beneficiaries and identified an elderly cohort (>30,000) attending at least one formal CRET session. They demonstrated a strong inverse relationship between CRET attendance and overall mortality. In fact, patients who attended all 36 CRET sessions had a 14% lower mortality risk and 12% lower risk of MI than those who attended just 24 sessions, a 22% lower mortality and 23% lower MI risk than those who attended 12 sessions, and a 47% lower mortality and 31% lower MI risk than those who attended just 1 session.

Although the benefits of CRET after MI have been noted for decades, the marked benefits have recently been noted after percutaneous coronary intervention (PCI). In a Mayo Clinic registry of 2395 consecutive patients who underwent PCI in Olmsted County, Minnesota, participation in CRET was associated with a 45% reduction ($p < 0.001$) in all-cause mortality during a 6 year follow-up.[70] Although a trend was noted for reduced overall CV mortality as well in CRET participants, there was no significant effect on subsequent MI or revascularizations. However, the association between CRET participation and reduced all-cause mortality was similar regardless of age, gender, and type of PCI (elective vs. urgent.)

BENEFITS OF CRET IN HF

For patients with stable, compensated chronic HF, numerous studies have established the potential benefits of ET for reducing symptoms, improving levels of CRF, reducing neurohormonal activation, improving overall health-related quality of life, and likely reducing major CV morbidity and mortality.[71] In fact, meta-analyses of ET and HF, where peak VO_2 typically increased by 15%–20%, reported 30%–35% mortality reductions.[72,73] However, a very large RCT of 2331 patients with HF, where patients were randomized to supervised ET versus usual care, had a suboptimal compliance with ET and demonstrated only a 5% improvement in peak VO_2.[74] Although this trial anticipated a 15% improvement in peak VO_2 and a 20%–25% reduction in major CV events and all-cause mortality, there was only a 7% reduction ($p = 0.13$) in the primary end-point (all-cause mortality or hospitalization). However, after preplanned adjustment for confounding factors (ejection fraction, baseline CRF, Beck Depression Inventory, and history of atrial fibrillation or flutter), there was a significant 11% reduction ($p < 0.03$) in the primary end-point in those randomized to ET. The unadjusted secondary end-point (CV mortality and HF hospitalization) was likewise only marginally reduced ($p = 0.06$) in the ET group, but after adjustment, the secondary end-point was reduced significantly ($p < 0.02$) in the ET group. Although this trial was less impressive than originally hoped, the constellation of findings support the use of ET and CRET in patients with HF, especially if peak VO_2 can be increased by at least 10% and preferably by 15% or greater with ET. Efforts are under way to obtain Medicare and insurance reimbursement for CRET in patients with a diagnosis of HF.

CONCLUSIONS

Substantial evidence demonstrates that formal CRET services improve major CHD risk factors, especially exercise capacity, lipids, inflammation, obesity indices, and psychological risk factors, and also reduces major CV morbidity and mortality. Despite these well-documented benefits, however, outpatient CRET referrals and participation rates remain disappointingly low. Therefore, a recent American Heart Association Science Advisory emphasizes the importance of efforts to reinforce the value of CRET programs among various health care systems, providers, and the general public, and thus hopefully increase referrals and participation rates.[7] With these and other efforts, hopefully the referral and participation in CRET programs will increase, thus leading to marked reductions in the prevention of recurrent CV events.

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88 Future of Cardiovascular Disease Prevention and Rehabilitation

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CONTENTS

Introduction 1109
Historical Perspective of Cardiac Rehabilitation 1109
Burden of Disease 1110
Benefits of CRPs 1111
Changing Paradigm of Health care Delivery 1111
References 1112

> Rehabilitation of the cardiac patient in the next millennium will likely differ substantially from that undertaken today owing to a number of different variables. Among these are changes in the demography of the population of the United States; changes in the demography of cardiovascular disease, and in particular changes in the clinical spectrum of coronary heart disease and of heart failure; a substantial expansion of the populations considered eligible for cardiac rehabilitative care; and an escalating emphasis on preventive interventions, with the boundaries of primary and secondary interventions tending to blur.[1]
>
> **(Nanette K. Wenger, MD, *Lifestyle Medicine*, James M. Rippe Ed., 1st edn., 1999)**

INTRODUCTION

Dr. Nanette Wenger accurately predicted important changes in health care needs and health care delivery for persons with coronary heart disease (CHD) in the first edition of *Lifestyle Medicine*. Over the past decade, our demographics have indeed dramatically changed. We are living longer lives but certainly not healthier lives. As the leading cause of death for both men and women in the United States, CHD continues to play an increasingly prominent role within today's health care framework. CHD affects more than 12 million people in the United States, 6.9% of the national population, and causes 40% of all deaths nationwide.[2] More than 2200 Americans die of CHD each day, averaging one death every 39 s. Nearly 33% of CHD-related deaths in the United States are in persons under 75 years of age. The direct and indirect cost of CHD for 2007 is estimated at $286.6 billion.[2]

In response to the epidemic of CHD, cardiac rehabilitation programs (CRPs) were developed to address both acute and chronic recovery. CRPs have evolved from exercise-based rehabilitation programs to centers for multifactor CHD risk reduction. Significant data exist to support this important evolution. In the 1990s, the Stanford Coronary Risk Intervention Program demonstrated angiographically that guideline-based systematic management of CHD risk factors resulted in reduction of atherosclerotic plaque, fewer deaths, and hospitalizations in persons with documented CHD.[3] More recently, the COURAGE Trial showed, in select persons with documented CHD, that intensive multifactor risk reduction alone was comparable to percutaneous interventions plus intensive multifactor risk reduction for CHD outcomes.[4] Thus, CRPs have an important role to play in supporting secondary prevention strategies in the twenty-first century.[5]

HISTORICAL PERSPECTIVE OF CARDIAC REHABILITATION

In the 1950s and 1960s, a heart attack was often seen as the end to a productive life. In 2012, with advances in medical therapies, surgical interventions, and CRPs, a major cardiovascular event has become an important turning point toward a healthier productive life. CRPs provide a safe and effective means of improving outcomes for patients with CHD. Improved outcomes include benefits for emotional as well as physical recovery. Over the past two decades, CRPs have grown to fully embrace exercise-based cardiac rehabilitation plus intensive secondary prevention. These programs, combining both exercise therapy and cardiovascular disease (CVD) risk reduction strategies, are now considered the standard of care. CRPs provide important resources necessary for a healthier life after a major cardiovascular event, optimizing the acute and chronic care of patients with CHD.[6]

Additional and important changes seen in many CRPs are moving the focus from "phases of care" to individualization of care. Historically, the structured phases of CRPs have included: Phase I, defined as the care provided during "early recovery" in the hospital, Phase II defined as the initial 6–12 weeks of recovery following discharge from the hospital, Phase III

TABLE 88.1
Guidelines Based Cardiac Rehabilition Services

Class 1 and IIa Recommendation for Cardiac Rehabilitation Services

Class I

1. All eligible patients with ACS or whose status is immediately post coronary artery bypass surgery or post-PCI should be referred to a comprehensive outpatient cardiovascular rehabilitation program either prior to hospital discharge or during the first follow-up office visit (*Level of Evidence: A*).
2. All eligible outpatients with the diagnosis of ACS, coronary artery bypass surgery or PCI (*Level of Evidence: A*), chronic angina *(Level of Evidence: B)*, and/or peripheral artery disease (*Level of Evidence: A*) within the past year should be referred to a comprehensive outpatient cardiovascular rehabilitation program.
3. A home-based cardiac rehabilitation program can be substituted for a supervised, center-based program for low-risk patients (*Level of Evidence: A*).

Class IIa

1. A comprehensive exercise-based outpatient cardiac rehabilitation program can be safe and beneficial for clinically stable outpatients with a history of heart failure (*Level of Evidence: B*).

Source: Smith, S.C. et al., *Circulation*, 124(22), 2458, 2011.

defined as recovery beyond the first 6–12 weeks, and Phase IV defined as the maintenance of healthy lifestyle including physical activity after 3 months of recovery. Phase II through IV CRPs can be hospital based, community or clinic based or home based.[7] Home-based programs can be supported through telemetry monitoring or other means of supervision by health care professionals. Ideally, all persons having an acute coronary event with acute myocardial infarction, bypass surgery, or percutaneous intervention, and those with chronic angina, heart failure, or peripheral arterial disease would participate in a CRP (see Table 88.1). Unfortunately, only a small percentage of patients with CHD are referred to CRPs. Additionally many persons with CHD do not have access to or do not attend "structured programs" due to lack of knowledge about CRPs, cost, distance, older or younger age, female gender, language or literacy barriers, depression, and lack of social support.[2,6,8–10]

BURDEN OF DISEASE

With the change in chronic disease worldwide and the growing need to individualize care, secondary prevention, a mainstay of cardiac rehabilitation, will continue to play a significant role for CRPs in the future. Secondary prevention of CVDs will remain at the forefront of CRP programs for both patients and family members.

Worldwide, chronic diseases are responsible for 70% of all deaths and 78% of health care costs.[11,12] Atherosclerotic vascular diseases include a variety of conditions that share common risk factors and treatments including guideline-based interventions that often overlap. These risk factors include dyslipidemia, hypertension, cigarette smoking, type II diabetes, physical inactivity, obesity, a diet high in saturated fat, and significant elevations in life stress. Outcomes from poorly controlled cardiac and vascular disease risk factors include heart attack, stroke, peripheral vascular disease, and renal disease.[2]

Our society and our health care system bear the burden of CVD prevalence and the accompanying expense of recovery and disability. While death rates from CHD have declined since 2007, the burden of disease remains remarkably high.[2] The number of disability-adjusted life years (DALYs) lost serves as an accurate measure of the total burden of a disease, as opposed to a measure of a disease's resulting deaths. In the United States, 18% of lost DALYs results from CHD, causing a projected 25% increase of national health care spending.[13] The epidemic of CVD is increasing locally and globally. The burden of CHD is projected to rise from around 47 million lost DALYs in 1990 to 82 million in 2020. Inarguably, the national and global burden of CHD is far-reaching and staggering.[14]

Prevention is key and action does work.[15] Approximately 78% of American adults aged 20–80 years alive today are candidates to participate in at least one prevention activity. If everyone participated in these activities, myocardial infarctions would be reduced by an estimated 63%.[14,16] Further studies indicate that, in the United States, for every 10 mmHg reduction of systolic blood pressure, there is a 30% decrease in risk of stroke for people aged 60–79 years.[17] Tobacco use is the most preventable cause of heart disease in the United States.[18] Contrary to public perception, smoking-related heart disease actually results in more deaths per year than smoking-related lung cancer. The CDC reports that cigarette smokers are two to four times more likely to develop CHD than nonsmokers and are twice the risk for stroke.[19] While the percentage of U.S. adults who use tobacco has declined since 1998, there has been no significant change in that reduction since 2005. Current smokers comprise highly addicted adults and new young smokers.[20] CRPs can reach out to these populations and family members of program participants through community health education and secondary prevention programs.[2,21]

Targeting hypertension and high cholesterol levels can dramatically reduce CVD incidence. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that 33.5% of U.S. adults over 20 years of age have hypertension. Strikingly, this results in an estimated 76,400,000 American adults with hypertension, with only 48% of those aware that their hypertension is being medically controlled.[2] As blood cholesterol rises, so does risk of CHD. An estimated 10% decrease in total cholesterol levels population-wide would result in an estimated 30% reduction in national CHD incidence.[2]

Coupled with these risk factors, obesity also increases CHD-associated morbidity and mortality. In the United States, 67.3% of adults are estimated to be overweight or obese, amounting to approximately 150 million Americans. Obesity is associated not only with marked excess mortality

but also with increased incidence of diabetes mellitus and the development of CVD conditions (CHD, stroke, heart failure).[2] Health problems related to obesity cost the United States an estimated $117 billion a year. Despite prevention efforts, the prevalence of diabetes mellitus and obesity continue to dramatically increase.[2]

The reduction of morbidity and mortality from CHD rests in prevention, not cure. It is estimated that if just 10% of adults engaging in aerobic exercise, Americans would save billions of dollars in costs related to heart disease, with an accompanying reduction in the societal burden of disease.

BENEFITS OF CRPs

Participating in a CRP has many benefits including an opportunity to extend these benefits to other populations with chronic diseases not presently served through programs as they are structured today. Most notably, this includes patients with type 2 diabetes.[22] More recently evidence suggests that CVD risk reduction benefits persons with chronic renal disease.[23,24]

One obvious benefit to participation in CRPs is improved survival. Studies have shown that cardiac rehabilitation reduces the chance of death after a myocardial infarction by 20%–25% and reduces the risk of a repeat event by 28%.[25] This improvement is comparable to the effects of rigorous use of pharmacologic agents.[17] The implementation of a comprehensive secondary prevention program as an integral component of CRPs targets the assessment and modification of risk factors, creating a potent strategy to increase survival and quality of life.[18] CRPs support the improvement of health outcomes through nutritional counseling, lipid and hypertension management, tobacco cessation interventions, weight and diabetes management, exercise training, and support of psychosocial well-being—all actions contributing to the slowing, stabilization, or reversal of CHD progression. In addition, CRPs have been shown to improve adherence to lifesaving medications.[26]

Studies of efficacy and effectiveness of CRPs have not only documented significant morbidity and mortality reductions but shown improvements in a wide range of clinical and behavioral outcomes.[15] These benefits exist because of cardiac rehabilitation's comprehensive prevention strategy.

The future holds great promise. Intensive secondary prevention interventions for CHD have been shown to be as effective in preventing subsequent cardiovascular events compared to percutaneous coronary interventions plus intensive secondary interventions in appropriately selected patients.[27] This coupled with the knowledge that CRPs are positioned to provide such care further emphasizes the importance of cardiac rehabilitation services. Their challenge is to meet the needs of all cardiovascular patients and their families by expanding services and making them more cost effective and affordable. Reaching out to those who are underserved must become a goal of CRPs.

CHANGING PARADIGM OF HEALTH CARE DELIVERY

The national health care reform legislation marks a movement toward integrated service delivery models, changing the way our current health services are organized, distributed, and financed.[28] Accountable care organizations (ACOs) and patient-centered medical homes (PCMHs) are two notable health care delivery programs recently developed to address this integrated service model.

According to Centers for Medicare and Medicaid Services, an ACO is an organization of health care providers (i.e., hospitals, nurses, physicians) that agrees to be accountable for the quality, cost, and overall care of Medicare beneficiaries who are enrolled in traditional fee-for-service program. The goal is to provide seamless care, bringing together the different parties of health care delivery: primary care physicians, nurse practitioners, specialists, and nurse case managers.[28] CRPs would fit well into these models. CRPs are well positioned to extend the capacity to supervise and coordinate comprehensive CHD risk reduction therapies for numerous populations and those at risk of CHD.

PCMH are an alternative model to ACOs. The PCMH is a promising model for transforming the organization and delivery of primary care. According to the Agency for Healthcare Research and Quality, medical homes aim to create a patient-centered, comprehensive, coordinated, accessible and systems-based approach to care.[29] PCMH are based on care concepts including improved access to and continuity of care, identification and management of specific patient populations, the use of evidence-based guidelines for chronic and urgent care needs, provision of self-care management tools and resources, tracking, and coordination of referrals including lab testing, and ongoing evaluation and continuous quality improvement.[30] The concepts of this new model of care matches well with the concepts upon which CRPs are built.

PCMH, chronic disease management, case management, secondary prevention centers, telemedicine, patient directed self-care, and group care meeting—all new models of preventive health care that are consistent with the mission and goals of CRPs. However, these new models of care present CRPs with new and complex challenges. Can traditional CRPs fit into the rapidly evolving health care paradigm in the twenty-first century? Is the current model of cardiac rehabilitation able to adapt to the increasing demands for lifelong secondary preventive care? Can CPRs evolve to embrace the needs of all patients requiring secondary prevention for CHD including those without access to a formal program and the underserved?

Over the past 50 years, CRPs have been shown to provide safe and effective care. Care that is individualized, scientifically based, guideline directed, and associated with increased survival and quality of life. No doubt, over next 50 years, CRPs will more fully embrace changes in the way health care is structured and emerging technologies including the potential of "virtual" care to better serve all patients with CHD. The value of CRPs is found in the individuals, the families, and the communities they benefit.

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89 Secondary Prevention
It's a Family Affair

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CONTENTS

Secondary Prevention 1113
Rationale for Family-Based Approaches: Importance of Family History 1113
Rationale for Family-Based Approaches: Importance of Health Behaviors 1114
Familial Associations of Dietary Intake 1114
Familial Associations of Physical Activity 1115
Familial Associations of Cigarette Smoking 1115
What Works: Models for Secondary Prevention of CVD 1115
Family-Focused Interventions for CVD Prevention 1116
Summary 1118
References 1118

Secondary prevention of cardiovascular disease (CVD) focuses on interventions designed to reduce the likelihood of CVD events and/or mortality in individuals who have established disease. Recent guidelines for secondary prevention include and encompass risk reduction therapies for individuals with coronary and other atherosclerotic disease. It is well established that CVD aggregates in families and those families have a critically important role in promoting adherence to therapeutic as well as preventive regimens. The purpose of this chapter is to review the evidence supporting family-based approaches to secondary prevention of CVD and provide suggestions for clinical and public health practice as well as future research.

SECONDARY PREVENTION

Evidence-based secondary prevention guidelines issued by the American Heart Association (AHA) and the American College of Cardiology Foundation (ACCF) reflect results of recent clinical trials in recommendations for targets for intervention, and in support of intensive risk-reduction therapies for patients with established and other atherosclerotic vascular disease (including peripheral artery disease, atherosclerotic aortic disease, and carotid artery disease) [1]. While details of these guidelines are beyond the scope of this chapter and discussed in chapter X, recommendations address the major risk factors for CVD including smoking, blood pressure control, lipid management, physical activity, weight management, and type 2 diabetes mellitus management. Other areas for intervention include recommendations for antiplatelet agents/anticoagulants, renin–angiotensin–aldosterone system blockers, influenza vaccination, depression, and cardiac rehabilitation [1]. The role of the family in promoting patient adherence to these recommendations and realizing treatment goals is not explicitly addressed in the 2011 update; however, reference to maintaining heart-healthy home environments (i.e., avoidance of environmental tobacco smoke) and, based on available evidence, recommendations for a home-based cardiac rehabilitation program for low-risk patients is also suggested. In addition, health care providers are encouraged not only to implement the therapies according to their class of recommendation but to assess and assist with patient compliance at each patient encounter. As discussed as follows, the family environment including patterns of family health behaviors as well as social support necessary for behavior change and adherence to prescribed therapies are central to optimizing secondary prevention.

RATIONALE FOR FAMILY-BASED APPROACHES: IMPORTANCE OF FAMILY HISTORY

Early in the twentieth century (1910), Sir William Osler first observed the occurrence of coronary heart disease (CHD) in successive generations of families [2]. Since then, numerous cross-sectional and longitudinal studies of diverse populations have documented intrafamilial clustering of CHD and other cardiovascular conditions [3–8]. Attributed to the interplay of genetic and shared common environmental and behavioral–lifestyle factors, familial aggregation of CVD is well documented, resulting in recognition and designation of family history as a major risk factor for CVD.

Results from several studies underscore the importance of family history in CVD risk prediction and disease prevention. Results from the Framingham Offspring Study, for

example, indicate that early onset parental CHD (prior to 55 years of age in males and 65 years of age in females) is an independent predictor of offspring cardiovascular events in middle-aged men and women (mean age, 44 years) [9]. After adjustment for other risk factors, premature CHD in at least one parent was associated with a significant doubling in risk for men and a 70% increase in risk for women over a period of 8 years. Of note, parental CHD was found to discriminate risk best among offspring with intermediate levels of cardiovascular risk as predicted by individual traditional risk factors and multivariable risk equations. Other studies of diverse population-based cohorts demonstrate associations of familial CHD with subclinical atherosclerosis including increased carotid intima-media thickness (CIMT) and coronary artery calcium (CAC), a surrogate measure of the presence and burden of atherosclerosis [10–13].

Of note and adding to the importance of sibling history of CVD are results of a cross-sectional study of 8549 asymptomatic individuals (69% men; mean age 52 ± 9 years) conducted by Nasir et al. indicating that sibling history of CHD may be more strongly associated with subclinical atherosclerosis than parental history of premature CHD [10]. Multivariate regression analyses indicated that the odds ratio (OR) (95% confidence interval) for the presence of CAC was 1.3 (1.1–1.6) among those with positive family history of premature CHD in parents only, 2.3 (1.7–3.1) and 2.5 (1.8–3.3) among those in siblings and a combined family history compared with those without family history of CHD in men, respectively. Among women, the corresponding ORs were 1.3 (1.0–1.8), 2.3 (1.7–3.6), and 1.9 (1.3–3.1), respectively. More recently, Nasir et al. assessed the strength of the association between a family history of premature CHD and CAC in 5347 asymptomatic individuals (47% men; 38% white; mean age 62 ± 10 years) drawn from the Multi-Ethnic Study of Atherosclerosis (MESA) [14]. The demographics-adjusted OR for CAC > 0 with vs. without a family history of premature CHD was 1.94 (95% confidence interval [CI], 1.64–2.29). On adjustment for CHD risk factors, the association was slightly attenuated to an OR of 1.84 (95% CI, 1.55–2.19). Of note, family history of premature CHD was significantly associated with CAC in all ethnic groups [14].

Taken together and placed in context of other clinical and epidemiological studies, the results support the importance of family history of premature disease in risk assessment and stratification and provided the impetus for the National Institutes of Health (NIH) Family History of Disease Initiative. This initiative encourages health care providers to include and emphasize multigenerational family history in assessment of risk for CVD and other chronic conditions [15].

RATIONALE FOR FAMILY-BASED APPROACHES: IMPORTANCE OF HEALTH BEHAVIORS

The associations of health behaviors, levels of established risk factors (i.e., low-density lipoprotein cholesterol [LDL-C]) and CVD endpoints have been investigated extensively. While the mechanisms through which these behaviors influence health outcomes remain to be fully explicated, accumulated data clearly indicate that patterns of dietary intake, physical activity, and smoking behaviors are important determinants of atherosclerotic and hypertensive processes [16]. Compelling evidence linking adverse health behaviors in children, adolescents, and adults with increased risk and progression of CVD processes has prompted inclusion of these health behaviors in primary [17,18] and secondary [1] prevention guidelines. The adoption and maintenance of healthy lifestyle behaviors and therapeutic lifestyle change remain as the cornerstone of primordial, primary, and secondary prevention [19].

Viewed within a social–ecological perspective and across cultures and operational definitions, families provide a critically important context for the development and maintenance of behaviors central to cardiovascular health [19]. Families also provide an important context in relation to initiation and maintenance of behavior change and adherence to therapeutic regimens. As discussed in the following, substantial data generated from clinical and epidemiological studies suggest intrafamilial associations of patterns of dietary intake, physical activity, and smoking behaviors.

Familial Associations of Dietary Intake

Early observations made in the population-based biracial Princeton School District Study of 6- to 19-year-old children and parents indicated significant parent–offspring associations of total energy intake ($r = 0.25$; $p < 0.001$) and selected macronutrients including carbohydrates, saturated, and polyunsaturated fatty acids [20]. In multiple regression analyses, parental nutrient intake explained a significant portion of the variance in children's intake with multiple R^2 ranging from 0.23 (cholesterol) for the total sample to 0.97 for total carbohydrates in Black fathers over age 40 and their children. In both correlational and regression analyses, parent–offspring associations in Black families exceeded those of their White counterparts. A report from the Framingham Children's Study, focused on White preschool children and their parents, is consistent with these results [21]. In the Framingham cohort, however, mother–child associations exceeded father–child associations for most nutrients. Other reports of White and Mexican American parent–child dyads provide additional evidence of familial aggregation of macro- and micronutrients relevant to CVD [22]. Of note, results from the Canadian Family Study, designed to quantify familial aggregation in daily energy intake in biological relatives and adoptees, reported that nontransmitted environmental factors, including home environmental effects, accounted for more than 50% of the variance observed in components of energy/dietary intake [23]. These results are consistent with a report from the Delaware Valley Twin Study (DVTS) [24]. In this cohort of school-age twins, significant monozygotic (MZ) ($r = 0.61–0.91$) and dizygotic (DZ) ($r = 0.39–0.84$) co-twin similarity of macro- and

micronutrients was observed; however, heritability analyses indicated negligible genetic influences.

Other studies of diverse populations of families are consistent with these results pointing to the family environment as an important and potentially modifiable context for developing and changing this important health behavior [25]. Less information is available regarding family-based dietary interventions in the setting of secondary prevention of CVD; however, results to date suggest the promise and potential of changing this health behavior in families with CVD [26].

Familial Associations of Physical Activity

Similar to dietary intake, familial resemblance of physical activity has been documented across the life course of families from diverse populations. Perusse et al. [27] quantified genetic and environmental determinants of physical activity (level of habitual activity and exercise participation) in n = 375 Canadian (Quebec) families using the BETA model of path analysis that allows the separation of the transmissible effect between generations (t^2) into genetic (h^2) and cultural (b^2) components. Transmission was significant but was accounted for by genetic factors for level of habitual physical activity ($t^2 = h^2 = 29\%$) and by cultural factors for exercise participation ($t^2 = b^2 = 12\%$). These results, supported by other research [28–31], indicate familial transmission of this health behavior, suggest the importance of both genetic and environmental influences, and indicate that nontransmissible environmental factors account for most of the variation in both indicators of physical activity in this population. Methodologic differences make cross study comparisons difficult to interpret; however, results from other studies are consistent in demonstrating parent–offspring and intrafamilial associations of this health behavior that is critically important to CVD prevention [28–31].

Familial Associations of Cigarette Smoking

Considerable multidisciplinary research attention has focused on the familial determinants and aggregation (including intra- and intergenerational familial transmission) of cigarette smoking. Data suggest that genetic and numerous environmental factors contribute to the initiation and persistence of cigarette smoking. Data also suggest that the relative contributions of genetic and environmental factors (including shared environments) vary by stage of smoking behavior (i.e., initiation, persistence), developmental phase, gender, and culture/ethnicity [16,32–34]. For example, in a population-based study of Dutch adolescents and young adults, Boomsma et al. [33] reported a heritability of smoking initiation of 31% with shared (family) environmental factors accounting for an additional 59%. A report from the National Academy of Science National Research Council (NAS-NRC) World War II twin panel indicated a heritability estimate of 59% with shared environmental effects accounting for an additional 21% of the variance [34]. For an Australian adult twin panel, heritability estimates of 28% for men and 77% for women were reported while shared environmental effects accounted for 43% and a nonsignificant 4% of the variance respectively [32].

While these results emphasize the population-specificity of such estimates, they also indicate the importance of both genetic and environmental factors in smoking initiation and persistence. Additional data, generated from studies of parent–offspring dyads and singletons, point to the importance of potentially modifiable familial and environmental influences and also suggest gender and ethnic differences in predictors of smoking initiation and persistence [35]. For example, data from Bogalusa and southern California suggest that parental smoking may be a more significant predictor of smoking initiation in White adolescents as compared with their Black counterparts [35].

Collectively, accumulated data suggest that patterns of dietary intake, physical activity, and cigarette smoking are influenced by both genetic and potentially modifiable environmental factors. Familial transmission and aggregation of these behaviors can be attributed to both shared genes and shared common family environments. Taken together, the results suggest the need and potential for family-focused behavioral–lifestyle interventions tailored to the individual family's developmental life course phase, structure, sociodemographics, and resources.

WHAT WORKS: MODELS FOR SECONDARY PREVENTION OF CVD

In the United States and globally, atherosclerotic cardiovascular conditions, particularly CHD and cerebrovascular disease, are leading causes of disability and premature death. CVD risk-reduction and evidence-based medical therapies play a critically important role in reducing the age-adjusted mortality due to CHD as exemplified in a report by Ford [36]. Specifically, Ford et al. applied an updated version of the IMPACT mortality model to data for the years 1980–2000 on the use and effectiveness of specific cardiac treatments and change in risk factors among U.S. adults, 25–84 years of age. The IMPACT model incorporates major potentially modifiable risk factors for CHD including smoking, high blood pressure, elevated total cholesterol, obesity, diabetes, and physical inactivity as well as standard evidence-based medical and surgical treatments for CHD. Results indicated that approximately half the decline in U.S. deaths from CHD in the period studied may be attributable to reductions in major risk factors while approximately half is due to evidence-based medical therapies [36]. These results are consistent with earlier U.S. and international studies and underscore the importance of potentially modifiable risk factors and behaviors in preventing mortality from CHD [19].

The evidence supporting the importance of multicomponent behavioral–lifestyle and pharmacological management in secondary prevention of CVD is compelling. As noted previously, over the past several decades, the AHA and ACCF

have issued evidence-based guidelines focused on secondary prevention/cardiac rehabilitation. The 2011 guidelines suggest a multifaceted and multidisciplinary approach to overall cardiovascular risk management [1]. With emphasis on behavioral–lifestyle modifications and patient adherence to individualized recommendations, the need for multidisciplinary team approaches and active involvement of the patient's family is imperative. The central and essential role of adherence to lifestyle modification and medication recommendations in preventing recurrent events in patients with documented CVD is well established [37]. Consistent with social–ecological models of health, optimal strategies for increasing adherence to preventive and therapeutic regimens consider and target individual (patient-level), provider, and health care system factors [39]. The role of the cardiovascular patient's family crosscuts each of these areas including providing social support and a shared family environment conducive to behavioral change/lifestyle modification, communicating with and clarifying treatment options with the patient's health care provider, and negotiating health care systems.

As discussed in the following, the efficacy and effectiveness of nurse-directed, multidisciplinary models for secondary prevention of CVD (and other chronic conditions) has been established. In addition, while less information is available on family-based approaches, results of studies conducted to date indicate the promise and potential of extending nurse-directed multidisciplinary models for secondary prevention to include and encompass the patient's family [38].

Lessons Learned: Essential elements of nurse-directed, multidisciplinary models of secondary prevention, including an often-cited meta-analysis [39] and recent systematic reviews conducted by Berra et al. [40,41], indicate that multidisciplinary, multicomponent secondary prevention programs are effective in reducing recurrent acute cardiovascular events and all-cause mortality and improving health-related quality of life and functional status in individuals with CVD. Of note, almost half (45%) of the 63 randomized trials included in Clark's meta-analysis were identified as nurse-led or nurse-managed [39]. Berra's systematic literature review focused on evaluating how nurse-based case management (NCM) according to recommended guidelines improves patient outcomes and enhances cardiovascular risk reduction [40]. Berra et al. also conducted a review of selected nurse-led case-management studies that were implemented in the United States and globally [41]. While the family was not the unit of intervention in the majority of studies included [26,42–45], observations made from these reviews combined with results of recent studies that included family subsystems (i.e., spouses/partners, parent–offspring dyads, siblings) apply to the effective implementation of family-focused CVD-prevention programs (see Table 89.1).

As illustrated in landmark and recent clinical and community-based trials, enhancing cardiovascular risk reduction and improving health outcomes in CVD patients from diverse racial, ethnic, and sociodemographic backgrounds is achievable but will require reforms in current systems of care. Key elements of successful secondary CVD-prevention programs identified in the research reviewed are consistent with the core components or pillars of the Chronic Care Model as defined by Wagner et al. [46] and Bodenheimer et al. [47]. These include self-management support, decision support (i.e., evidence-based clinical practice guidelines), computerized clinical information systems, community resources and policies (i.e., linkages between provider organizations and community-based resources), delivery system design (i.e., case-managed, multidisciplinary team approach), and health care organization (i.e., structure, goals, and values of provider organization that prioritize provision of care for chronic conditions). More specifically, as operationalized in effective CVD-prevention programs, essential elements include systems for coordination of services with multiple providers (nurse-directed, case-managed, multidisciplinary team approach), comprehensive lifestyle management programs that incorporate evidence-based principles of behavior change including self-management support and social support, clinical information systems (universal use of electronic health record that includes patient and family health behaviors, computerized participant management, tracking reports, and outcomes analysis systems), and efficient mechanisms for patient follow-up to monitor adherence, safety, and effectiveness of interventions. An essential component of effective nurse-led, case-managed programs is the use of evidence-based protocols and algorithms for management of patients with single and multiple risk factors [39–41].

Family-Focused Interventions for CVD Prevention

As noted previously, minimal research has focused on the family as a unit of intervention in the setting of secondary and/or primary prevention of CVD. Based on evidence that underscores the importance of family history of CVD, the family environment, and parental role-modeling of CVD-related health behaviors, guidelines for CVD prevention in children and adolescents have emphasized family-focused approaches to assessment and management of CVD risk factors and health behaviors [17,18]. Of note, the efficacy of family-focused interventions has been demonstrated in the management of childhood obesity [48]. For example, Epstein et al. conducted a prospective, randomized controlled study of obese 6- to 12-year-old children over a period of 10 years. The obese children and parents assigned to joint health behavior management sessions showed significantly greater weight loss after 5- and 10-year follow-ups than the families with child-centered behavior management [48]. More recent studies [49] reaffirmed the role of the family in the management of childhood obesity; the collective results have guided and informed weight management programs for obese children [50].

A recent study conducted by Mosca et al., FIT Heart: Family-Based Intervention Trial to Improve Heart Health, illustrates both the challenges and opportunities for family-focused interventions in the setting of secondary prevention of CVD [38]. Specifically, FIT, a randomized controlled trial, was conducted in healthy adult family members (n = 501;

TABLE 89.1
Selected Successful Nurse-Led Case Management Studies

Study, Mean Age (MA), % Male (% M)	Year	Country	Location	Patient Population	Number Randomized	Multifactorial Approach	Primary Outcomes
EUROACTION (hospital arm), MA 63 years, 63% M [26]	2008	Europe (United Kingdom, Sweden, France, Italy, Spain, Poland)	Hospital	Acute MI, unstable angina, stable angina	3088 (cluster randomization)	Smoking, diet, physical activity, weight, waist, BP, lipids and glucose, HRQoL, illness and risk perception	INT vs. UC: Hospitalized with CHD: reached goal for: BP (65% vs. 55%[a]); LDL-C (81% vs. 74%; NS); BMI (27% vs. 21%; NS); waist circumference (31% vs. 21%)
EUROACTION (general practice arm), MA 62 years, 53% M [26]	2008	Europe (United Kingdom, Denmark, the Netherlands, Poland, Italy, Spain)	General Practice	High multifactorial risk, on treatment for BP lowering, lipid modification, and diabetes	2317 (cluster randomization)	Smoking, diet, physical activity, weight, waist, BP, lipids and glucose, quality of life	GP high risk: Reached goal for BP (58% vs. 41%[a]); LDL-C (45% vs. 35%); BMI: (23% vs. 22%); waist circumference (23% vs. 15%; NS) significant improvements in diet[a] and physical activity[a] INT (both groups) vs. UC
ELMI (extensive lifestyle management intervention), MA 64 years, 83% M [42]	2006	Canada	Hospital	Patients with ischemic heart disease postcardiac rehabilitation	302	Smoking, diet, physical activity, weight, waist, BP, lipids, and glucose, quality of life	4.1 year of follow-up: significant reduction in global risk including TC, LDL-C, and BP
Campbell-Nurses primary care study, MA 66 years, 83% M [43]	1998	Scotland	General practice	Working diagnosis of CHD	1343	Smoking, diet, physical activity, BP and lipids	1 year: INT vs. UC improved use of aspirin (81.0% vs. 66.4%[b]); lipids (96.5% vs. 87.9%[b]); BP (96.5% vs. 87.9[b]); INY vs. UC overall OR,0.55[b]; 4.7 year: total mortality INT vs. UC (14.5% vs. 18.9%[a])
MULTIFIT MA 57 years, 79% M [44]	1994	United States	Hospital	Post-AMI	585	Smoking, diet, exercise, and lipids	INT vs. UC: improved: smoking cessation (70% vs. 53%[c]), functional capacity (9.3 vs. 8.4 METs[b]) LDL-C (107 vs. 132 mg/dL[b])
SCRIP (Stanford Coronary Risk Intervention Project), MA 56 years, 83% M [45]	1994	United States	Hospital	Angiographically defined coronary atherosclerosis	300	Smoking, diet, physical activity, weight, BP, lipids, glucose	47% less CAD progression by arteriography, INT vs. UC: (0.0024 vs. 0.045[a]); INT vs. UC: LDL-C –0.95 vs. –0.16 mmol/L,[b] TG –0.34 vs. –0.01[c]; increased in lipid lowering medications 80.7% vs. 24.4%[b]; fewer no. of primary cardiac events INT vs. UC (OR = 0.57[a])

Source: Adapted from Berra, K. et al., *Eur. J. Cardiovasc. Nurs*., 10(2), s45, 2011.

AMI, acute myocardial infarction; BP, blood pressure; CHD, coronary heart disease; HRQol, health-related quality of life; INT, intervention; LDL-C, low-density lipoprotein cholesterol; NS, not statistically significant; OR, odds ratio; TC, total cholesterol; UC, usual care.

[a] $p < 0.05$.

[b] $p \leq 0.001$.

[c] $p \leq 0.01$.

66% female; 36% non-White; mean age, 48 years) of patients hospitalized with CVD and designed to evaluate a special intervention (SI) with personalized risk factor screening, therapeutic lifestyle-change counseling, and progress reports to physicians versus a control intervention (CIN) on the primary outcome, mean percent change in LDL-C, and other risk factors. At baseline and one year, validated dietary assessments and standardized risk factors were obtained. For 93% of the subjects at baseline, saturated fat comprised ≥7% of total caloric intake and 79% had nonoptimal LDL-C levels (50% were unaware). There was no difference in the SI versus the CIN with respect to the mean percent change in LDL-C (−1% vs. −2%, respectively; p = 0.64), owing to a similar significant reduction in LDL-C in both groups (−4.4 and −4.5 mg/dL, respectively). Diet score, however, significantly improved in the SI versus the CIN (p = 0.04). Further, cardioprotective high-density lipoprotein cholesterol (HDL-C) declined significantly in the CIN but not in the SI (–3.2% [95% CI, −5.1 to −1.3] vs. +0.3% [95% CI, −1.7tp +2.4]; p = 0.01). Relatedly, at 1 year, SI subjects were more likely than controls to exercise >3 days per week (p = 0.04).

While these results indicate that SI was not more effective than the CIN in reducing the primary end point, LDL-C, the screening process did identify many family members of hospitalized patients with CVD who were not aware of their risk factors. Relevant to implementation in "real-world" clinical practice settings, the special intervention included personalized risk factor screening and lifestyle counseling by certified health educators at regular intervals as well as progress reports to physicians. Participants in the CIN received a general prevention message at baseline. Of note, both groups significantly improved their intakes of saturated fat and cholesterol and the SI was more likely to exercise >3 days a week at 1 year. While these behavioral–lifestyle changes are modest, if sustained over time, it could be clinically important independent of lipid effects. As the investigators conclude, and supported by other data, physicians (and nurses and other health care providers) should ask about recent family cardiac events at each patient encounter and screen family members during this "motivational moment" [38].

While this study focused on adult family members, the design allows for extension to multigenerational family members of probands (individuals hospitalized for acute events or interventional procedures). Using age-appropriate, evidence-based guidelines for CVD prevention and implemented by a multidisciplinary, nurse-led, case-managed team approach, FIT could be adapted and implemented with multigenerational families. Essential to successful implementation of this family model of CVD prevention are elements of the chronic care model (discussed previously) and integrated systems of care.

SUMMARY

CVD aggregates in families and is attributable to the interplay of shared genes, and potentially modifiable environmental exposures, and health behaviors. The importance of health behaviors in the prevention and management of CVD across the life course is well established [19]. As reflected in current evidence-based guidelines, the adoption and maintenance of heart-healthy behavior patterns and therapeutic lifestyle change is the cornerstone of primary and secondary prevention of CVD [1,17,18]. The efficacy and effectiveness of multigenerational, nurse-based case-management in prevention of CVD (enhancing risk reduction and improving patient outcomes) has been demonstrated [39–41]. Accumulated data support the need for family-focused CVD prevention and the promise and potential of adapting multidisciplinary, nurse-based case-management models for implementation with multigenerational families. Research is needed to guide and inform optimal family-focused approaches designed to prevent and reduce the risk and burden of CVD in families from diverse populations [25,51,52].

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Part XVI

Lifestyle Components of Pediatric Medicine

Thomas W. Rowland, MD

90 Pediatric Preventive Medicine
An Introduction

Thomas W. Rowland, MD

CONTENTS

Reduction of Risk for Chronic Disease 1124
Creation of Health-Promoting Habits 1125
Conditioning 1125
Imitation 1125
Imprinting 1125
Biological Influences on Health-Related Behaviors 1125
Central Control of Physical Activity Energy Expenditure 1126
Gene–Environment Interaction 1126
Venues for Behavioral Modification in Youth 1126
Family 1126
School 1127
Physicians' Offices 1127
Coming Chapters 1127
Summary 1128
References 1128

The rationale for preventive medicine is based on the concept that human behavior is a strong determinant of one's health. How we eat, how much we exercise, how prudent we are in avoiding accidents, how we protect ourselves from risk of infections, how we restrict use of tobacco, alcohol, and drugs—they all act as primary determinants of health. Such influences can be immediate—wearing of seat belts, for example—while others contribute to long-term health, such as reduction in cancer rates with smoking cessation. By modifying certain behaviors, then, improvements in physical and mental health, translated into *well-being*, can be expected on both an individual and population-wide basis.

The implication here is that such a salutary effect is directly under the control of the individual. Individual choices in lifestyle truly matter; personal responsibility is central to effective preventive medicine interventions. Importantly, too, adopting a healthy lifestyle bears more than minor significance. The accumulated scientific evidence convincingly indicates that the list of diseases implicated as behavior-related includes the major causes of morbidity and mortality in the population.

Preventive medicine in children carries the same precepts, but with some important differences. First, lifestyle decisions—brushing teeth, nutritional choices, wearing bicycle safety helmets—are typically not under the control of the child him- or herself but rather fall to a parent or caretaker. Indeed, educating children as to the wisdom of proper health-related behaviors, and assuring they are carried out, are primary responsibilities of raising children. Obviously, autonomy in such decision making increases as the child grows. That means that preventive medicine strategies aimed for children need to be adjusted to the developmental stage of the child. Such considerations are important in educational initiatives as well as the means that evidence-based preventive medicine strategies are confirmed by scientific research. Structuring and evaluating the effectiveness of smoking cessation messages to teenagers, for example, can be expected to be very different from those presented to parents promoting early physical activity habits in preschoolers.

The other aspect that sets pediatric preventive medicine apart from that in adults is that of *time*. With an entire lifetime ahead of him, establishment of a healthy behavioral lifestyle in a 7-year-old boy is more likely to pay health dividends in the long run than if such habits are suddenly introduced at age 45 years. That's why interventions to establish patterns of healthy behavior in youth are often said to take advantage of a "window of opportunity" provided by an early start.

The kinds of lifestyle patterns in children that will offer protection from future health issues in the adult years are the topics of the chapters that follow. It is clear that behavioral influences in the growing years might affect salutary outcomes down the road by at least two possible mechanisms. First, by retarding the biological development of long-term disease processes that begin during the pediatric years (such as atherosclerosis and obesity), the risk clinical outcomes of these processes in the adult years (myocardial infarction, stroke)

might be reduced. And second, habits such as regular physical activity and good nutrition established during childhood may persist throughout the life span and provide long-term benefits.

The rationale for those aspects of pediatric preventive medicine whose goal is long-term health benefits rests on these two effects of behavioral conditioning during the growing years. While both are intuitively attractive, pediatric exercise scientists and health-exercise professionals face a number of challenges in providing evidence-based practices based on these premises. In the sections that follow, both perspectives will be reviewed. It will be obvious that while a number of significant obstacles need to be overcome, the potential benefit of appropriate behavioral initiatives in children offers to provide enormous benefit to the health and well-being of the population.

REDUCTION OF RISK FOR CHRONIC DISEASE

It is important to consider behavioral factors that might reduce or even interrupt chronic disease processes early in life, which would otherwise eventuate in disease in the adult years. Most attention here has been focused on physical activity and fitness in youth, and we can consider this as a strategic preventive health model. Certain facts are clear. Research data in the adult population have clearly documented what has been considered true since antiquity—exercise is good for your health. What's more, the list of diseases for which regular physical activity and fitness reduce risk includes those which are most responsible for morbidity and mortality in developed nations (myocardial infarction, hypertension, obesity, type 2 diabetes mellitus, osteoporosis, certain malignancies).

Important to recognize, though, is the fact that although adverse clinical outcomes from these diseases occur in adults, they often reflect the end-result of lifetime pathological processes that begin in the pediatric years. Early atherosclerotic vascular changes are commonly evident, for example, in teenagers. The majority of obese adolescents become obese adults. Youth who gain less bone density during the growing years carry a greater risk for osteoporosis and bone fractures when they are elderly.

By deductive reasoning, then, it makes sense that early institution of regular exercise habits during childhood and adolescence should be expected to retard the development of chronic disease processes over the course of a lifetime [1]. The result, goes this line of thinking, would be a reduction of disease risk later on in the older adult years. This is a solid concept that is intuitively attractive and which has served as a convincing rationale for promoting high levels of physical activity and fitness in children, sometimes as early as the preschool years [2].

The difficulty lies, though, in that scientific proof of the efficacy of this approach is elusive, since clinical outcomes of exercise interventions won't be obvious for another 30 or 40 years. Designing a long-term longitudinal study that would consider eventual adult health outcomes in active versus inactive children, while considering all the influencing variables, is a daunting proposition. Thus, specific proof of this rationale will probably therefore never be at hand.

As an alternative, then, researchers have focused on examining the influence of activity behavior in children on factors considered to reflect risk of future adverse health outcomes. The evidence, as will be addressed in the chapters that follow, has been mixed. Children who are more physically active generally have been found to exhibit superior bone density, supporting the idea that early accumulation of bone strength will limit the decline in bone density, which is the natural progression in the later adult years. So, here is a behavior—weight-bearing activity that places growth-stimulating stress on bones—which can be confidently supported in children as an effective preventive health initiative.

At the same time, studies examining the relationship in youth between levels of activity and fitness with risk factors for adult atherosclerotic coronary artery disease (abnormal serum lipids, blood pressure) have generally been disappointing [3]. Unlike research findings in adults, no associations have typically been observed. So, there may be differences in such effects between children and adults. However, when such risk factors are considered as clustered together in children, significant associations are observed with activity levels [4] (Chapter 96). And new ultrasound techniques for looking at the physical nature and reactivity of peripheral arterioles in children are showing unfavorable changes in those with other risk factors, particularly obesity [5] (Chapter 92). It is observed, too, that increases in level of physical activity and fitness in youth do appear to lower traditional coronary artery disease risk factors when such factors are abnormal to start with (i.e., in youth with obesity, or hypertension, or hyperlipidemia). It may be, then, that during the growing years, activity and fitness serve to *prevent* the development of cardiac risk factors [2].

Overall, a good deal of indirect information does support the concept, then, that behavioral change (in this case, improved activity habits) in youth can suppress long-term pathophysiologic processes and reduce risk of disease outcomes later in life. Improved noninvasive methods for assessing the development of such processes, as well as the extent that lifestyle changes in children might alter them, should provide better insights in the future.

The concept that behavioral interventions during childhood can result in improved adult health by retarding lifelong pathological processes is not without its challenges. There is currently no means by which the effect of various behavioral changes in the growing years on such disease processes can be directly assessed. The mechanisms by which behavioral interventions might influence pathologic processes is presumably different for the various disease outcomes (that is, one needs to restrict calories to prevent obesity but engage in weight-bearing activities to effect growth in bone strength). Also, establishing dose–effect relationships (how much activity is needed?) for each of these different relationships will be difficult.

CREATION OF HEALTH-PROMOTING HABITS

One of the linchpins of pediatric preventive medicine is the expectation that lifestyle behaviors adopted during the childhood years will persist through to the adult years. This idea serves as the basis for the strategy of introducing children to pleasurable physical activities that will become habit, for instance, rather than prescribing some specific threshold of amount of routine exercise (i.e., 1 h daily). So this is classic behavioral modification, attempts to alter behavior early on that will then hopefully "stick" through the course of a lifetime.

The argument for this approach is intuitively attractive. We expect that behaviors gained during the pediatric years will form the foundation for personal characteristics in adulthood. Such an approach has not, however, been met without criticism. Within the constraints offered by both biologic and external environmental influences, how possible is it to permanently alter lifestyle behaviors in youth? And if this can be accomplished, are there critical periods when attempts at behavior modifications are likely to be most successful? What types of interventions to alter behavior would be most successful?

Unfortunately, there exists a surprising dearth of research information on which to address these issues [6]. A number of studies have attempted to assess whether a physically active youth is more likely to be active as an adult. These have generally failed to show an impressive relationship, but such reports have been weakened by inadequate measures of activity, use of sports play instead of activity levels, and a focus on adolescents rather than young children [7]. Indeed, the key question, whether increasing a sedentary child's level of routine physical activity will result in long-term improvements in activity habits, has never been addressed.

Developmental psychologists have long been interested in what happens to children's behavior patterns over the course of time. Most of this literature has addressed the question of learning behavior, trying to tease out the answer to the question of whether early education will have an impact on future cognitive abilities. Also, much of the research information on acquisition of behavioral habits comes from studies in animals, in which the possible influence of cognitive mechanisms presumably can be disregarded.

In these reports, a number of possible means by which behavioral habits are acquired—and sustained—have been considered. Which, if any, truly reflect central mechanisms for habit formation remains controversial. But within these data might come some clues as to the influence of behavior modification in youth on health-related lifestyles in the adult years.

Conditioning

This is the well-known "Pavlovian reflex" whereby a certain behavior in response to an external cue (a bell ringing) is reinforced by a reward that supports the behavior. This approach has been a common one in efforts to establish intrinsic rewards to regular physical activity. Factors which might support this have included fun, lack of embarrassment or competition, peer acceptance, and charismatic exercise leaders. These have all been considered strong positive reinforcers for engaging in physical activity in youth, but the extent that they are successful in instilling exercise behaviors that persist long term is unknown.

Imitation

Behaviors in children are certainly to a great extent adopted in response to those they witness in family, peers, and what is viewed in the popular media. Development of language, musical tastes, and smoking habits are clear examples. When investigators have examined the importance of parent modeling of physical activities on their children, however, the results have been mixed. Too, the permanence of imitated behaviors might be suspected to change with time in respect to exposure to different social environments (i.e., college).

Imprinting

Studies in animals have convincingly demonstrated that persistent, permanent behavioral patterns can be established in young animals by stimuli presented at certain critical periods in development. These behaviors have generally been social in nature—mating activity, search-and-following behavior, and social attachments—that, interestingly, do not have any functional importance in immature animals and are formed without reinforcement by external rewards.

Whether or not permanent imprinting can occur in human children has been long debated by developmental psychologists, with no consensus of opinion. Moreover, if imprinting of social (or health-related) behaviors can be achieved in humans, the particular vulnerable periods in a child's life when this might occur are unknown.

Whether a child's health-related behaviors, particularly physical activity and nutrition, might be established early on for a lifetime by mechanisms such as conditioning, imitation, and/or imprinting remains an intriguing but unresolved question. Clearly, an impetus in developmental psychology research addressing this question might provide important dividends. The success of pediatric preventive medicine strategies designed to support future health of the child will depend on insights into just how youngsters can be motivated into sustained health-related behaviors.

BIOLOGICAL INFLUENCES ON HEALTH-RELATED BEHAVIORS

At the beginning of this chapter, the traditional concept was presented that behavior that influences one's health is under the willful control of the individual. This is based on the idea that self-determinism exists in making decisions regarding lifestyle and forms the foundation for preventive health efforts to encourage altering such behavior, both on an individual and population-wide basis. That is, when it comes to health lifestyles, one is free to choose.

In fact, however, recent data have indicated that certain biological factors may also influence not only lifestyle choices, such as how much one exercises, but also the extent that these decisions affect health risk factors. Some evidence suggests, too, that these intrinsic determinants might be more influential in the pediatric years. The extent that such biological factors might control the exercise-health link is not clear at present, but greater insights into such influences will be important in designing public health strategies and understanding outcomes of interventional strategies.

Central Control of Physical Activity Energy Expenditure

If one plots amount of daily physical activity observed in a child as he or she grows, and expresses this relative to body size, a progressive decline is observed [2]. The fall in activity with age is evident both in boys and girls and is consistently observed regardless of whether one uses measures of direct observation, activity monitors, or caloric expenditure. The drop-off in activity is more than minor, amounting to a decline of approximately 45% between the ages of 6 and 16 years. (This decrease in daily activity relative to body size actually continues throughout the life span, but with a less precipitous decline.)

Such a drop-off in regular activity has often been viewed by public health officials with alarm, being interpreted as a trend for adopting an increasingly sedentary lifestyle as the child grows. In fact, however, the persistent decrease in physical activity with age during childhood is a normal biological phenomenon. The best proof of this is that identical declines in daily energy expenditure are observed in all animals as well—from nematodes to chimpanzees. They all demonstrate dramatic decreases in body movement as they age [8].

What is the biological "meaning" of this decrease in energy expenditure as children grow? The clue to the answer to this question may lie in the observation that other major components of energy balance, caloric intake (appetite), and resting metabolic rate demonstrate parallel declines with age. The fall in daily energy expenditure via physical activity may represent, then, one means for the body to maintain a strict energy balance (and body composition) over time [9].

The obvious implication here is that, de facto, there must be an intrinsic, biological controller of daily motor activity that resides in the central nervous system. This conclusion is supported by other evidence, such as the recognized effects of certain pharmacological agents on daily activity as well as changes observed in motor activity after brain damage, either experimentally in animals or in humans with brain lesions [10].

When one considers the goals of strategies to improve physical activity in children, it is important to recognize this natural curve of activity with age. For instance, the significant drop-off in normal activity level indicated by this curve needs to be taken into account when attempting to establish recommended amounts of daily activity for health in children and adolescents of different ages. It is important, too, to realize that interventions to improve activity habits in children are actually attempting to "bend" upward a curve of normal decline in activity with age. The good news is that evidence exists that this biological curve of activity during childhood is, in fact, "plastic," that is, extrinsic factors can influence its shape [3]. Future research models might be best constructed with this concept in mind. Parallels to other health-related behaviors, such as caloric intake, are obvious. Preventive health interventions need to be conceived considering the natural developmental progression of the behavior during the growing years.

Gene–Environment Interaction

The role that genetic information might play in controlling how behaviors affect health risk is an intriguing issue that is just beginning to be investigated. To start with, the evidence is clear that factors such as one's body composition, physical activity habits, and serum lipid profiles are at least partially under genetic control [11]. The next questions, then, have drawn research interest: To what extent can purposeful behavioral modification modify this genetic expression? And what part might genes play in defining the interaction between modifiable risk factors?

As an example of new information, early studies in adults have suggested that an interaction might exist between physical activity and the ACE I/D genotype with blood pressure [12]. Limited studies in children, however, have failed to bear out such a genetic influence [13].

Genetic influences do, in fact, affect behaviors that bear on health and well-being. But the extent that these intrinsic factors control lifestyle "decisions" in contrast to those resulting from self-determined behavior, particularly in the pediatric years, remains uncertain. It does appear evident, however, that the potential biological influences on behavioral preventive health initiatives need to be appreciated when assessing outcomes of these interventions.

VENUES FOR BEHAVIORAL MODIFICATION IN YOUTH

Opportunities for altering health-related behaviors in children arise in a number of venues. Where such strategies might be best focused remains to be defined, though, since each possesses its own particular advantages and disadvantages.

Family

Since it is within the family structure that children first learn behaviors, striving to create a healthy lifestyle in the home setting has obvious appeal. The ways in which the family environment can influence factors such as physical activity and eating habits in youth, however, is complicated. In respect to physical activity, most studies have examined how

parents' role modeling (their own participation in physical activities) and support (verbal, providing exercise resources, or via transportation) are related to level of their child's activity. The results have not always been consistent, and in fact, are sometimes surprising.

Literature reviews have indicated that a significant positive relationship between children's overall daily physical activities and that of their parents (mostly by questionnaires) has been observed in only about one-third of studies. It is possible that this surprisingly weak association may be explained by inadequate measurement tools. In the few studies using more objective activity measures (i.e., accelerometers), positive relationships between parent and child activity levels have been observed. Too, a strong association has been reported between parents' role modeling and children's participation in organized sports.

Important relationships have been described between parent support and overall physical activity in youth. However, how this influence might differ with age and gender has not been consistent among different reports. Similar relationships in respect to age would appear to be obvious for factors such as eating habits, smoking, and sexual activity. More insights are needed on the forms of family-based activity interventions for health-related behaviors which might be most efficacious during different phases of the growing years.

School

The potential role of the school in educating youth regarding wise decision making in matters of healthy behavior would seem to be obvious. However, along with other subjects such as art and music that do not fit into a traditional academic curriculum, health education has often been relegated as a subsidiary and dispensable part of the school curriculum.

This has been particularly true in physical education, in which the school setting has been considered the optimal means of promoting exercise habits in youth. Participation is requisite, with supervision by knowledgeable instructors in a safe setting with proper facilities and equipment. It is particularly frustrating to health-exercise professionals, then, to witness the steady decline in physical education opportunities via its exclusion from the school curricula. Moreover, there appears to be no immediate sign that this trend will be reversed, indicating that efforts to enhance activity levels of youth will need to be expanded to other settings.

Even among the physical education leaders there exists some indecision regarding the particular role of PE classes in the schools for promoting activity. Should physical education class be a place where children actually expend their time in physical activity? Or should the focus be concentrated instead on not only teaching children motor skills but also teaching them why and how to develop a healthy lifestyle. That is, should "education" be the role of physical education?

Physicians' Offices

The advice of physicians carries considerable credibility, and exposure to young patients is high. Indeed, what doctors caring for youth typically do in their offices all day is practice different aspects of preventive medicine. But, in general, physicians have not played a major role in confronting specific issues of inadequate physical activity and poor nutritional choices in their patients. Since health care providers recognize that "exercise deficiency" carries medical risk, for example, one would expect they would. That this opportunity has not been widely embraced can be traced to several barriers: (1) there exists no evidence-based approach by which physicians can provide a specific exercise prescription for the sedentary child, (2) physicians have received little or no training regarding physical activity counseling or nutrition, (3) activity and nutrition counseling is hampered by the time constraints of a busy office, and (4) uncertainties exist regarding reimbursement for behavioral counseling.

COMING CHAPTERS

With the foregoing comments as a preamble, the chapters that follow will provide the reader with an update on some of the more exciting issues that are currently in the forefront of pediatric preventive medicine. It will be obvious, too, that a good number of topics are missing, a necessity given page restrictions and the very global nature of how behaviors in youth can influence lifelong health and well-being. It should be recognized that neglected subjects such as smoking, drug abuse, sexual behavior, sleep and time management, social relations, stress management, sports injury prevention are all pertinent to youth as well as adults.

Pediatric preventive medicine might be expected to encompass issues varying from those of the infant all the way up to maturity. But one of the most intriguing new ideas in this field is that prenatal exposures—even before the fetus confronts the external world—might have important bearing for future health. And, in conforming to the construct of preventive medicine, many of these intrauterine influences might be modifiable. In Chapter 96, Debbie Lawlor reviews current information regarding prenatal influences on future health. It's a new perspective, not entirely well understood, but one which offers the promise of unique insights into factors influencing chronic disease processes.

Elevated cholesterol levels are associated with risk for coronary artery disease in adults, and limited information suggests that hypercholesterolemia bears the same triggering effect early on in the atherosclerotic process during the pediatric years. But the management decisions regarding identification and treatment of youth with abnormal lipid levels have not always been clear and, indeed, have been open to some debate. For clinicians confronting such patients, however, a well-defined approach is necessary. Frank Greer and Steve Daniels provide an overview of this issue in Chapter 94.

One of the most exciting advances in the field of preventive medicine has been the development of the capability for

examining the health of peripheral vessels by high-resolution ultrasound techniques [5]. Based on such studies, one can evaluate early changes in wall thickness, compliance, and reactivity that are reflective of initial phases in the atherosclerotic process. As noted earlier, a major obstacle for pediatric exercise scientists is linking behavioral interventions, particularly physical activity, in children with long-term adverse clinical outcomes. How can one establish, for instance, if a program of 1 h of activity daily in a 10 year old will suppress the development of atherosclerosis and reduced risk of myocardial infarction at age 50? Or determine if disease states in a child, such as obesity or systemic hypertension, accelerate that risk? Early studies, reviewed by Bo Fernhall in Chapter 92, indicate that ultrasound examination of the peripheral vasculature may provide some direct answers to these questions. Evidence of the utility of this approach in answering questions of epidemiology, causality, and intervention success in the field of pediatric preventive medicine is just beginning to accumulate. Whether application of ultrasound techniques to assess vascular health might eventually become useful in the future as a clinical tool in patient management is a tantalizing but as yet untested possibility.

Of all the childhood risks for future health problems, the dramatic escalation in frequency of obesity and the associated metabolic syndrome in the pediatric population has raised greatest concern. A strong link is recognized between childhood and adult obesity, and a distinct relationship exists between obesity and hyperlipidemia, hypertension, glucose intolerance, and insulin resistance as well as orthopedic, gynecologic, oncological, and other chronic health issues. All this adds up to an expected tsunami of adverse disease outcomes as the increasingly obese pediatric population moves into the adult years. This disturbing pattern is examined by Scott Owens in Chapter 91.

The role of physical activity in reducing risk factors for adult cardiovascular disease is described by Lars Bo Andersen and Robert McMurray in Chapter 95. From the standpoint of understanding these relationships in youth, the most important recent findings tell us that amount of daily activity is linked to clustered risk factors. Moreover, such studies have been able to estimate the volume of physical activity that might be necessary to achieve such an association. This information provides hope that future interventional studies looking a clustered risk may be able to establish evidence-based thresholds for salutary activity levels in the childhood population.

Of all the behavior-health links proposed for youth, the impact of early optimization of bone density development on reducing future risks for osteoporosis and bone fractures in the elderly years is perhaps the most compelling. Saija Kontulainen and Don Bailey provide an update on evidence supporting this construct in Chapter 93. This information is particularly useful in indicating that a certain *type* of exercise—weight-bearing activities that put stress on bones—is efficacious for a particular health outcome.

SUMMARY

Behaviors adopted during the growing years (and maybe even in fetal life) bear promise to positively affect health and well-being in respect to lifelong outcomes. In fact, when one considers the potential impact of such health-related behaviors on the major chronic diseases of adults, the importance of pediatric preventive medicine efforts in improving the health of the population becomes quite convincing. The "window of opportunity" of suppressing the early course of development of pathologic processes such as atherosclerosis and obesity offered by early preventive interventions in youth can be expected to pay significant long-term health dividends.

The rationale for the strategy of early lifestyle modifications for their salutary effects on long-term health is compelling and intuitively strong. Nonetheless, in implementing initiatives based on this model, practitioners of preventive pediatric medicine face a number of significant obstacles. Absolute scientific proof of this concept will probably never be available. The lack of immediacy of health outcomes from altered behaviors during childhood creates a problem of motivation. How can one convince a child and his family to exercise a certain amount, or eat a certain way, when any possible benefits won't be evident until 40 years later down the road? Perhaps as a consequence, health practitioners, while recognizing the importance of regular exercise and good nutrition, have traditionally had little confidence in their ability to make such behavioral changes in their patients.

Physicians, health-exercise professionals, physical education teachers—all those involved in guiding youth in positive health-related behaviors—are in need of better methods for modifying behavior. Disillusionment with the ability to change a child's activity or eating behavior on the art of professionals is likely if the means of achieving such results have not been established by good scientific research. Indeed, much more needs to be known before such strategies of behavior modification in youth can be expected to be successful. What strategies are useful? What factors influence success? How do we recognize and manage children at particular risk? And we need to consider children's activity in their social setting. What are the determinants of health-related behaviors in families? The challenges facing pediatric preventive medicine are considerable, but the potential rewards in creating a healthier population are great.

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91 Childhood Obesity and Metabolic Syndrome

Scott Owens, PhD

CONTENTS

Childhood Obesity 1131
Defining Childhood Obesity 1131
Prevalence of Childhood Obesity 1132
Causes of Childhood Obesity 1132
Consequences of Childhood Obesity 1132
Prevention and Treatment of Childhood Obesity 1133
Prevention 1133
Treatment 1134
Childhood Obesity: Summary 1135
Childhood Metabolic Syndrome 1135
Definition and Prevalence of Childhood Metabolic Syndrome 1135
Predictors of Childhood Metabolic Syndrome 1136
Consequences of Childhood Metabolic Syndrome 1136
Treatment of Childhood Metabolic Syndrome 1136
Conclusion 1137
References 1137

The prevalence of childhood obesity and the metabolic syndrome (MetS) has increased dramatically in the United States and other industrialized nations during the past two decades. While the social and psychological burdens often encountered by obese children might seem like challenge enough, there is the additional issue of the short- and long-term medical consequences of their obesity. Since it is likely that primary care clinicians and other health care professionals will have increasingly frequent interactions with obese children, it is important to stay abreast of the latest research in the field.

This chapter will present an overview of the current state of knowledge regarding childhood obesity and the MetS. Childhood obesity will be discussed first, focusing on issues related to definition, prevalence, consequences, causes, prevention, and treatment. Presentation of similar issues related to childhood MetS will follow.

CHILDHOOD OBESITY

Defining Childhood Obesity

Defining childhood obesity is difficult and no single definition is universally employed [1]. Ideally, the definition should reflect adiposity, or the amount of body fat, and be related to morbidity and mortality outcomes. An ideal measure of body fat would be the following: (1) accurate in its measure of body fat; (2) precise, with a small measurement error; (3) accessible in terms of simplicity, cost, and ease of use; (4) acceptable to the subject; and (5) have published reference values [2]. Unfortunately, no current measure satisfies all these criteria, and there is no precise, widely accepted definition of obesity in children based on body fatness [3]. Due to its simplicity, cost, and published reference values, large-scale national surveys have tended to describe and assess childhood overweight and obesity utilizing body mass index (BMI), which is calculated as weight in kilograms divided by height in meters squared. To account for variability due to age and sex, BMI in children is compared to age- and sex-specific reference values. In the United States, the Centers for Disease Control and Prevention (CDC) year 2000 growth charts serve as reference values [3]. The National Center for Health Statistics (NCHS) and the CDC now use the term "overweight" for childhood BMI values between the 85th and 95th percentiles (formerly called "at risk for overweight") and the term "obesity" for childhood BMI values at or above the 95th percentile (formerly called "overweight") [3]. Recently, two alternative approaches to defining childhood obesity have become popular: waist circumference (or indices based on waist circumference such as waist to height ratio) and BMI values interpreted relative to the International

Obesity Task Force cut-points rather than national percentile cut-points [1]. However, a recent systematic review concluded there was no compelling evidence for use of waist circumference or International Obesity Task Force–based BMI values in preference to national BMI percentiles for the identification of children with excess fatness or adverse cardiometabolic risk profile [1]. Other commonly used thresholds for overweight and obesity in childhood are 110% or 120% of ideal weight-for-height and weight-for-height z-scores of higher than 1 or 2 [4].

Prevalence of Childhood Obesity

The prevalence of childhood overweight and obesity has more than tripled in the United States over the past three decades with rates high among most age, sex, racial/ethnic, and socioeconomic groups [5]. Data from the 2007 National Survey for Children's Health (ages 10–17) reported the prevalence of overweight (BMI ≥ 85th sex- and age-specific percentile) as 31.6% and the prevalence of obesity (BMI ≥ 95th sex- and age-specific percentile) as 16.4% [6]. Thus, nearly one in three U.S. children is either overweight or obese [7]. Ethnic differences are also apparent. After adjusting for socioeconomic and behavioral factors and for state of residence, Black and Hispanic children, respectively, had 71% and 76% higher odds of obesity than their White counterparts [5]. Nor is the obesity epidemic limited to the United States, with estimates for overweight and obesity of 38% for Europe, 40% for the eastern Mediterranean, 27% for the western Pacific, and 22% for Southeast Asia [8].

Causes of Childhood Obesity

At the fundamental level the cause of childhood obesity can be seen as a greater imbalance between energy intake and energy expenditure than expected for normal growth and development [9]. Still, an epidemiologic perspective informs us that the causes of childhood obesity are complex and multifaceted [10]. A risk factor perspective for childhood obesity as summarized by Kipping et al. [11] and Han et al. [4] is shown in Table 91.1. Concomitant with the risk factor perspective is the notion that childhood obesity has been fostered by the presence of an "obesogenic" culture that relentlessly exposes children to a food environment that promotes overconsumption of calorie-dense, nutrient-poor foods while supporting a physical activity environment that favors sedentary behavior [12]. Thus, a complicated interplay of risk factors, an obesogenic environment, and genetic susceptibility appear responsible for the current epidemic in childhood obesity.

TABLE 91.1
Risk Factors Associated with the Development of Childhood Obesity

Risk Factor	Comment (References)[a]
Single-gene defects	Obesity is the specific abnormality, e.g., those related to the leptin signaling pathway [14]
Genetic obesity syndromes	Obesity is a manifestation of Prader-Willi, Cohen, Alstrom's, and Bardet-Biedl syndromes [14]
Endocrine disease	Diseases include hypothyroidism, Cushing's disease, Cushing's syndrome, growth hormone deficiency, growth hormone resistance, pseudohypoparathyroidism [15]
CNS pathology	Can result in hypothalamic obesity syndrome [16]
Inheritance	Genome-wide association studies have identified genetic variants that are associated with obesity [17]; children with obese parents are at high risk for becoming obese [18]
Ethnicity	Hispanic children have an increased risk of obesity compared with White children [19]
Intrauterine exposure to gestational diabetes	In populations at high risk for obesity (such as Pima Indians), exposure to gestational diabetes is associated with increased risk of childhood obesity [20]
Birthweight	High birthweight is associated with increased fat and lean mass [21]; Small-for-gestational-age babies who show catch-up growth might be at increased risk for childhood obesity [22]
Diet	High energy intake and high consumption of sweetened drinks are prospectively associated with increased risk for childhood obesity. Evidence for other dietary habits is not strong [23]
Physical activity	Low levels of physical activity are associated with high childhood obesity risk [24]
Television viewing	High television viewing hours associated with increased childhood obesity risk [25]
Sleep	Short sleep duration is associated with increased risk for childhood obesity [26]
Socioeconomic status	In developed countries, children in lowest socioeconomic groups have increased risk for childhood obesity [27]
Urban vs. rural residence	Urban residence increases risk for childhood obesity [8]

[a] References are generally for recent systematic reviews of the various risk factors.

Consequences of Childhood Obesity

Overweight children are at risk for significant health problems both during their youth and as adults [9]. As shown in Table 91.2, adverse associations have been observed between childhood obesity and numerous organ systems. Not only are obese children more likely to become obese adults [13], but obesity during childhood carries risk for adult mortality and morbidity. Greater BMI in childhood was associated with increased adult mortality risk from cardiovascular disease [28], being overweight or obese between the ages of 14 and 19 was associated with increased mortality (from age 30 years) from various systemic diseases [29]. In addition to health risks, obesity influences children's quality of life, impacting their physical, social, and psychological functioning [30].

TABLE 91.2
Adverse Associations with Childhood Obesity by Organ System

Organ System	Adverse Associations (References)
Cardiovascular	Dyslipidemia [31]
	Elevated blood pressure [32]
	Atherosclerosis [33]
Pulmonary	Obstructive sleep apnea [4]
	Asthma [34]
Endocrine	Insulin resistance [35]
	Proinflammatory cytokines [36]
	Pubertal advancement [37]
	Metabolic syndrome [38]
Gastrointestinal/ nutritional	Low vitamin D concentrations [39]
	Iron deficiency [40]
	Nonalcoholic fatty liver disease [41]
Orthopedic	Lower-limb malalignment [42]

PREVENTION AND TREATMENT OF CHILDHOOD OBESITY

Prevention and treatment of childhood obesity have progressed along dual tracks, employing both the medical and public health models. According to Schwartz and Brownell [12], the medical model frames childhood obesity as a disease or illness that strikes individuals due to internal or external causes, while the public health model frames it as a disease that strikes a population as a consequence of individual vulnerability combined with exposure to environmental elements. Within the medical model, childhood obesity is an individual child's physical problem identified by a health professional requiring individual treatment. Researchers and clinicians have developed individual and family treatments that address the needs of individual cases. From a public health perspective, epidemiological questions related to childhood obesity are addressed, causal factors for the population are identified, and community, state, or national changes are proposed that appear feasible and likely to have an impact on prevalence. Aspects of both approaches are discussed in the following.

Prevention

Although prevention is universally viewed as the best approach to reverse the rising prevalence of childhood obesity [4], the evidence base for how best to prevent childhood obesity is still incomplete [43]. From a medical perspective, Murray and Battista [44] note that primary care clinicians are in a unique position relative to preventing childhood obesity; no other professional has access to the child and the family in the early critical period before the influences of the obesogenic lifestyle have become fully manifest. They argue that primary care clinicians need to be unambiguous and direct about what the family should and should not do relative to the obesity threat. As a starting point, they recommend the 10 core evidence-based messages and suggestions developed by the Expert Committee on the Prevention and Treatment of Childhood Obesity [45]. Those 10 recommendations are as follows:

- Support exclusive breast feeding for the first 6 months
- Limit sweetened drinks
- Limit TV to 2 h/day and no TV in the child's bedroom
- Do 60 min/day of moderate-to-vigorous physical activity
- Consume five to nine servings of fruits and vegetables per day
- Consume a nutrient-rich diet, high in calcium and fiber
- Eat dinner as a family five to six times per week
- Limit eating away from home, especially fast foods
- Limit portion sizes
- Consume a nutritious breakfast everyday

While primary care clinicians cannot curb the childhood obesity epidemic in isolation from other allied health professions, it is of paramount importance that they continually encourage families to establish daily habits that strengthen their children's nutrition and activity levels [44].

Outside the clinical setting, the majority of prevention programs for childhood obesity have been conducted in schools with targeted outcomes that include reducing weight status or weight gain, changing dietary patterns, and increasing physical activity. The popularity of school-based interventions is not surprising as there are several benefits to the school environment as a context for childhood obesity prevention efforts [43]. For one, nearly all children attend school; the percentage of U.S. children aged 10–14 years of age attending school is greater than 98% [46]. Schools also provide context for the eating and physical activity behaviors that influence body weight, and provide staff and resources (e.g., teachers, coaches, and nurses) that can support the dissemination of interventions [43]. Gonzalez-Suarez et al. [47] conducted a meta-analysis to evaluate the effectiveness of school-based programs in the prevention of childhood obesity. Both short-term (measured at the conclusion of the intervention) and long-term (measured at least 6 months after the intervention) outcomes and odds ratios (OR) were determined. The interventions were generally designed to decrease overweight by increasing physical activity, decreasing sedentary activities, and decreasing intake of foods high in fat and sugar content. A total of 19 studies met the authors' inclusion criteria and were included in the meta-analysis. The results showed that school-based obesity prevention interventions were more effective than the control arms in decreasing the number of children who became overweight or obese (OR = 0.74, 95% CI = 0.60–0.92). Interventions that were conducted for more than 1 year had a higher OR of decreasing the prevalence of

obesity than interventions of shorter duration. The authors concluded that school-based interventions can be effective, at least short term, in preventing childhood overweight and obesity.

The importance of the physical activity component in childhood obesity prevention deserves special mention. In a systematic review of 28 controlled intervention trials to prevent childhood overweight and obesity, Connelly et al. [48] found 11 interventions were effective and 17 were ineffective in reducing adiposity. The main factor distinguishing effective from ineffective trials was the provision of relatively compulsory, rather than voluntary, moderate-to-vigorous physical activity in the effective as compared to the ineffective interventions. Data also suggest that excess abdominal fat accumulation in children can be prevented by regular participation in vigorous physical activity [49]. Based on their review, Watts et al. [50] suggested that obesity prevention in children should emphasize increased physical activity rather than diet since physical activity can help preserve lean body mass normally lost during dietary energy restriction. De-emphasizing diet may also reduce the odds of a child developing disordered eating attitudes and behaviors. The effectiveness of reducing sedentary behavior as an intervention strategy for prevention of childhood obesity has also been investigated. Although the literature is not extensive, a review by DeMattia et al. [51] concluded that an emphasis on reducing sedentary behaviors is an effective intervention to decrease sedentary behaviors and control weight in children and adolescents.

Despite some evidence of success, school-based obesity prevention efforts have several important limitations. For one, they don't include the preschool population [43]. By the time children enter school, more than 20% of 2- to 5-year-olds are already overweight or at risk for overweight [52], suggesting a prime opportunity for preventing childhood obesity is being missed [43]. Unfortunately, programs focusing on infants are lacking [43] and only two of five prevention studies focusing on preschoolers reported significant reductions in weight status or body fat [53]. It should also be kept in mind that even for children attending school, most of a child's day is spent outside of school where opportunities for obesogenic behaviors are abound. The household or family, therefore, plays a key role. Randomized controlled trials focusing solely on household or family-based interventions to prevent childhood obesity are lacking [4].

Current opinion is that in order for childhood obesity prevention efforts to have a consistent, meaningful, and widespread impact prevention efforts must include the larger social environment in which children reside [12,30,54]. The first fully embedded, community-based initiative designed to change the environment to prevent obesity in early elementary school children appears to be the Shape Up Sommerville: Eat Smart, Play Hard project conducted in Somerville, MA [55]. In this intervention, which targeted children in grades 1–3, academics partnered with community members to conduct a controlled trial evaluating whether an environmental change intervention could prevent a rise in BMI z-scores in young children through enhanced access and availability of physical activity options and healthy food throughout their entire day [56]. Year-one results showed that BMI z-scores in the intervention community (n = 385) decreased by −0.1005 (p = 0.001, 95% CI = −0.1151 to −0.0859) compared with the children in the control communities (n = 793). The authors suggested that the effectiveness of a community-based model represents a step forward in society's approach to childhood obesity.

While some limited successes in preventing childhood obesity can be pointed to, it has been suggested that legislative and regulatory action will be needed if substantial progress is to be made [12]. Some states have already taken action. For example, 28 states and the District of Columbia have set nutritional standards for school lunches, breakfasts, and snacks that are stricter than current USDA requirements, 20 states have passed requirements for BMI screenings for children and adolescents or have passed legislation requiring other weight-related assessments in schools, 23 states and the District of Columbia have laws that establish programs linking local schools farms to schools, and 23 states impose a sales tax on soda [57]. In addition, the White House Task Force on Childhood Obesity was created in 2010 and included a national action plan, with all agencies of the federal government participating, that included the goal of reducing childhood obesity rates from 17% to 5% by 2030 [57]. The impact of these recent legislative actions awaits evaluation.

Treatment

For the foreseeable future, treatment of childhood obesity will be an important individual and national health challenge. The Expert Committee on the Prevention and Treatment of Childhood Obesity has developed a set of recommendations for primary care clinicians that are prescriptive and specific [45]. Murray and Battista [44] note the intent of the expert committee was to put the responsibility for initial counseling and follow-up on the primary care clinician and to anchor the problem with one health care provider who could sustain long-term follow-through. Development of a care plan might begin with one or two easily achievable goals selected from the expert committee's evidence-based 10 core messages (listed previously). The process of shared goal setting by clinician and family, with subsequent close follow-up and establishment of fresh goals, is the central strategy for obesity treatment.

Recent meta-analyses indicate that multicomponent, family-based obesity treatment interventions are associated with modest, but clinically important, short-term improvements in child obesity status compared to standard care or no treatment control conditions [58–61]. While Epstein et al. [29] also noted that family-based behavioral pediatric obesity treatment programs have demonstrated both short-term and long-term efficacy, they

add that there is likely to be an increase in the prevalence of very overweight youth who require more powerful interventions than those currently available. They suggest that traditional clinical treatments that focus on the child and family may need to be combined with public health approaches that focus on the school and community to change the environment that promotes unhealthy eating and sedentariness.

Although schools have not been regarded as the main site for treatment of childhood obesity (as opposed to prevention), promising results from a randomized trial of classroom-based weight reduction in obese Mexican American children appear relevant [4]. In this study [62], 60 children between the ages of 10 and 14 years at or above the 85th percentile for BMI were randomly assigned to a 6 month intensive intervention or self-help condition. Children in the 12 week intervention group received nutrition instruction 1 day/week and physical activity training 4 days/week during a standard school period lasting 35–40 min. In addition, their parents were invited to attend monthly meetings to teach them how to adapt family meals and activities to facilitate healthy changes. Children and parents in the self-help group were provided *Trim Kids*, a book to be used for weight management by children and their families. Children in the intervention condition significantly reduced their z-BMI when compared to the children in the self-help condition at both 3 and 6 months. The authors noted that further efforts are needed to evaluate the long-term lifestyle changes.

At the community level, results on the effectiveness of the *Mind, Exercise, Nutrition, Do It (MEND) Program*, a multicomponent, community-based childhood obesity intervention, appear promising [63]. In this study, conducted in the United Kingdom, 116 obese children (BMI > 98th percentile) were randomly assigned to intervention or waiting list control (6 month delayed intervention). Parents and children attended 18 two hour educational and physical activity sessions held twice weekly followed by receipt of a 12 week free family swimming pass. At 12 months, children in the intervention group had reduced their waist circumference and BMI z-scores by 0.47 ($p < 0.001$) and 0.23 ($p < 0.001$), respectively. High attendance rates suggested the families found this intensive, community-based intervention acceptable.

Schwartz and Brownell [12] note a prime challenge for the future is to discover which childhood obesity interventions, policies, or programs have the greatest impact. They argue this will require a major research effort, one that is much larger than currently funded by the government. It must involve sensitivity to global factors that affect diet and activity and take into account broad social forces such as economics and the influence of industry.

CHILDHOOD OBESITY: SUMMARY

The prevalence of childhood obesity has risen to unacceptable levels. Progress has been made regarding our understanding of the causes of this epidemic, its current and future health consequences, and potentially effective prevention and treatment interventions. Much work is yet to be done, including increasing our knowledge of childhood obesity and its relationship to the MetS.

CHILDHOOD METABOLIC SYNDROME

The notion of a MetS, that is, the clustering in an individual of a set of risk factors thought to put the individual at increased risk for cardiovascular disease and type 2 diabetes, was developed more than 20 years ago [64]. Originally and most commonly applied to adults, the utility of a MetS designation for children has generated considerable clinical and research interest, coincident with the rise in childhood obesity. Although divergent opinions exist regarding the diagnostic value of MetS in children [65], it has been argued that the presence of several cardiometabolic risk factors in one individual, even at subclinical levels, predict future progression to overt chronic disease and potentially make MetS a sentinel marker for highlighting the need for more aggressive intervention efforts beyond the traditional treatment options for overweight and obese youths [66].

Definition and Prevalence of Childhood Metabolic Syndrome

Despite many publications on MetS in children, there are no standard criteria for what constitutes a pediatric MetS [44]. A number of diagnostic criteria for childhood MetS have been utilized, typically based on risk factors identified for adults, but with modifications in the cutoff values [66]. Recent consensus conferences have differed as to what the cutoffs should be [67–69]. The only consensus about the use of an adult definition of MetS for pediatrics is that none of the adult definitions can be applied without problems [44,65]. Pediatric-specific cut-points that are sensitive to age, gender, and ethnicity have not been determined for the majority of the MetS components [44,65].

The differing cut-off values used with children, even when relatively small, have resulted in widely varying MetS prevalence rates. For example, Goodman et al. [70] studied 1098 students in an Ohio public school district and reported a MetS prevalence of 3.4% using criteria suggested by the American Heart Association (AHA) that included the presence of three or more of the following: glucose ≥100 mg/dL, triglycerides ≥150 mg/dL, HDL-C ≤ 40 mg/dL for boys and ≤ 50 mg/dL for girls, waist circumference ≥ 102 cm for boys and 88 cm for girls, or diastolic BP ≥85 mmHg, systolic BP ≥ 130 mmHg. The prevalence was 4.5% when using the criteria suggested by the International Diabetes Federation (IDF), whose criteria were the same as those of the AHA except for waist circumference (≥94 cm for boys and 80 cm for girls). When these two sets of criteria were applied to a subset of obese children (BMI ≥ 95th percentile or BMI ≥ 30), the MetS prevalence rates were 14.8% using the AHA criteria and 18.5% using the IDF criteria.

Cook et al. [71] applied several different MetS criteria to the 1999–2002 National Health and Nutrition Examination Survey (NHANES) data set and obtained MetS prevalence rates that ranged between 2.0% and 9.4% for a nationwide sample of 12- to 19-year-olds. In obese children, the different criteria yielded prevalence rates that varied from 12% to 44%. Although these results illustrate the variability of prevalence rates based on the particular MetS criteria employed, they also consistently show that obese children have a higher prevalence of MetS regardless of MetS criteria employed. Data also suggest the prevalence of childhood MetS is increasing [72], with the 4.2% prevalence in NHANES III rising to 6.4% in the 1999–2000 NHANES data [73], and increasing to 8.6% using the 2001–2006 NHANES database [65]. The 2001–2006 NAHANES data also revealed gender and ethnic differences. Prevalence of MetS was higher in males (10.8%) than in females (6.1%) and higher in Hispanic (11.2%) and White (8.9%) individuals than in Black individuals (4.0%) [65].

Predictors of Childhood Metabolic Syndrome

Several predictors of childhood MetS warrant mention. Hirschler et al. [74] determined MetS in 1009 elementary school children and reported an overall MetS prevalence of 5.8%, which increased to 16.4% in overweight/obese children, and to 32% in the severely obese children. Multiple regression showed that BMI and insulin resistance (assessed using HOMA-IR) predicted MetS after adjustment for gender and Tanner stage. The predictive power of insulin resistance for MetS harkens back to Reaven's original hypothesis that insulin resistance was the driver and pathophysiological link for the clustering of the metabolic components [44,63]. Although physical activity was not assessed by Hirschler et al., its association with childhood MetS has been observed by others. Kelishadi et al. [75] determined MetS and physical activity levels in 4811 children aged 6–18 years and reported that in both genders, before and after adjustment for BMI and age, low levels of physical activity significantly increased the risk of having MetS (in boys: OR = 1.8, 95% CI = 1.2–2.1; in girls: OR = 1.6, 95% CI = 1.1–1.9). In the European Youth Heart Study, MetS risk score was inversely related ($p = 0.008$) to objectively measured physical activity (3 days of accelerometry) among 589 Danish children participating [76]. Okosun et al. [77] examined the independent and joint association of BMI and leisure time physical activity with MetS risk score in 12- to 17-year-old children in the 2003–2004 NHANES database. There was a gradient of increasing MetS risk score by increasing BMI and a gradient of decreasing MetS risk score when progressing from sedentary to moderate-to-vigorous leisure time physical activity. The authors suggested that promoting leisure time physical activity at all levels of weight status may help to reverse the increasing trends of MetS in U.S. children. In a group of 212 healthy 7- to 12-year-old children, Casazza et al. [78] reported that diet composition was a significant predictor of several components of the MetS, with a greater intake of energy from carbohydrate being associated with a greater waist circumference and higher triglyceride and glucose concentrations.

Consequences of Childhood Metabolic Syndrome

Debate over whether the clustering of risks of the MetS is synergistic or additive is probably less important than the recognition that finding any or all of the components of MetS in a child indicates a negative prognosis [44]. For example, it has been estimated that the number of years of life lost due to type 2 diabetes for an individual diagnosed at age 10 ranges from 16 to 23 years, depending on gender and ethnicity [79]. At the same time, MetS in childhood has been reported to be a predictor of adult type 2 diabetes [80]. Obesity associated with MetS comorbidities markedly increases the risk for early adult cardiovascular disease [81]. Diagnosis of MetS in adolescence appears to be a good predictor for developing adult MetS within a short period of time [82]. The extremely high prevalence of MetS in obese children indicates that children of excess weight should be considered as targets of any future screening initiatives [83].

TREATMENT OF CHILDHOOD METABOLIC SYNDROME

The first line of treatment of MetS in adults is generally approached with diet and physical activity (in lieu of pharmacologic treatment) [77]. This approach has also been recommended for childhood MetS [84]. Although the research literature specifically targeting childhood MetS with diet and physical activity is not extensive, some encouraging data have emerged. Reinehr et al. [85] examined changes in MetS prevalence (using IDF criteria) in 476 obese children receiving or not receiving a 1 year outpatient lifestyle intervention. The intervention included physical activity, nutrition education, and behavior therapy. Prevalence of MetS for children in the intervention group decreased significantly from 19% at baseline to 9% at 1 year, whereas the nonintervention group experienced no significant change in MetS prevalence. Kelishadi et al. [86] conducted a 6 week diet and exercise intervention with 35 obese children aged 12–18 years. Participants performed supervised moderate-to-vigorous aerobic activity for 60 min, 3 days/week for 6 weeks and received dietary advice from a registered dietician. At the end of the study, the prevalence of children classified as having MetS (using National Cholesterol Education Program Adult Treatment Panel III criteria) decreased from 32.4% to 14.2% ($p = 0.02$). Coppen et al. [87] conducted a retrospective review of 135 children and adolescents (aged 6–19 years) who completed a 10 week, medically supervised, weight-loss program that focused on healthy eating and physical activity. Initially, 53 of the 135 participants (39%) were diagnosed with MetS. After the 10 week program, resolution of MetS was seen in 75.5% of the participants originally diagnosed with MetS. These studies indicate

that lifestyle interventions can reduce the prevalence of MetS in children. Questions about optimal "dose" to achieve results remain, as do issues related to long-term effectiveness and whether treating childhood MetS differs in some meaningful way from treating childhood obesity.

CONCLUSION

Childhood obesity and childhood MetS are likely to be common in many societies in the near- and possibly longer-term future. It should be the goal of the health care professional to make that future as short as possible. The enormity of the problem suggests that all components of the culture will need to be participants in working toward solutions.

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92 Arterial Function in Children
Effect of Exercise and Lifestyle

Bo Fernhall, PhD

CONTENTS

Carotid IMT 1141
Endothelial Function 1143
Arterial Stiffness 1147
Conclusions 1149
References 1149

Cardiovascular disease (CVD) is the leading cause of death in the United States and the Western world, and it is growing fast in developing countries, to the point where CVD has been called a global epidemic [1]. It is now clear that atherosclerosis, the underlying disease process in CVD, is a lifelong disease, starting in early childhood [2]. The beginning of lipid accumulation in the intima of large arteries eventually creates fatty streaks, recognized as a beginning stage of the atherosclerotic process [2,3]. Fatty streaks are common in the aorta by 3 years of age, and continue to increase throughout childhood as shown by autopsy studies [4,5]. Actual atherosclerotic plaque may be present in the coronary arteries during adolescence and early adulthood [6]. These changes in the artery result in alterations in arterial structure and function, which can be measured relatively easily in children using noninvasive technology [7].

Traditional risk factors for CVD, such as hypertension, elevated LDL-cholesterol, low HDL-cholesterol, diabetes, and obesity, are associated with early manifestation of atherosclerosis [8]. The prevalence of risk factors among children has also been increasing, concomitant with the increase in the incidence of obesity [1,7]. This is disconcerting as traditional cardiovascular (CV) risk factors that are present in childhood can predict CVD risk in adulthood [8–10]. CVD risk factors present in childhood also predict pathological changes in the arterial tree in adulthood [11,12]. These data suggest that there may be an increase in the incidence of CVD in the future, as children and adolescents progress into adulthood [1].

The ability to evaluate the risk for CVD more directly than through risk factor analyses is desirable, especially in children, since the presence of overt symptomatic disease will usually not present until later in adult life. Being able to evaluate arterial structure and function prior to the development of angiographically measurable atherosclerotic plaque is an important aspect of early detection and risk classification in both adults and children [1,13–15]. Although this can be done very accurately using noninvasive technology such as electron beam CT, the radiation exposure of this technique makes it less appropriate in children [1]. Other noninvasive measures more appropriate for children include measurement of carotid intima–media thickness (IMT), endothelial function, and arterial compliance [16–21]. These variables may be particularly useful in children, given their noninvasive nature and relative ease of measurement.

Collectively, IMT, endothelial function, and arterial stiffness can be considered markers of subclinical atherosclerosis, and alterations in these subclinical markers are associated with coronary artery disease, stroke, and CV mortality in adults [22–25]. Decreased endothelial function and increased arterial stiffness may also affect the ability to exercise due to reduced peripheral blood flow, impaired myocardial performance, and decreased myocardial blood flow [15,26,27].

CAROTID IMT

Carotid IMT is the most commonly measured IMT due to its accessibility and because it is predictive of adverse CV events in adults [22,23,28]. The artery can be reliably imaged using high-resolution B-mode ultrasound. The leading edge of the lumen–intima interface to the media adventitia interface is measured. The far wall carotid IMT from the ultrasound image provides an accurate representation of IMT compared with data from histological exams [1,16]. The image is normally obtained of the common carotid artery, 1–2 cm proximal from the bifurcation. Using wall tracking software, a segment of the artery can be selected and the maximal and mean IMT can be selected from that entire segment, as shown in Figure 92.1. For accurate determination in children, it is essential that the image is obtained using a high-frequency probe. For more detail on recommended procedures of how to obtain valid and reliable measures of IMT in children, the reader is referred to Urbina et al. [1].

The developmental changes in IMT with age during childhood are unclear at this time. There is some evidence that carotid IMT increases with age in a linear manner, but the

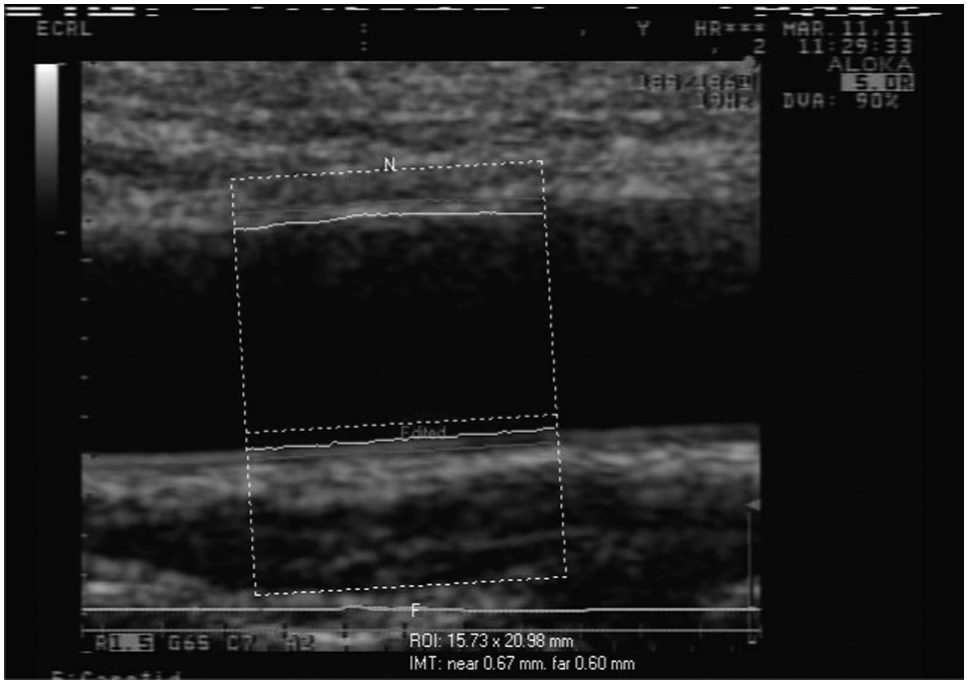


FIGURE 92.1 An example of a carotid artery image with automated detection of IMT, showing how a section of the common carotid is selected and IMT is evaluated over the entire section. This image also demonstrates the difference in image clarity between the near and far wall.

correlations are very low, usually 0.15 or less [29,30]. Others have found no correlations between age and IMT during the developmental stages of childhood [31,32]. This is likely a function of the small changes observed in IMT between 7 and 18 years of age. For instance, the median carotid IMT was shown to increase from 0.384 to 0.400 mm between 10 and 20 years of age [30]. This is only a 0.016 mm increase in 10 years and the clinical or functional significance of such a small change is unclear. These changes in carotid IMT are also accompanied by increases in arterial size [30,32], thus increases in carotid IMT may only be a reflection of an overall growth in vessel size. Nevertheless, since others have shown no change in carotid IMT with age in childhood, no clear conclusions can be made. It is also difficult to determine what would be a clinically "abnormal" IMT in children, since a child's IMT is usually considerably smaller than what is considered clinically significant in adults. However, mean carotid IMT in studies on normal children is rarely above 0.50 mm with 95% confidence intervals of ±0.07 mm. This would suggest that one could potentially consider a carotid IMT above 0.6 mm as "abnormal" in children regardless of age, but empirical and clinical support for this notion is lacking. However, it is likely that there are developmental changes in thickness and density of the media, as shown by postmortem studies of the aortas of children [33,34]. This suggests that even without developmental changes in carotid IMT, the arterial wall properties change, which will likely affect arterial function regardless of the absolute level of IMT [35].

Obesity is strongly associated with increased carotid IMT in children [36,37] although not all studies [38] have found increased IMT in obese children. Importantly, a recent large-scale study found not only increased carotid IMT in obese children, but the association between carotid IMT and body mass or adiposity was also present in children who were not overweight or obese [39]. Carotid IMT may be 25% higher and is directly correlated to body mass index (BMI) in obese children, but the increased IMT appears to be independent of vessel size. Furthermore, waist circumference was as strongly associated with carotid IMT as BMI, suggesting that abdominal obesity in particular may affect arterial structure [39]. This is important considering that obese children with metabolic syndrome have greater IMT and greater cross-sectional area of the intima–media complex compared to healthy control children [40]. Children with familial hypercholesterolemia [41–43] and type 1 diabetes [44–47] also exhibit increased carotid IMT. This suggests that the effect of obesity and other CVD risk factors on carotid IMT may be additive. However, it appears that obesity may have a greater effect on carotid IMT than other CVD risk factors. Mittelman et al. [39] found that the association between adiposity and carotid IMT remained after controlling for conventional risk factors such as blood lipids and blood pressure (BP). This is especially disconcerting since obesity in childhood is linearly related to carotid IMT in young adults, and those individuals with largest BMI who had been obese the longest exhibited the greatest IMT as young adults [48].

Recent studies have shown that both sex and race, and also possibly socioeconomic status affect IMT [39,49]. Mittelman et al. 2010 found boys to have greater IMT than girls, but this is not a uniform finding [30,32]. A more uniform finding is that African American children exhibit 4%–5% greater IMT values than Caucasian children [39,49].

The higher IMT values in African American children cannot be explained by traditional risk factors such as obesity, BP, or lipid profiles. However, since lower socioeconomic status is also related to higher IMT, it is possible that this contributes to the racial differences, since African Americans are overrepresented in the low socioeconomic strata [49]. The higher IMT in African Americans is consistent with data on adults, which also show higher IMT in this group [50,51].

Lifestyle interventions have not been found to affect carotid IMT in normal healthy children. However, lifestyle interventions may be effective in obese children. Longer-term interventions (6 months or more) may improve carotid IMT in overweight or obese youth [37,52,53]. For instance, carotid IMT decreased significantly in obese youth 11–16 years of age compared to age-matched controls following 6 months of exercise training [37]. Similar results were shown in 9- to 12-year-old children following 12 month programs of dieting alone or a combination of diet and exercise, although the diet and exercise program elicited greater benefits [52]. Interestingly, intervention-induced weight loss may be important to reduce carotid IMT, as a 12 month-long intervention in obese prepubescent children (the program included exercise training, nutrition education, and behavior therapy) reduced carotid IMT only in those children who experienced substantial weight loss [53]. In contrast, short-term lifestyle interventions have shown no effect on carotid IMT in children [52], suggesting that lifestyle interventions need to be sustained for a longer period of time to be effective. This notion is supported by data from a trial on pravastatin versus a placebo in children with familial hypercholesterolemia [54]. Following 2 years of therapy, carotid IMT was reduced in the statin group but not in the placebo group. Consequently, to have an effect on carotid IMT it appears that interventions need to be long term, suggesting that arterial structure is not easily modified in children.

The potential mechanisms for changes in IMT with lifestyle interventions are not currently known. It is possible that the detrimental effects of hypercholesterolemia on the arterial wall, which lead to increased expression of adhesion molecules, LDL infiltration and oxidation, and increased inflammation [2] are altered with lifestyle interventions. However, LDL-cholesterol has not always been associated with improvements in arterial structure [41,42,55], suggesting a more complex interactive process. Hypertension may also affect IMT and most lifestyle interventions lower BP, but there are no data in children linking changes in BP to changes in IMT [1]. The success of statin treatment in IMT in children, regardless of LDL-receptor genotype, suggest that other mechanisms such as the anti-inflammatory effect of statins may play a role; however, this remains to be elucidated.

ENDOTHELIAL FUNCTION

The endothelium controls the balance between vasodilatation and vasoconstriction and has a number of other functions related to vascular health, including control of coagulation and fibrinolysis, inflammation, and angiogenesis [56]. The vasoactive substance produced by the endothelium that has received the most attention is the production of nitric oxide (NO). NO is produced from L-arginine as endothelial nitric oxide synthase (eNOS) essentially cleaves NO from L-arginine. NO then produces vasodilatation through relaxation of the vascular smooth muscle [13,14,57–59].

Endothelial function can be evaluated using high-resolution ultrasound where the brachial artery is visualized and artery diameter is measured in response to various stimulators. This is commonly accomplished by the arterial response to infused vasoactive substances, such as acetylcholine, which increases NO production [58,59]. However, the invasive nature of this approach is probably not appropriate for use in healthy children. Thus, the more common approach is a noninvasive assessment using flow-mediated dilation (FMD). By inducing a hyperemic stimulus, the artery dilates as a result of NO release produced by shear stress. The amount of dilation can be accurately measured using high-resolution ultrasound, thus providing a measure of the ability of the artery to dilate in response to shear stress, a measure of endothelial function [13,14,58,60].

Endothelial function is usually evaluated in the brachial artery, as a measure of conduit artery function. With subjects in a supine position, the artery is visualized in the longitudinal plane above the antecubital fossa. The artery is imaged at rest with pulsed mid-artery Doppler measures of blood flow performed as well. In addition, a simultaneous ECG should be recorded, and the ultrasound images need to gated to the ECG, usually the R-wave, to ensure end-diastolic measurements. This is important because the size of the artery changes a great deal between diastole and systole. After the resting images, a BP cuff is typically placed on the forearm (but could be placed on the upper arm) and inflated to 250 mmHg, or to at least 50 mmHg above systolic pressure, for 4–5 min. It is important to standardize the time of inflation, as this will affect the outcome. Also, upper arm cuff placement generally produces greater vasodilatation but it is more challenging obtaining good images. Following release of cuff pressure, the artery is continually imaged for 2–5 min and evaluated for %maximal dilation, using automatic edge detection software [1,13,14,57,61]. This allows for a selected segment of the artery to be evaluated, resulting in more reliable measures [1,61]. An example of this is shown in Figure 92.2. The hyperemic response is also evaluated using pulsed Doppler, at least during the first 15–20 s, but ideally throughout the measurement period following cuff release [1,61]. The Doppler measurements are used to evaluate the hyperemic stimulus from the calculated shear rate. This is important, because the amount of vasodilatation needs to be standardized to the shear rate stimulus provided [61]. After the FMD measurement (and a 10 min rest period), the endothelium-independent vasodilatory response is often evaluated following administration on nitroglycerin. This is done without any cuff inflation, but otherwise using the same technique as described previously. The artery is visualized continuously for 4–5 min after nitroglycerin administration and the maximal amount arterial dilation is measured.

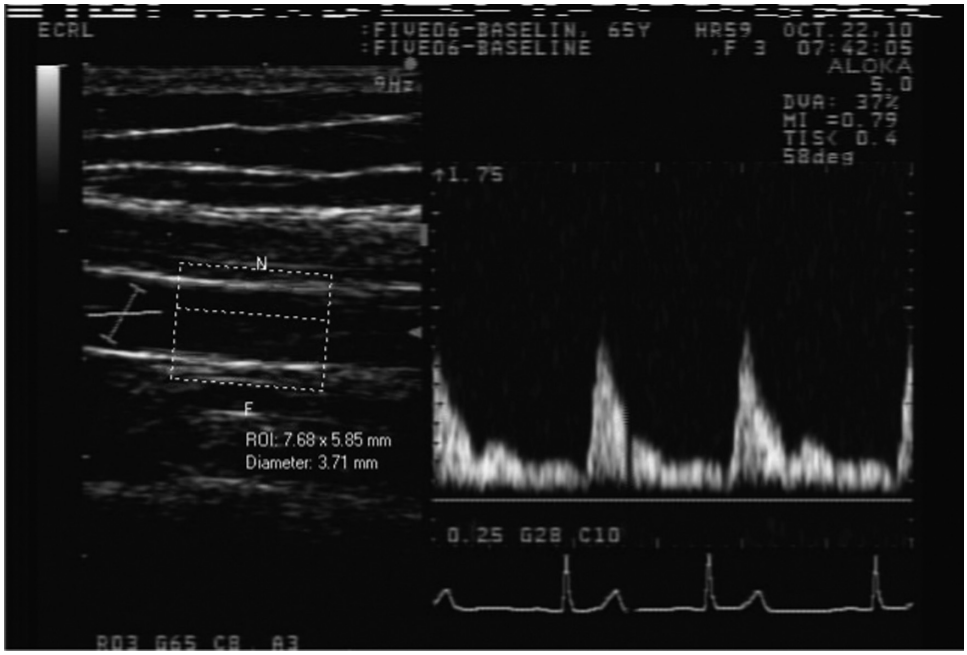


FIGURE 92.2 An example of a brachial artery image with automated wall detection and Doppler images as used for FMD.

The nitroglycerin-induced vasodilation is considered an index of smooth muscle function [14], which is not dependent on the function of the endothelium. It is also important to control for many other factors that affect endothelial function. This includes time of day of measurement, medication, caffeine, antioxidants, high-fat foods, smoking, alcohol, exercise, and menstrual status. (For a more complete description of the specific methodology, please consult the other following papers [1,13,14,61].)

Endothelial function does not appear to change throughout childhood in normal, healthy, nonobese children [37,38,52,62]. The mean FMD in healthy nonobese children is typically between 8% and 11% (Figure 92.3) [35], but values as low as 4% have been reported [63]. However, the range of a normal FMD response is very large, with the 95% confidence interval reportedly between 2% and 18% among healthy children [38,52,64]. This response is similar to that of healthy young and middle-aged adults [13,14], but also overlaps with values for populations with reduced endothelial function, making it difficult to address what a "normal" value for FMD is in healthy children [35]. It is also unclear if the large range of normal FMD values is due to normal biological variability or to measurement error, making comparisons of data between studies very difficult. However, FMD is reduced in both children and adults with CV risk factors [13,14,65,66] when compared with control groups. Although FMD has been shown to predict clinical outcome in adults [25,67], the clinical implications of low FMD in children are uncertain, even though children with standard CVD risk factors usually present with low FMD compared to controls [1,7,35].

Endothelial function is reduced in children with CVD risk factors compared to controls, and is also reduced in children with infectious diseases such as human immunodeficiency virus [1,7,35]. In addition, FMD is reduced in children with

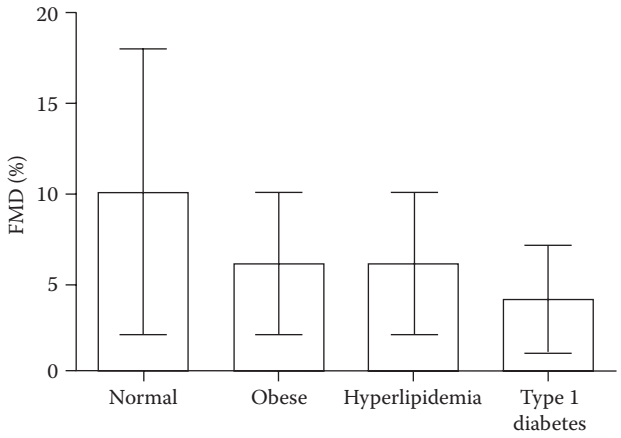


FIGURE 92.3 Common mean values with 95% confidence intervals of FMD for different groups of children demonstrating that children with CVD risk factors have reduced FMD, but the 95% confidence intervals are very large creating a great deal of overlap between all groups.

type 1 diabetes and in children with kidney disease, and this reduction does not appear to be related to other CVD risk factors [1,68,69]. This might suggest that other factors, such as inflammation and oxidative stress, have important influence on FMD in children, in addition to CVD risk factors, a phenomenon that is well accepted in adults [56]. A comparison of FMD between normal healthy children and children with CVD risk factors and/or other conditions is shown in Figure 92.3. It should be noted that even though the average FMD is higher in normal healthy children, the 95% confidence intervals are very large and, thus, there is a great amount of overlap between all groups.

Most studies have shown a decrease in endothelial function in obese or overweight children, with a mean FMD of

5%–6% in the obese cohorts compared to approximately 10% in normal-weight controls [35,38,70]. One study has also found smooth muscle function to be significantly lower in the severely obese children, but not in the middle-obese/overweight children, suggesting severe obesity may directly impact smooth muscle function [38]. Obesity may also present with a constellation of arterial deterioration as impaired endothelial function in children may coexist with hypertension, arterial stiffness, and impaired smooth muscle cell function [36,71–73]. Endothelial dysfunction may be due to increased inflammation, as obese children consistently exhibit higher levels of C-reactive protein (CRP) compared to nonobese children [37,40,74]. However, BMI alone contributes to endothelial dysfunction, even when controlling for CRP, suggesting an inflammation independent, but obesity-dependent factor [35]. Higher leptin levels in obese individuals may explain this, since there is a dose–response relationship between leptin and atherosclerosis [66,75]. Several other factors, including insulin resistance, increased blood lipids, and BP, may also have a role [37,38,40,74].

Endothelial dysfunction manifested as reduced FMD is often present in children with elevated blood lipids [13,65,76]. This may be related to detrimental effects of hypercholesterolemia on the arterial wall, leading to increased expression of adhesion molecules, LDL infiltration and oxidation, and increased inflammation [2]. This is probably a somewhat simplistic explanation though, because LDL-cholesterol may not be associated with decreased FMD [41,42,55]. Furthermore, children with a family history of CVD also display reduced FMD, even without familial hypercholesterolemia [77]. As shown in Figure 92.3, the FMD typically reported for children with hypercholesterolemia is similar to the FMD of obese children. It is likely that there is overlap between these conditions, both in terms of the phenotype and the potential mechanisms of the reduced FMD response.

It is well documented that children with type 1 diabetes have reduced FMD often in the magnitude of 50%–60% less than controls [44,47,69,78]. This is clearly illustrated in Figure 92.3 and is a larger reduction than what is observed in children with other CVD risk factors. However, it has been shown that the reduced FMD was only present if children with type 1 diabetes who had hypercholesterolemia [44] or with concurrent acute inflammation as a result of infection [79]. Others have also found that the reduced FMD was related to increased inflammatory status [80] or a combination of inflammation and expression of human leukocyte antigen, suggesting a genetic influence as well [35]. Folate status was also related to FMD in children with type 1 diabetes, suggesting a potential influence of homocysteine levels [78]. However, HbA1c levels do not appear to be related to FMD in children with type 1 diabetes, suggesting that glycemic control per se is not related to impaired FMD in these children [81]. Thus, the available data suggest that the reduction in FMD in children with type 1 diabetes may be associated with oxidative stress, leading to reduced NO bioavailability [1].

Various intervention strategies, such as physical activity, diet, and supplementation with antioxidants, may improve arterial function in children [37,38,53,76,77,82–85]. However, there are very limited data on normal healthy children, especially on the effect of exercise training. Cross-sectional data from Abbott et al. showed habitual physical activity levels measured with doubly labeled water independently predicted brachial FMD among 5- to 11-year-old children [86], with the most active children exhibiting significantly greater FMD compared to their least active peers. However, due to the cross-sectional nature of the study, they were unable to demonstrate that changing physical activity improves endothelial function in healthy children. More recent data, although also cross-sectional, showed that high-intensity physical activity measured using either accelerometry or questionnaire, was an independent predictor of FMD in children [87,88]. However, a subgroup analysis showed that only children in the low-FMD tertile benefited from high-intensity physical activity. Physical activity did not impact FMD in children in the highest FMD tertile [87]. This suggests that only children with substandard FMD, or those with endothelial dysfunction, will actually benefit from physical activity. Interestingly, Pahkala et al. showed that children with the highest leisure time physical activity also had higher FMD [88], but this was only true in boys. In girls there was no association between FMD and physical activity, suggesting a sex difference in this relationship. However, follow-up analysis showed that boys and girls with similar physical activity also exhibited similar FMD. Thus, the lack of a relationship between physical activity and FMD in girls was likely due to the lower physical activity levels in girls [88].

Cross-sectional research also suggests that CV fitness is associated with endothelial function in healthy children [70,87,89]. CV fitness may explain up to 23% of the variance in femoral FMD among children aged 11–14 years [70]. Although Hopkins et al. supported the overall relationship between CV fitness and FMD, they did not find an association between FMD and CV fitness within FMD tertiles [87]. Instead, only high-intensity physical activity was associated with FMD within tertiles, but only in the lowest FMD tertile. Consequently, although fitness may affect FMD to some extent, it appears that high-intensity physical activity is more important in normal healthy children. The seemingly favorable response of endothelial function in healthy children to physical activity and fitness is probably related to increased (or decreased in the low-FMD tertile) NO bioavailability. This is thought to result from the up- or downregulation of eNOS gene expression in response to vascular wall shear stress [56,90,91]. Thus, for children who are not physically active, the eNOS expression is presumably downregulated, resulting in reduced FMD. Conversely, in active children, eNOS is upregulated resulting in improved FMD.

There is a dearth of data on the longitudinal effect of exercise training on endothelial function in normal healthy children. One recent study showed that a randomized controlled school-based exercise program improved the number and migratory capacity of circulating endothelial progenitor cells [92]. The authors provided a daily exercise program to the intervention group, whereas the control group continued

the twice a week normal physical education program. The intervention group showed a significant increase in this marker of endothelial function whereas the control showed a nonsignificant decrease. Unfortunately, these positive results of exercise training have not been replicated using FMD as the outcome variable. There is however, strong evidence that a reduction in physical activity actually reduces FMD [93]. Hopkins et al. found that seasonal variations in physical activity, as measured objectively using accelerometry, affected FMD. More specifically, a reduction in high-intensity physical activity, comparing summer to late fall, was significantly correlated with a reduction in FMD [93]. Thus, these findings support the prior studies showing that high-intensity physical activity or exercise is an important contributor to FMD in normal healthy children.

Another lifestyle intervention, using an 11 year-long dietary intervention (low saturated fat) showed remarkably similar results to those of the cross-sectional studies on FMD and physical activity. The program had long-term beneficial effects on endothelial function in boys, but not in girls [94]. The intervention, which was initiated in infancy, improved brachial FMD in boys at age 11 compared to controls. Importantly though, this effect was nonsignificant after adjustment for cholesterol levels at age 3, suggesting that the relationship between endothelial function and diet was mediated by changes in cholesterol levels [35].

Many more studies are available on the effect of various interventions on the FMD in youth with comorbidities, such as obesity, type 1 diabetes, hypertension, and hyperlipidemia. This is likely because children with these conditions show disrupted endothelial function (Figure 92.3) [37,38,53,76,77,82–85]. Interestingly, several interventional strategies have shown endothelial function is nearly normalized following several types of interventions in various populations of children with risk factors [35].

FMD is improved among overweight and obese children and adolescents, following short-term lifestyle interventions, using either exercise training or dietary modification, or a combination of exercise and diet [52,95–98]. Exercise training alone improves and near-normalizes brachial FMD in obese children and adolescents [96–98]. Only 6–8 weeks of exercise training was needed to obtain these results. These programs were conducted three to four times per week and incorporating either 60 min of sport and play activities [98] or 30–50 min of progressively increased aerobic exercise at 50%–80% of the age-predicted maximum heart rate [96], or a combination of aerobic and resistance exercise training [97]. Interestingly, 6 weeks of inactivity reversed the exercise-induced improvement in FMD [97], suggesting that physical activity and exercise need to be adopted as part of a lifetime lifestyle to realize the benefits [52,97]. However, not all studies show improved FMD in obese children with exercise training. Recent findings from Farpour-Lambert et al. showed that FMD was unaltered following 3 months of exercise training in about 9-year-old obese children [72]. This lack of an effect was observed despite significant improvements in CV fitness and reductions in BP, BMI, and abdominal fat.

Dietary interventions, as short as 6 weeks, consisting of a well-balanced hypocaloric diet, can improve FMD in overweight and obese children [52]. Similar benefits have been obtained from combinations of dietary modification and exercise training [52,95]. The benefits of combining exercise and diet were greater than those of diet only, suggesting that this combination intervention may be the most effective in obese children [52].

Longer interventions also improve endothelial function of overweight or obese children [37,52,53]. Exercise training for 6 months improved FMD in 11–16 year-old obese children compared to age-matched controls [37]. Twelve month interventions of either dieting alone or diet and exercise in 9- to 12-year-old children also improved endothelial function [52]. In this study, the combination of diet and exercise also provided greater benefits than diet alone. However, another 12 month-long exercise training, nutrition education, and behavior therapy intervention in obese children, only showed improvements in brachial FMD in those children who experienced substantial weight loss [53]. This would suggest that weight loss is a determining factor for improving endothelial function in obese children. Unfortunately, only one of the three long-term studies included a control group. Although the results are promising, the lack of a control group makes it difficult to make conclusions regarding the effectiveness of these long-term lifestyle modifications in obese children [35].

Although the physiologic mechanisms responsible for the previous favorable outcomes in children with obesity remain speculative, they are likely multiple mechanisms given the multidimensional nature of interventions. Exercise-induced upregulation of eNOS is one possible mechanism for the improvements in the atherogenic risk profiles in youth with obesity. However, changes in proinflammatory markers may also contribute to this favorable effect [66]. Accordingly, increases in FMD following lifestyle interventions have been accompanied by reductions in proinflammatory markers [37,53,95]. These reductions in inflammation may be mediated by accompanying weight loss and/or decreases in abdominal fat [47].

Cross-sectional evidence shows that physical activity is related to FMD in children with type 1 diabetes [69]. Children with type 1 diabetes who were physically active for more than 60 min/day exhibited significantly higher levels of FMD compared to those children with less than 60 min of physical activity per day. Furthermore, the FMD in the active group of children with type 1 diabetes was similar to less active healthy children without type 1 diabetes [69], suggesting that physical activity can "normalize" endothelial function in children with type 1 diabetes. Nevertheless, the healthy children who were physically active for more than 60 min/day exhibited better endothelial function than any of the other groups, showing that type 1 diabetes has a negative effect on endothelial function even in active children. Only one study has evaluated the effect of exercise training on endothelial function in children with type 1 diabetes. In a small study (n = 7) without a control group, Seeger et al. showed a large improvement in FMD, from 7.5% to 12.4%,

following 18 weeks of exercise training [99]. Unfortunately, the small number of subjects and lack of a control group makes it difficult to evaluate the significance of the findings.

Other lifestyle or dietary practices may also improve endothelial function in children with type 1 diabetes. Folic acid or vitamin B6 supplementation, or a combination of the two, improved endothelium-dependent dilation of the brachial artery within 2 h compared to placebo [78,100]. This effect was also maintained during 8 weeks of supplementation [100]. The improved endothelial function following folic acid therapy is likely due to prevention of peroxynitrite-mediated BH_4 oxidation, leading to improved eNOS bioavailability [101]. Since children with type 1 diabetes also have inflammatory and blood lipid profiles that differ from children without type 1 diabetes, this may favor a positive response of endothelial function to folic acid. However, FMD was not improved by folic acid supplementation in obese children [102] even though they had higher levels of inflammation and blood lipids than children with type 1 diabetes [84]. Since the effect of folic acid supplementation in children with type 1 diabetes was reversed 8 weeks after cessation of supplementation, to gain benefit, continuous supplementation would likely be needed [78].

Various diets and supplementation regimens in children with familial hyperlipidemia have also been shown to improve endothelial function [77,82,83,103,104]. Following a diet using the National Cholesterol Education Program Step II recommendations coupled with supplementation with docosahexaenoic acid (DHA), an omega-3 fatty acid found in fish oil increased brachial artery in FMD [103]. This may have been related to possible improvements in eNOS upregulation induced by DHA [103]. Similar results were reported when the same diet was used in conjunction with antioxidant vitamin C and E supplementation [104]. However, short-term dieting alone does not appear to improve FMD [103,104]. Conversely, marked improvements in FMD were shown following 6 weeks of antioxidant therapy in children with hyperlipidemia compared to controls [77]. This is likely related to the effect of antioxidants on free oxygen radicals reducing inactivation of eNOS, thus increasing NO availability and improving endothelial function.

ARTERIAL STIFFNESS

Arterial stiffness has become an important aspect of evaluating subclinical arterial disease, as it is related to CVD outcomes in both clinical and healthy populations [15,24]. The current gold standard for evaluating arterial stiffness is pulse wave velocity (PWV), but other noninvasive methods, such as high-resolution ultrasound, are also common. Ultrasound measurements of the carotid artery or the aorta are common, but measures of peripheral arteries such as the brachial artery can also be made. Arterial distensibility (inverse of stiffness) and a measure of the elastic properties of the artery, and compliance, a measure of the capacity to respond to changes in blood volume, are common measures used [1]. These measures provide information on the amount of change in lumen size from diastole to systole, by evaluating the increase in lumen diameter during systole. Local distending pressure is an important determinant of compliance; thus the local artery BP needs to be measured. Carotid BP is usually measured in the contralateral carotid artery, using handheld applanation tonometry [65,105], but measuring the local BP in the aorta is more complicated. An estimation of aortic BP can be made from applanation tonometry-created pulse wave forms using a transfer function [15]. The beta (β) stiffness index, a measure of arterial stiffness shown to be somewhat independent of BP [106], and the incremental elastic modulus (Ep) are also often derived from the ultrasound measures. Ep is a measure of the intrinsic elastic properties of the arterial wall material, independent of vessel geometry [30].

PWV has emerged as the gold standard in adults studies, probably because of its widespread use in large clinical studies [1], and is a measure of the speed of the arterial pressure wave propagation [65,107]. A higher PWV indicates a stiffer artery. PWV is recorded using pressure sensitive transducers or Doppler ultrasound, and a simultaneously recorded electrocardiogram is often used as a timing marker. The PWV from the carotid to the femoral artery (central stiffness) or from the femoral to the dorsalis pedis artery (peripheral stiffness) are the most commonly used measures [35]. However, radial to dorsalis pedis artery measurements are also common (whole body compliance). The time delay of pulse wave propagation from the proximal to the peripheral artery is measured and then divided by the distance between the measurement sites to calculate the velocity [107]. Central (aortic) PWV is lower than peripheral PWV because the aorta is more compliant and less muscular than peripheral arteries. Since BP significantly influences PWV, it is important to measure PWV and BP simultaneously.

Although both aortic and carotid compliance change throughout childhood and adolescence, aortic compliance increases [108,109] whereas carotid compliance decreases with age [30,31]. This apparent difference is probably a function of the different measures of compliance used rather than a real difference between the aorta and the carotid artery. Both Senzaki et al. [109] and Ahimastos et al. [108] measured compliance as a change in flow volume for a given change in pressure. This measure is dependent on both mechanical properties of the artery wall and on vessel geometry, and better reflects arterial capacitance. Even though aortic compliance almost doubled between 5 and 20 years of age, this was primarily a function of increased arterial size, and the distensibility of the arterial wall actually decreased [108,109]. This is in support of the findings of carotid compliance [30,31], which was defined as the change in arterial diameter for a given change in distending pressure. There was a linear decrease in carotid compliance of 10%–28% over the same age range, coupled with an increase in Ep and β-stiffness of 9%–30% [35]. Thus, arterial wall stiffness increases during the developmental years in children; however, the amount of the increase in wall stiffness is highly variable between studies.

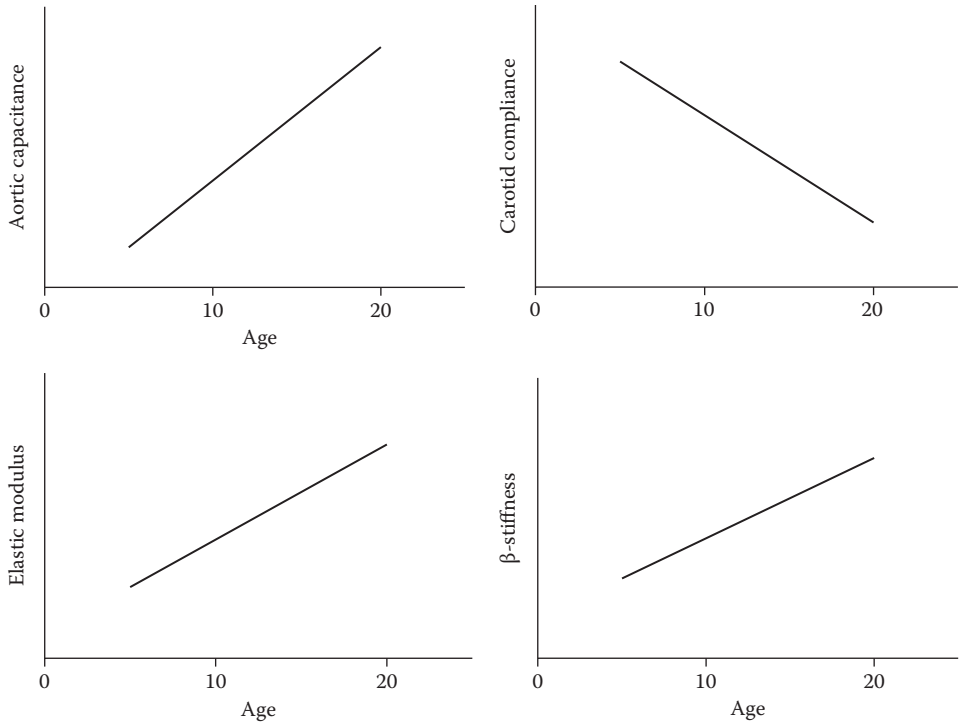


FIGURE 92.4 An example of how age affects various measures of central arterial stiffness in children. All measures of central arterial stiffness increase, whereas measures of central arterial compliance decrease as children grow older.

Figure 92.4 shows a schematic of the expected changes in arterial compliance, Ep and β-stiffness from 5 to 20 years of age. The increase in arterial wall buffering capacity is independent of changes in arterial wall elasticity in children, since both Ep and β-stiffness continually increase throughout childhood [109]. Thus, the increase in arterial size appears to offset the increase in wall stiffness. It is possible that this may prevent an increase in afterload, affecting ventricular performance [15,26,27]. This differs from the effect of adult aging. In older adults, arterial capacitance decreases concomitant with an increase in arterial wall stiffness [110,111].

Data on PWV support that arterial wall stiffness increases with age in children. Both aortic and peripheral PWV increases from childhood through puberty [110–114] as demonstrated in Figure 92.4. The increases in arterial stiffness are usually observed in both boys and girls [30,31,114] although at least one study has shown gender differences in the developmental changes in PWV and these changes were also influenced by puberty [108].

It is often assumed that developmental changes in elastin and collagen in the arterial wall are responsible for the changes in wall stiffness with age in children [115]. Since the atherosclerotic process begins in childhood, it is possible that decreases in elastin and increases in collagen is the start of arterial wall degeneration, indicative of the start of the atherosclerosis [114,115]. Considering that CVD risk factors including hypertension, BMI, physical inactivity, and high dietary fat intake are associated with arterial stiffness in healthy children, it appears plausible that arterial stiffness is indeed a marker of the atherosclerotic process in children [30,55].

Arterial stiffness in children also appears to be influenced by sex, race, socioeconomic status [49], and this is independent of CVD risk factors. African Americans have higher PWV than Caucasians [49,116] in both males and females, regardless of age, a finding that is consistent with data in young adults [117,118]. Boys have higher PWV than girls also consistent with data in adults [119]. Although more controversial, it also appears that low socioeconomic status is associated with higher PWV in children [49].

Obesity detrimentally affects arterial stiffness, as obese children have been consistently shown to exhibit higher arterial stiffness compared to normal-weight children [38,120,121]. This applies to multiple aspects of arterial stiffness and distensibility as obese children have been shown to have 38% higher aortic stiffness index, a 58% higher aortic elastic modulus [120], and 75% higher carotid Ep [38] compared to normal healthy children of similar age [35]. Even prepubertal children as young as about 8–9 years of age exhibited higher Ep than nonobese children, showing that obesity can detrimentally alter arterial stiffness at a very early age [71,72]. Metabolic syndrome appears to accentuate the effect on obesity alone, as Iannuzzi et al. [74] showed higher carotid artery stiffness in children with metabolic syndrome compared to obese children (with a similar BMI) without metabolic syndrome.

The mechanisms through which obesity impacts arterial stiffness are not completely understood at this time. Arterial stiffness may be related to increased low-level inflammation, and obese children have elevated levels of CRP [37,40,74]. Leptin levels may also be involved since leptin has been associated with arterial stiffness independent of inflammation

and insulin resistance [122]. However, other, more traditional CVD risk factors play a role, including insulin resistance, hyperlipidemia, and hypertension [37,38,40,74]. It is not surprising that BP contributes to arterial stiffness in children, since high BP is a substrate for development of arterial stiffness [15,35,123]. Consequently, it is no surprise that hypertensive children have higher arterial stiffness than normotensive children [124]. Insulin resistance and hyperinsulinemia have consistently been shown to be associated with increased arterial stiffness in both children and young adults [118,125]. It is also possible that autonomic dysfunction may contribute, as vagal tone is related to arterial stiffness following exercise [62,126]. Consequently, it appears clear that children with elevated CVD risk factors are likely to also exhibit higher arterial stiffness, consistent with early subclinical development of atherosclerosis.

There is some cross-sectional evidence that exercise and physical activity are associated with reduced arterial stiffness in healthy children. The amount of time spent in play or sport participation was inversely related to the arterial stiffness in 10-year-old children [55]. In contrast, others found no significant relationship between the total amount of physical activity, estimated with a 7 day questionnaire, and arterial compliance of 9- to 11-year-old children [89]. These disparate results probably reflect low accuracy in estimating physical activity levels, but no data exist with objectively measured physical activity levels in children. CV fitness has been shown to contribute to arterial compliance in healthy children [89]. Performance on a 20 m shuttle run contributed to large and small artery compliance (15% and 7%, respectively) [89]. Children with the highest performance score also had significantly higher arterial compliance than those in the lowest performance quartiles, providing evidence for a positive effect of CV fitness on arterial compliance.

In contrast, 12 year-old boys who had participated in 8–10 h/week for at least 4 years of swimming training exhibited higher upper limb PWV and lower distension index compared to age- and gender-matched nonswimmers [127]. More disturbingly, the child swimmers had similar PWV to adults. This may suggest that high-volume swim training has detrimental effects on upper limb arterial stiffness in children. Unfortunately, no data on central PWV were provided.

Longitudinal studies on the effect of exercise training on arterial function in healthy children are almost nonexistent. One study that did not include a control group [128] found decreased PWV after training 6 of 12 boys. The common characteristic among those who decreased PWV was that they also showed improvements in $\dot{V}O_{2max}$. Those children who did not improve $\dot{V}O_{2max}$ with training showed no improvement in PWV. Thus it is possible that arterial stiffness improves only with improvement in $\dot{V}O_{2max}$. However, physical growth during the training period often interacts with potential training-induced changes; thus, young children do not always improve $\dot{V}O_{2max}$ with training [129].

Very little information is available on the effect of exercise training using longitudinal study designs in children with CVD risk factors. Only one study in obese children has been conducted to date. Farpour-Lambert showed that 3 months of exercise training had no effect on arterial stiffness in obese children, despite a significant reduction in BP [72]. This suggests that arterial stiffness may be resistant to change through exercise training, or that a longer time period of training may have been needed. However, in adults, as little as 4 weeks of aerobic training significantly decreases both BP and PWV [130], suggesting that the response in children may differ from that in adults. Clearly, much more research is needed in this area.

CONCLUSIONS

Measures of subclinical atherosclerosis are becoming increasingly important in pediatric populations as they demonstrate early signs of arterial remodeling and functional changes related to the atherosclerotic process. Recently, the American Heart Association issued recommendations for testing of subclinical atherosclerosis in children [1], substantiating the increased focus on these measures. All measures of subclinical atherosclerosis are associated with both traditional and more novel CVD risk factors providing credence to their relationship with increased CVD risk. Furthermore, risk factors in childhood are associated with subclinical atherosclerosis in young adulthood. However, the effect of the development of subclinical atherosclerosis in childhood on the CVD risk in adulthood is currently unknown.

Both exercise training and various regimens of dietary supplementation and dietary interventions aimed at weight loss have been shown to improve some aspects of subclinical atherosclerosis in children. However, the long-term effect is unknown, and which interventions might be most effective is also not elucidated to date. There is very little information on the effect of lifestyle interventions on arterial stiffness in children. It is also unknown if reducing evidence of subclinical atherosclerosis in childhood through lifestyle intervention programs affects the risk of future CVD events in adulthood. Consequently, well-designed longitudinal studies are needed in the future.

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93 Prevention of Osteoporosis and Bone Fragility
A Pediatric Concern

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CONTENTS

Bone Growth Processes 1155
Skeletal Growth and Bone Fragility 1156
Optimizing Bone Mass and Strength Development during Growth 1156
Non-Modifiable Factors: Genetics and Sex 1156
Modifiable Factors 1157
Physical Activity and Muscle 1157
Nutrition 1158
Smoking 1158
Recommendations 1159
References 1159

Osteoporosis, through its association with age-related fractures, is one of the most common causes of longstanding pain, functional impairment, disability, and death in elderly populations [1]. The importance of optimal bone growth in childhood and adolescence has been recognized as one of the key strategies in osteoporotic fracture prevention [2]. Low birth size, poor childhood growth, and low peak bone mass at the cessation of growth have been linked to the later risk of osteoporosis and hip fracture [2,3]. Formerly, the focus was merely on maximizing bone mineral accrual since a high peak bone mineral mass may prevent the attainment of a critical "fracture threshold" associated with age-related bone loss and osteoporosis [4]. More recently, the focus has shifted away from bone mineral accrual—as measured by dual energy x-ray absorptiometry (DXA)—toward the optimization of bone strength. This is due in part to the advances in bone imaging that have enabled the estimation of bone strength beyond bone mass [5,6]. New imaging techniques, such as peripheral quantitative computed tomography (pQCT), can provide information on bone size, geometry, and tissue density within the imaged portion of the long bone and these parameters may be used to estimate bone strength. Moreover, pQCT can distinguish trabecular (spongy bone) and cortical (compact bone) bone compartments [7]. It should be noted that peripheral imaging techniques can measure long bones in the upper and lower extremity only, and thus the obtained information is limited to the assessment of long bone growth and development. We will first shortly describe the long bone growth and structural development in terms of alterations in length and size in addition to mineral mass and density. These considerations are important for our understanding of factors that contribute to the development of strong, healthy bones. Those factors will be summarized in the following sections.

BONE GROWTH PROCESSES

The human skeleton consists of two main types of bones: flat bones like the scapula and long bones like the femur. Flat bones are formed by a process called (intra)membranous ossification while long bones develop by a combination of membranous and endochondral bone formation [8]. Since it is the long bones that are most susceptible to fragility fractures, a brief discussion of long bone growth is warranted. During childhood and adolescence, bone structure is altered by growth in length and size (e.g., width or area) [9]. Bone growth in length occurs at the growth plate (also called the epiphyseal plate or physis), located just before the bone ends. At the growth plate, cartilage is replaced by bone and this process is known as endochondral ossification. A child's bone lengthens when bone formation proceeds outward from these growth plates. In order to maintain the structural stability of the growing long bone, the bone diameter needs to enlarge along the long bone shaft [9,10]. Growth in diameter occurs by apposition of new bone on the outer (periosteal) bone surface. Concurrently, resorption in the inner (endosteal) bone surface excavates the marrow cavity in the tubular long bone shaft. When periosteal apposition is greater than endocortical resorption, the cortical wall thickens or drifts further from bone center [11]. Growth in length and diameter are associated with increases in mass, density, and alterations in bone structure.

Changes in skeletal length and size are closely tied to changes in bone mass, with approximately one-quarter of adult total body bone mineral accrued during the 2 years around the adolescent growth spurt [12]. These structural and material changes are under mechanical regulation and influenced by the hormonal environment [6,8,13]. During growth, bones must continually adapt their structure and mass to withstand loads from increases in bone length (i.e., stature), muscle mass, and external forces [9]. However, the tempo, timing, and extent of such adaptations are also closely regulated by several systemic hormones. Changes in the bone mass, size, and structure are modified by three distinct processes: growth, modeling, and remodeling [14]. During the life span, a single process may dominate at certain times or the three processes may function concurrently at other times. In the immature skeleton, all three processes may be active simultaneously, with each having a different function.

Growth is the expression of the genetically programmed, hormonally mediated process of enlargement of the entire skeleton without regard to concurrent changes in shape that may be occurring regionally in response to local loading factors. In humans, skeletal growth is largely completed before the third decade of life.

Modeling takes place primarily during growth and is the main process altering the shape and mass of the skeleton [8]. Modeling represents a regional response to specific loading conditions whereby new bone is formed without prior resorption, resulting in a change in shape and size of bone. Since the young bone has a greater potential for adaptation to loading than the aging bone [15], the modeling process occurs primarily during growth and results in a net gain in bone over time [16].

Remodeling, although present in young individuals, is the predominant process modifying bone shape and mass in adults. It allows for the replacement of fatigue-damaged bone with new bone [17]. In addition to serving a preservation function, it provides a mechanism for the maintenance of calcium homeostasis. The remodeling cycle begins with an activation phase, followed in sequence by a resorption phase and a formation phase, which are coupled [8]. Since new bone never completely replaces the bone that has been resorbed, bone remodeling results in a net loss of bone over time, resulting in a decrease in bone mineral mass (i.e., bone mineral content, BMC) and alteration in bone structure that accompanies old age [18].

SKELETAL GROWTH AND BONE FRAGILITY

Total body bone mineral mass more than doubles between 8 and 15 years [12,19]. The peak gains in BMC at the lumbar spine, femoral neck, and total body occur at about age 13.0 for girls and 14.4 years for boys, which is explained by the earlier onset of sexual maturation in girls [12]. Longitudinal data from the Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) indicated that in the 3 years around peak height velocity (i.e., growth spurt), about 30% of BMC in the total body and lumbar spine was laid down and about 20% of femoral neck BMC was accumulated [12,20]. These data are consistent with other studies showing that bone mineral accrual increases progressively in early childhood [21,22] and then accelerates during adolescence [19,22]. In a PBMAS cohort, both girls and boys achieved about 90% of their final adult height at the time of the peak height velocity, but had only achieved about 57% of their estimated adult total body BMC and lumbar spine and about 70% of the estimated femoral neck values [23]. For all sites, peak velocity in BMC occurred over a year later than PHV in both girls and boys [23]. This lag time between linear growth and bone mineral accumulation has clinical implications. Increased fracture incidence during adolescence is partly explained by this dissociation between rapid growth in bone length, size, and mineralization [24–27].

Growth during infancy, childhood, and adulthood is important for bone health later in life. Infant and early childhood growth predicts adult bone mass independently of adult lifestyle [2]. Both low birth size and poor childhood growth are directly linked to the later risk of hip fracture [28]. The evidence of mineral accrual during adolescence indicates that the population variance in bone mass, and also in structural traits, is probably largely established by the end of the second decade. Pubertal timing seems to determine some variance in development. Early or late maturation may be important for bone development and fracture risk in adolescents and young adulthood [29]. Cross-sectional evidence from a large cohort of young adult men indicated that maturational age negatively predicts both cortical and trabecular bone size and volumetric BMD and previous fractures [29]. In females, subjectively assessed maturational timing has been associated with adult BMD and osteoporosis [30]. The earlier maturing child may therefore have an advantage in their bone development over the late maturing child. Current literature, however, does not provide any retrospective evidence of maturational timing influences on adult bone structure, strength, or fracture risk in either of the sexes.

OPTIMIZING BONE MASS AND STRENGTH DEVELOPMENT DURING GROWTH

To optimize bone strength development, we need to identify those modifiable factors which can enhance or retard the attainment of bone mass, structure, and strength during growth. Bones adapt their strength according to the mechanical forces they experience. Studies with healthy children and adolescents highlight the potential of modifiable factors such as physical activity, lean mass, or muscle cross-sectional area in determining bone mass accrual, bone size, tissue density, and estimated strength. Key factors that determine and influence the development of bone mass, structure, and strength are listed in the following.

Non-Modifiable Factors: Genetics and Sex

Evidence from familial resemblance and twin studies indicates that genes control about 50%–85% of the variance in

bone mass or areal bone mineral density (aBMD) [31] but a much smaller (<20%) proportion of the variance in the rate of bone loss [32] or fractures [33–36]. Genetic influences on the skeleton are thought to contribute mainly to the acquisition of bone mass during childhood and adolescence [37,38], possibly by interacting with environmental factors such as physical activity and diet. The trait variance in the *population* is largely the result of diversity in genetic makeup rather than lifestyle [31,39]. However, at the *individual* level, environmental effects such as muscle paralysis [40] or exercise [15] have profound effects on bone structure and estimated strength.

As the heritability of bone mass is stronger than aBMD, some of the familial resemblance in aBMD may simply reflect the heritability of body size [41]. Only one study has reported the genetic influences on bone size, showing a heritability estimate of 27% for the cross-sectional area at the distal radius in young adults [41]. Heritability estimates for trabecular and cortical bone density have been shown to be higher: 40%–60% depending on the bone site [42]. These results are in accordance with a meta-analysis of genome-wide scans which concluded that genetic regulation of bone mass is sex and site specific [43]. Part of the collinearity between the heritability of body and bone size (or mass) may also be related to lean mass, muscle size, and their development [44–47]. An important aspect regarding bone fragility prevention is that these traits can be enhanced by a physically active lifestyle and healthy diet.

Fractures of the wrist and hip have strikingly different age- and sex-specific incidence patterns [48]. To optimize preventive efforts, we need to understand how bone strength develops and declines for both sexes. Small or nonexistent sex differences in bone mineral content (BMC), density, and structure at axial or appendicular skeletal sites have been reported in childhood and adolescence [10,23,49–57]. Observations appear specific to the measured site, used technology, and how body size and composition—especially lean mass or muscle size—were controlled for in the analysis. The most comprehensive evidence of sex differences in bone development during pubertal growth comes from longitudinal PBMAS data. After adjusting for differences in maturation, height, and body composition, BMC development in total body and femoral neck were noted to be slightly greater in boys than girls across puberty [23]. Structural analysis of hip bone scans from the same cohort indicated a greater estimated strength (section modulus) in the femoral neck across the pubertal growth in boys when compared to girls but a smaller increase in the femoral neck area after the growth spurt [53]. This evidence of a greater bone mineral gain (relative to muscle) in the female skeleton occurring later in the pubertal growth period is supported by cross-sectional comparisons between males and females [44,52,58–60]. It has been suggested that this "extra" bone mineral provides a calcium reservoir for reproductive purposes [18,61,62]. Observations of similar cortical thickness between sexes have indicated that girls have either endosteal apposition [63] or diminished resorption at the endosteal (inner) bone surface [10] in puberty. Since females may gain more endosteal than periosteal bone, their bones strengthen less than in males who tend to have more periosteal bone formation and thus greater increase in overall bone size during the growth. Absolute sex differences in adult BMC and bone size may also reflect greater overall body growth due to the longer pubertal growth period in males than females. In females, earlier completion of longitudinal growth with epiphyseal fusion and earlier inhibition of periosteal apposition likely result in smaller bone size and generally weaker bone when compared to that in males [10,63].

Modifiable Factors

Physical Activity and Muscle

It is important to note that modeling and remodeling described earlier in the chapter are essentially under the control of the mechanical strain environment (such as strain magnitude, rate, and frequency). This functional model of bone development is based on the mechanostat theory [18,64,65]. In this model, bone cell action is coordinated by the mechanical requirements of the bone [64,65]. If bone is not exposed to mechanical loading, the lack of stimulus (strain) results in increased remodeling with subsequent loss of bone mineral and likely alterations in bone structure. Mechanical loading that is familiar to bone will be sufficient to maintain bone mass and structure, thereby maintaining remodeling and modeling in a steady state. Loading that produces an unusual strain environment to bone tissue can initiate a remodeling and/or modeling response. Increased body and muscle mass during growth may, in part, increase the forces placed upon bones, leading to greater bone strain and adaptation [64]. For example, if a girl unaccustomed to gymnastics practices handsprings, her bones at the wrist are exposed to a new strain environment. Modeling response in these bones will adapt bone by increasing bone mineral mass, size, or altering mass distribution (i.e., bone structure). After adapting bone structure and mass, the bone is able to resist the strains better than prior to adaptation and strains will return to a steady state. Progressively increased training stimulus is needed for continuous bone adaptation, thereby avoiding acute and chronic injuries related to intensive training [66].

Observational studies have provided evidence of greater bone mineral mass not only in child and adolescent athletes involved in gymnastics or other high-impact activities but also in children and adolescents who simply had a more physically active lifestyle [12,67–69]. Exercise trials have supported this evidence by showing a 3%–6% greater bone mineral accrual in children randomized to exercise intervention when compared to the bone accrual in the control group [70–75]. However, less is known about bone structural and strength adaptation to exercise [76]. Further, it remains inconclusive if the bone mass benefit acquired during the growing years persists into adulthood. To date, studies examining the effects of physical activity during childhood and adolescence on adult bone mass have been limited to retrospective assessments of physical activity [77–79] or earlier measured youth physical activity [80,81] to adult bone mineral status. Follow-up data

of retired athletes have provided evidence of both sustained [82,83] and partially lost [84] bone benefit after reduced or ceased activity, whereas exercise-induced bone gain has been reported to persist 1–8 years after exercise intervention in pre- or early pubertal children [85–87].

Previous prospective observational data from Saskatchewan PBMAS cohort showed a 9%–17% greater bone mineral accrual in physically active children when compared to their less active peers [12]. These studies have lent credence to the concept that physical activity in pre- and early puberty provides a unique opportunity to enhance bone accrual and peak bone mass. However, even if exercise during the growing years affects bone accrual, the importance of these effects from a clinical perspective depends on their permanence. The long-term implications of these benefits on adult bone mass can only be established with prospective longitudinal studies that follow subjects from childhood to adulthood. The follow-up data of these same individuals in young adulthood suggest that these benefits in bone mass persist into early adult life [88].

Little is known about the influence of physical activities and loading on growing bone structure and strength [76]. Unilateral tennis studies that compared side-to-side differences between players who begin their career prior or after the growth spurt have provided the strongest observational evidence that the increased BMC is due to enlarged bone size, which leads to greater estimated strength in long bone [15]. Studies in young and retired gymnastics support these findings [89,90]. Intervention studies assessing structural changes in the tibia have shown modest effects only in prepubertal boys [91], whereas estimated strength in the proximal femur has increased in pre- and early pubertal girls only [92].

Pediatric bone studies have provided compelling evidence of the importance of lean mass [93–96] and muscle cross-sectional area [97–99] on bone mass accrual and strength development during childhood and adolescence. Lean mass and muscle size have been used as surrogate measures for forces from mechanical loading and these traits have been associated with enlarged bone mass, size, and strength [100,101]. These findings are in accordance with the mechanostat model which postulates that the growing skeleton adapts its mass, structure, and strength to keep loading-induced strains within an acceptable range [47,98,102,103]. The age of peak lean tissue velocity precedes the peaks in estimated size and strength at the proximal femur [104]. These observations support the theory that muscle development is an important factor in affecting bone strength. However, there are currently no comprehensive longitudinal investigations using novel bone structure and strength measurements to link bone strength development in growing years to bone structure and strength in adulthood.

Nutrition

In addition to physical activity, diet during the growing years has been associated with bone mineral accrual in childhood and adolescence [19,46,80,105,106]. Two important nutritional aspects related to bone mineral have been noted in the past years: (1) a shift in emphasis from calcium to vitamin D as the major dietary influence on bone [107] and (2) an interest in dietary patterns, in particular the importance of fruit and vegetable consumption on bone health [108,109]. The average calcium accretion is 92–210 mg/day in 9- to 18-year-old boys and girls [110] and bone calcium accretion can peak at 300–400 mg/day [19]. The current recommendation of 1300 mg calcium per day for 9- to 18-year-olds meets the needs for skeletal growth in practically all adolescents [111]. Calcium supplementations produce a small 1%–2% effect in the upper limb areal bone mineral density [112]. This small increase is probably not likely to result in a clinically significant decrease in fracture risk in the growing skeleton, and thus, current evidence does not support the use of calcium supplementation in healthy children as a public health intervention [112]. However, according to Institute of Medicine 2010 guidelines, adolescent girls continue to be a group at risk for low calcium intakes from food sources [111].

Recommended intake of vitamin D is 600 International Units (IU) per day for children and adolescents in North America [111]. Recommendations for vitamin D intakes from dietary sources are complicated because vitamin D is also synthesized in the skin through sunlight exposure, which varies from person to person. Minimal sun exposure was assumed when the current vitamin D recommendations were established [111]. Inconsistent vitamin D tests used in studies and variance in the description of normal and abnormal ranges for vitamin D (25OHD) serum levels in children further challenges vitamin D recommendations [113]. In northern latitudes, without assurance of adequate sun exposure, requirements and recommendations for vitamin D should probably be higher than those currently in place [107,114]. Estimated mean daily vitamin D intakes in PBMAS participants have been relatively constant: 200–240 IU for girls and 280–320 IU for boys. These are comparable to Canadian youth intakes [110] and lower than the recommended dietary allowance for vitamin D (600 IU/day) [111]. The evidence of dose, time, and form of vitamin D for bone strength development and maintenance requires further evidence, especially from children and adolescents with limited exposure to sunlight (e.g., northern latitude) and poor nutrition due to socioeconomic factors.

Some investigations have indicated a positive relationship between fruit and vegetable consumption and bone mineral accrual [108,109]. This evidence has provided some support to a theory that a low-fruit and low-vegetable diet may lead to chronic, low-grade metabolic acidosis which may have detrimental effects on long-term bone health [115–117]. On the other hand, vegetable and fruit consumption may reflect healthy dietary patterns. Further evidence is needed to better clarify the role of dietary patterns of fruit and vegetable consumption in determining bone development during growth.

Smoking

A few studies have shown a negative association between bone mineral and smoking during growth and adulthood

in young men [80,118] and women [119], while others have not demonstrated such a relationship [47]. Smoking during adolescence was negatively associated with areal bone mineral density only in men, but not in women [80]; therefore this relationship may be gender dependent or related to the amount of cigarette consumption [118]. In elderly smokers (both men and women), in whom the effect of smoking has accumulated over several years, areal bone mineral density has been reduced, bone resorption markers increased, and the fracture risk elevated. There is limited evidence of an association between smoking and bone size, structure, and volumetric density. In a cohort of young Swedish men, daily smoking was associated with lower cortical thickness [120], whereas no association was reported in older Spanish women [121].

RECOMMENDATIONS

There are still many questions remaining about the complicated mechanisms controlling bone mineral accretion and structural development during the growing years. Prospective studies and well-designed trials are needed to assess whether the bone benefits related to physical activity during growth are maintained into later years irrespective of adult activity levels. We need to know more about the threshold levels of physical activity and vitamin D intake required to elicit a significant bone mineral response. From a public health perspective, perhaps the greatest questions have to do with the development of strategies directed at relating a condition of the elderly to a largely disinterested teenage population that will not be at risk for 40 or 50 years. The ultimate target population for the prevention of osteoporosis may be the young and not the elderly [122]. Taking into account the fact that our knowledge of the complicated mechanisms controlling bone mass and structure is still incomplete, on the basis of what we do know it is possible to offer some sound and prudent lifestyle advice to young people.

With regard to exercise programs designed for skeletal health and bone mineral acquisition in the young, the following fundamentals should be kept in mind: (1) the skeletal response to exercise is greatest at the loaded site and (2) to cause an adaptive response, the training stimulus must be greater than that habitually encountered. On the basis of these fundamentals and the review of the pertinent literature, the following recommendations can safely be offered to the public at large:

1. An individual should make a lifelong commitment to physical activity at an early age. Growing bones respond to mechanical loading by the addition of new bone and/or a strengthened bone structure. The growing skeleton has better ability to adapt to mechanical loading than the mature skeleton.
2. Weight-bearing activities that provide impact loading like gymnastics, skipping, aerobics, squash, and basketball are better for the skeleton—especially for the lower extremity bones—than weight-supported activities such as swimming or cycling.
3. A variety of vigorous daily activities of short duration that provide a versatile strain distribution throughout the entire skeleton is better for bone health than a prolonged repetitive activity. Activities should be diverse and vigorous enough to ensure loading with odd and varied strain distribution and magnitude.
4. Progressive increased training allows musculoskeletal adaptation and prevents overloading and related injuries.
5. Activities that increase muscle size and strength should be encouraged as these can be osteogenic.
6. Inactivity and immobility should be avoided: when this is not possible because of sickness or injury, even brief periods of activity can help to conserve bone mineral.

The responsiveness of the growing skeleton to physical activity is dependent on the sensitivity of bone to circulating hormone levels and nutritional adequacy. This has important implications for exercise prescription in adolescents, which leads to the following important recommendations:

1. Children should have a diet of nutritious foods that will meet the recommended dietary intake for calcium and vitamin D, provide adequate but not excessive protein, and limit the intake of sodium and caffeinated beverages (soft drinks, coffee).
2. A well-balanced diet that is sufficient to meet the energy demands of growth and physical activity should be encouraged.
3. Cigarettes should be avoided: they may interfere with the attainment of an optimum level of bone mineral and structure following skeletal maturation.

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94 Identification and Management of Children with Elevated Cholesterol Levels

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CONTENTS

Introduction....1163
Relationship between Dyslipidemia in Children and Adult Cardiovascular Disease....1163
Cholesterol Concentrations in Children and Adolescents with a Brief Overview of Pediatric Dyslipidemias....1164
Dyslipidemias....1165
Lipid Screening in Children....1165
Treatment of Abnormalities in Lipid and Lipoprotein Concentrations in Children....1166
Non-Pharmacological Lifestyle Approach—Diet and Activity....1166
Dietary Adjuncts....1167
Pharmacologic Intervention....1167
Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors (Statins)....1167
Bile Acid-Binding Resins (Cholestyramine)....1168
Cholesterol Absorption Inhibitors (Ezetimibe)....1168
Other Pharmacologic Agents....1168
Summary and Recommendations....1168
References....1168

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death and morbidity in the United States [1]. Though most of the clinical burden occurs in adulthood, cumulative research over the last 40 years has provided strong evidence that the process of atherosclerotic cardiovascular disease begins early in life and is progressive throughout the life span. The number of children with dyslipidemia is increasing as the population of obese children with decreased insulin sensitivity continues to grow [2–5].

Cardiovascular risk factors in children are strongly correlated with body fatness. Therefore, it is not surprising that the most common dyslipidemia pattern seen in children today is the so-called combined dyslipidemia pattern associated with obesity. It consists of mild elevations of total cholesterol (TC) and low-density-lipoprotein cholesterol (LDL-C), moderate to severe elevation in triglycerides (TG), and low high-density-lipoprotein cholesterol (HDL-C). The combination of elevated TG and low HDL-C, which is often seen in the presence of obesity, has been called atherogenic dyslipidemia. In autopsy studies, early atherosclerosis is associated with both increased LDL-C and decreased HDL-C [6].

In 2008, the American Academy of Pediatrics (AAP) published its guidelines for lipid screening and cardiovascular health in childhood [7]. At this time, the AAP recommended targeted screening of children at risk for hyperlipidemia with a fasting lipid profile. It also recommended the use of statins for children with severe hyperlipidemia not responsive to dietary and lifestyle changes, which was not without controversy [8]. More recently, the NHLBI (The National Heart, Lung, and Blood Institute) published guidelines for lipid management of the pediatric patient which have been endorsed by the AAP and include recommendations for universal screening between the ages of 9 and 11 years with a non-fasting, non-HDL cholesterol determination [9]. It has also recommended the use of pharmacologic agents including statins for children and adolescents with severe hyperlipidemia. A review of these new guidelines is included in this chapter.

RELATIONSHIP BETWEEN DYSLIPIDEMIA IN CHILDREN AND ADULT CARDIOVASCULAR DISEASE

Postmortem studies in children and adolescents such as the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) and the Bogalusa Heart Study have clearly demonstrated that the atherosclerotic process begins in childhood [6,10,11]. The PDAY study evaluated atherosclerosis at postmortem in adolescents and young adults between 15 and 34 years who died accidentally. The investigators determined

the indicators of CV risk status at the time of autopsy. These included cholesterol concentration and vascular pathologic features indicative of hypertension. The presence of increased coverage of the arterial intimal surface with fatty streaks and fibrous plaques was associated with elevation in cholesterol levels, elevated blood pressure, obesity, and cigarette smoking [10,11]. Using a risk score derived from this study, non-HDL cholesterol was shown to be a major correlate of coronary atherosclerosis in this age group, with a 30 mg/dL increase in non-HDL-C equivalent to 2 years of vascular aging [12,13]. The Bogalusa Heart Study found similar results to the PDAY study. In this study, the investigators identified a cohort of children whose risk-factor status for CVD was measured during a school examination [6]. As this population aged, some people died of accidental causes and were evaluated by autopsy for the extent of atherosclerotic lesions which again were associated with elevations of TC, LDL, and TG, but lower concentrations of HDL. Increased atherosclerotic lesions were also associated with dyslipidemia, high blood pressure, and obesity [6].

More recently, noninvasive methods of imaging (ultrasonography, computed tomography) have been used to study atherosclerosis development in children. These include the assessment of endothelial function by flow-mediated dilation (FMD) of the brachial artery, and the assessment of coronary artery calcium (CAC), and increased carotid intima-media thickness (CIMT), as precursors of atherosclerosis. Both the Muscatine study and the Cardiovascular Risk in Young Finns Study used carotid ultrasonography to evaluate CIMT [14,15]. In these studies, an association between childhood CVD risk factors and CIMT measurements made at or after 9 years of age was the best predictor of subclinical atherosclerosis in adulthood [16]. However, the American Heart Association (AHA) has recently concluded that improved noninvasive methods of assessing atherosclerotic risk in youth need to be developed and standardized before these methods can be adopted in clinical evaluation [17]. This includes longitudinal studies in low risk populations and collection of normative data across age, race, and sex.

Both the AAP and the NHLBI have concluded that the tracking of lipid and lipoprotein levels occurs and that elevated lipid levels from childhood and adolescence are predictive of future adult lipoprotein profiles [7,9]. The strongest statistical correlation occurs between the lipid levels measured in late childhood (prior to onset of puberty) and those found in the third and fourth decades of life. This has been rated as Grade B level of evidence, which indicates that "fair scientific evidence suggests that benefits substantially outweigh any potential risks" [9].

CHOLESTEROL CONCENTRATIONS IN CHILDREN AND ADOLESCENTS WITH A BRIEF OVERVIEW OF PEDIATRIC DYSLIPIDEMIAS

Data from the Lipid Research Clinics Prevalence study in children 0–19 years of age at multiple centers in the United States and Canada from 1970 to 1976 have shown that the concentration of serum lipids and lipoproteins are very low in cord blood at birth, increase during early childhood, and reach concentrations similar to those seen in young adults by approximately 2 years of age [18]. They remain stable until approximately 11 years of age. During puberty, paradoxically, the TC and LDL-C levels decrease with increasing age, before rising again in the late teens and again in the third decade of life. Thus, concentrations before 2 years of age and in the early adolescent years may not reflect values in older children or adults. In this survey [18], the mean TC level was 160 mg/dL and the mean LDL-C level was 100 mg/dL between 2 and 11 years. The 95th percentile for these two measures were 200 mg/dL for TC and 130 mg/dL for LDL-C [18,19]. Subsequent data collected 10 years later from the population-based National Health and Nutrition Examination Surveys (NHANES) have provided further information for the trends in lipids and lipoproteins during childhood and adolescence. Data from the 1988–1994 NHANES for ages 4–19 years showed that the mean total cholesterol concentration had increased to 165 mg/dL and the 95th percentile had increased to 216 mg/dL. Peak total cholesterol was 171 mg/dL between 9 and 11 years of age [20].

The NHANES 1988–1994 also demonstrated cholesterol concentration differences by gender [20]. Females had higher total cholesterol and LDL concentration than males. Females also tended to have higher HDL concentrations than did males after pubertal development had occurred. There are also differences in cholesterol and triglyceride concentrations according to ethnic group. In the 1988–1994 NHANES, black children had higher HDL-C and lower triglyceride concentrations than did non-Hispanic white children or children of Hispanic descent. On the other hand, in a second study of 8- to 10-year olds in North Carolina, black children had the highest prevalence of a total serum cholesterol concentration of >200 mg/dL: 18.7% compared to 11% in white children [21].

A substantial proportion of children and adolescents have elevated concentrations of lipids and lipoproteins. In the North Carolina study, in all ethnic groups, the overall prevalence of having a total cholesterol level of >200 mg/dL was 12.6% [21]. In the Children and Adolescent Trial for Cardiovascular Health, 13.3% of children in the fourth grade had a total cholesterol concentration of >200 mg/dL. The prevalence was 15.6% in girls and 11.1% in boys [22]. In the 1988–1994 NHANES, approximately 10% of adolescents had total cholesterol concentrations of >200 mg/dL [20].

There have also been trends over time in lipid and lipoprotein concentrations in children and adolescents as observed in adults. Comparing 1988–1994 and 1999–2000 NHANES, triglyceride concentrations decreased about 8.8 mg/dL in adolescents aged 12–17 years and total cholesterol, LDL, and HDL concentrations remained relatively stable [23]. The reasons for these changes or non-changes that have been seen in adults as well are unclear, but may be related to the increased efforts to alter diet and prevent CVD that have been in effect since the 1950s.

Dyslipidemias

Dyslipidemias are abnormalities in lipoprotein metabolism associated with any abnormal level of lipoproteins. There are a number of known genetic disorders of lipids in children. The most important ones are listed in Table 94.1. These include familial combined hyperlipidemia, familial hypercholesterolemia, and the familial and severe types of hypertriglyceridemia. The genetic disorders associated with dyslipidemias may be the result of a single-gene defect but usually are due to defects involving several genes that lead to abnormal lipoprotein metabolism [24].

The most common genetic disorder is familial combined hyperlipidemia with VLDL-C overproduction and associated elevations of TG and LDL-C and reduced HDL-C. Elevated non-HDL-C is also present in this phenotype. Twenty to thirty percent of obese children have evidence of this dyslipidemic pattern [25]. The presence of this cluster of findings in childhood predicts the development of type 2 diabetes, the metabolic syndrome, and premature clinical CVD in adulthood [26]. No single-gene defect is associated with this disorder and the expression of the several genes involved is exaggerated by obesity and other lifestyle factors. This dyslipidemic pattern in children has been shown to persist until adulthood [27], and a recent report from the longitudinal Young Finns study revealed that at 21 year follow-up, subjects with the combined dyslipidemia pattern beginning in childhood had significantly increased CIMT compared with normolipidemic controls [16].

Familial hypercholesterolemia is an autosomal dominant genetic disorder due to gene mutations in the LDL receptor with isolated LDL-C elevation. Homozygous familial hypercholesterolemia is very rare, but the heterozygous form affects 1:500 children in the United States. If untreated, both forms result in premature atherosclerosis and CVD events by 50 years of age [24].

Severe hypertriglyceridemia is rare in childhood and is a genetically based recessive metabolic defect. TG can be as high as 5,000–10,000 mg/dL and produces pancreatitis and eruptive xanthomas. However, it is not associated with premature atherosclerosis because the TG-enriched particles are too large to enter the vascular wall [24].

TABLE 94.1
Summary of the Most Important Lipid Disorders in Children and Adolescents

Lipid Disorder	Lipid/Lipoprotein Abnormality
Familial combined hyperlipidemia[a]	Type IIa: LDL-C Type IV: VLDL-C, TG Type IIb: LDL-C, VLDL-C, TG Types IIb and IV often with HDL-C
Familial hypercholesterolemia	Homozygous: LDL-C Heterozygous: LDL-C[a]
Familial hypertriglyceridemia (200–1000 mg/dL)	VLDL-C, TG
Severe hypertriglyceridemia (≥1000 mg/dL)	Chylomicrons, VLDL-C, TG

HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; VLDL-C, very-low-density lipoprotein cholesterol.

[a] These are the two lipid and lipoprotein disorders seen most frequently in childhood and adolescence; the familial combined hyperlipidemia is most often associated with obesity.

LIPID SCREENING IN CHILDREN

In 2008, the American Academy of Pediatrics reaffirmed using the 1992 National Cholesterol Education Program (NCEP) Pediatric Panel Guidelines for a targeted approach to cholesterol screening in children [7,28]. This approach recommends screening children with a family history of premature CVD or high blood concentrations of cholesterol (dyslipidemia). They also recommended screening pediatric patients with a fasting lipid profile for whom family history is not known or those who have risk factors for CVD such as obesity (BMI ≥ 95%), hypertension (BP ≥ 95%), cigarette smoking, and diabetes mellitus. This screening requires a 12 h fast and is often inconvenient for patients and families as it typically requires a return visit for phlebotomy after the fast.

However, in 2011, the AAP endorsed the NHLBI Expert Panel's new recommendations for *universal* screening in children between 9 and 11 years of age, or before the onset of puberty [9]. The report cites evidence that using family history of premature CVD or of cholesterol disorders as the primary factors in determining lipid screening for children overlooks many children with dyslipidemias. This is related to the fact that accurate and reliable measures of family history are frequently not available. The increasing prevalence of obesity [29] and the possibility that the prevalence of high blood pressure is also increasing [30] strengthened the argument for universal lipid screening in children. The Expert Panel report notes that there are advantages for identifying dyslipidemia and initiating treatment earlier in childhood, which may allow for some reversibility or slowing of the disease process. The report states that lifestyle changes and attention to risk are more readily accomplished in childhood than with older individuals [9]. In addition, the pediatric population generally has more regular contact with the health care system. There is also the potential for parental involvement in making lifestyle changes. However, it is not entirely clear that universal screening in children will impact on the future development of CVD as there have been no clinical trials demonstrating this [31].

The Expert Panel has also recommended using non-HDL cholesterol as a non-fasting screening test for evaluating dyslipidemia in children and adolescents [9]. This test has been shown to be a measure of atherogenic particles and is now used in evaluating adults, and is better than LDL cholesterol alone at predicting cardiovascular risk. Levels of LDL-C have been the primary focus of

TABLE 94.2
Cut Points for Total, LDL, and HDL Cholesterol Levels and Triglycerides in Children and Adolescents

Category	Acceptable (<75%)	Borderline (75–95%)	High (>95)
TC	<170	170–199	≥200
LDL-C	<110	110–129	≥130
Non-HDL-C	<120	120–144	≥145
TG	<75	75–95	≥95
0–9 years	<75	75–99	≥100
10–19 years	<90	90–129	≥130

Note: Values given are in mg/dL; to convert to SI units, divide the results for TC, LDL-C, HDL-C, and non-HDL-C by 38.6; for TG, divide by 88.6.

cholesterol screening until recently, though it is known that half of all heart attacks occur in subjects with normal LDL-C levels. To determine non-HDL-C, the HDL cholesterol is simply subtracted from the total cholesterol. The resulting value measures not only LDL cholesterol but also cholesterol contained in metabolic "remnants" of very low-density lipoproteins (VLDL), the main carriers of triglycerides. Like LDL-C, these remnants promote the buildup of plaque in arteries. Cut points for non-HDL-C in children are shown in Table 94.2 with acceptable levels being less than 120 mg/dL and unacceptable levels being equal to or greater than 145 mg/dL. 120–144 mg/dL is borderline high. Otherwise the cutoffs in Table 94.2 for TC, LDL-C, and TG are nearly identical to those recommended in the 2008 AAP report [7].

Others have noted that there may be very little differences in fasting and non-fasting TC, HDL, and LDL cholesterol in children after reviewing data from the 12,744 lipid profiles measured in children and adolescents in the NHANES 1999–2008 surveys [32]. The Expert Panel report [9] notes that in two large pediatric cohorts from the Bogalusa Heart Study, non-HDL-C was shown to be both sensitive and specific for identifying children who will have elevated LDL-C levels and other dyslipidemias as adults [33,34]. Those in the top quartile of non-HDL-C as children were approximately four times more likely to have dyslipidemia as adults. The top quartile also correlated with the top decile of CIMT as well as any other lipoprotein measure [34]. Thus, for children as in adults, non-HDL-C levels appear to be more predictive of dyslipidemia and atherosclerosis than TC, LDL-C, or HDL-C levels alone [33]. In a recent report of a nationally represented sample of children, unimportant differences in lipid panel results were found between children who had fasted and those who had not fasted before testing, supporting the recommendation that fasting before lipid screening in children may not be necessary in a screening situation [32]. However, in the follow up of LDL-C during treatment, fasting lipid profiles are recommended as they provide the most accurate and precise determination of LDL-C.

TREATMENT OF ABNORMALITIES IN LIPID AND LIPOPROTEIN CONCENTRATIONS IN CHILDREN

Non-Pharmacological Lifestyle Approach—Diet and Activity

The 1992 NCEP guidelines for children and adolescents, the AAP, and the recent NHLBI Expert Panel report all recommend diet and levels of physical activity that are appropriate for children and adolescents children greater than 24 months of age which follow the U.S. Dietary Guidelines [7,9,28,35]. These dietary guidelines include recommendations that children and adolescents generally should have a balanced caloric intake with sufficient physical activity to achieve an appropriate weight. They should also consume more fruits, vegetables, fish, whole grains, and low-fat dairy products. It is also recommended that the intake of fruit juices, sugar-sweetened beverages, and foods containing added sugar, saturated fat, trans fats, and sodium be reduced. In general, for healthy children over the age of 2 years, it is recommended that no more than 30% of the calories come from fat, less than 10% of the calories come from saturated fat, and cholesterol intake should be less than 300 mg/day. For all children, 1 h/day of moderate to vigorous physical activity with less than 2 h/day of sedentary screen time are recommended. The emphasis on a healthy lifestyle with a healthy diet is key in the prevention of the development of abnormal lipid and lipoprotein concentrations and has been shown to safely and effectively reduce the levels of total cholesterol and LDL-C in healthy children [7,9].

Given that a third of the pediatric/adolescent population is overweight or obese with or without family histories of early onset CVD and hyperlipidemia, there will be pediatric patients in the high-risk category in which the AAP, AHA, and NHLBI Panel have recommended even further dietary modifications for children over the age of 2 years [7,9,36]. This would include all children with LDL-C > 190 mg/dL and hereditary hypertriglyceridemia. For these high-risk groups, the recommendations are mostly the same as for the general population (25%–30% of calories from fat), but saturated fats are further restricted to less than 7% of total calories and dietary cholesterol to less than 200 mg/day. A trial of dietary modification is still warranted as there may be some lowering of the LDL-C concentration which will allow for lower doses of pharmacologic agents if needed. Implementation of this more aggressive diet will likely require involvement of a dietitian to help families make the appropriate changes without compromising overall adequate nutrition. Dietitians can also help families navigate the food environment outside the home including school, the homes of friends, and fast-food restaurants. Generally, a 6 month trial of lifestyle changes with appropriate dietary modification is recommended before pharmacological intervention is considered. According to the NHLBI Panel report, "A behavioral approach that engages the child and family when delivered by a registered dietitian, has been shown to be the most consistently effective approach for achieving dietary change" [9].

Dietary Adjuncts

Another non-pharmacological approach to treatment of dyslipidemia in children is the use of plant sterols or stanol esters (2 g/day) as dietary adjuncts, which lower the absorption of cholesterol. One of the few randomized controlled trials in children showed that a plant-stanol-enriched margarine supplying 1.5 g of plant stanol per day reduced LDL-C concentration by 8% [37]. Though long-term studies of stanol use in children have not been completed, the most significant safety concern is that they also result in decreased absorption of fat-soluble vitamins and beta carotene. Fiber has also been used as a dietary adjunct and is thought to bind with cholesterol in bile acids, removing it from enterohepatic circulation. Some studies have shown a reduction in cholesterol of up to 7% with dietary fiber, but others have shown no benefit [38].

Pharmacologic Intervention

The use of pharmacologic interventions for lipid abnormalities has increased since the 1992 NCEP report [28]. In 2007, the AHA recommended statins as a first-line agent for children who met certain criteria. The AAP Committee on Nutrition in 2008 recommended that pharmacologic treatment be considered after age 10 years, but acknowledged that, rarely, initiation of treatment with medications could be considered in FH patients 8 years or older [7]. Children younger than age 8 years with extreme elevation of LDL-C levels, above 500 mg/dL, as would be found in the homozygous form of familial hypercholesterolemia, also should be considered for pharmacologic therapy. The AAP also recommended that children with diabetes mellitus and LDL-C > 130 mg/dL be considered for therapy [7]. These recommendations have been controversial [8].

It is unlikely that randomized controlled clinical trials will ever be done to confirm that treatment of lipid abnormalities in children will reduce the risk of CVD when children become adults. Recent studies in children and adolescents have established the effectiveness and safety of available pharmacologic agents. However, it is not known whether there is an age at which development of the atherosclerotic process is accelerated, though pathologic studies have shown that the frequency of fibrous plaques increases with age [6,10,11]. Also, recent studies in children using noninvasive assessment of vascular markers have shown an increase in arterial abnormalities with an increasing number of risk factors for CVD [14–16]. It is also thought that early lesions are more effectively treated and reversed than more advanced lesions, making the case for initiating drug therapy in the pediatric age group with severely elevated LDL-C [7,9].

The new report from the NHLBI Expert Panel endorsed by the AAP has also recommended the use of drug therapy in children and adolescents with lipid disorders after 10 years of age when certain conditions are met [9]. It also advises that any decision for using medication be based on the average results from two fasting lipid profiles obtained at least 2 weeks but no more than 3 months apart, and only after a 6 month trial of lifestyle management change [9]. Recommendations for LDL concentrations for pharmacologic treatment of children and adolescents 10 years and older are given in Table 94.2. Several classes of medications are available for treatment of dyslipidemia in children and adolescents and will be summarized in the following.

Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors (Statins)

There have been a number of well-designed short-term studies with statins in children and adolescents as noted in the AAP 2008 report [7,39–48]. Statins inhibit the rate-limiting enzyme 3-hydroxyl-3-methyl-glutarate coenzyme A reductase for endogenous synthesis of cholesterol in the liver. It then decreases the intracellular cholesterol pool, which results in the upregulation of the LDL receptors resulting in increased clearance of LDL-C from the circulation. Typically, the serum cholesterol is lowered by 20%–50% below baseline, depending on the baseline value and the statin dose prescribed. In adults, statins also decrease inflammation as indicated by decreased serum CRP measurements. Adverse effects of statins include myopathy and hepatic enzyme elevation. Asymptomatic hepatic enzyme elevation is common in adults on statin therapy, but is reversible and not clearly linked to liver disease. In a study of statin use in children, evidence of hepatic enzyme elevation did not differ between statin (n = 28) and placebo (n = 22) groups [47,48]. The bigger but rare cause for concern is the possibility of myopathy, myositis, and rhabdomyolysis. Patients on statin medications should be instructed to inform their health care provider if they are experiencing muscle pain, aches, cramps, or weakness that is disproportionate to activity. Finally, statins may be teratogenic and should not be used during pregnancy. When statins are used in adolescent females, the patient should be counseled regarding prevention of pregnancy.

The clinical trials in children with statins have shown them to be safe and effective in lowering cholesterol concentrations [39–48]. In at least some studies, statins have also been shown to improve endothelial function in children with high cholesterol levels. One of these studies in children with familial hypercholesterolemia demonstrated improvement in brachial artery flow-mediated dilatation after 28 weeks of statin therapy [47]. In a second study using ultrasound over a 2 year period, carotid intima-media thickness was shown to increase in children with familial hypercholesterolemia treated with a placebo, compared to a regression of carotid IMT in patients on statin therapy [48]. The latter study included prepubertal children as young as 8 years of age, and on the basis of these results and reassuring safety data, the U.S. Food and Drug Administration approved pravastatin for children with familial hypercholesterolemia who are 8 years and older, regardless of pubertal status [7]. The AAP has recommended the use of statins for patients 8 years or older with an LDL concentration ≥190 mg/dL (or ≥160 mg/dL with a family history of early heart disease or with ≥2 additional risk factors present or ≥130 mg/dL if diabetes mellitus is present) [7].

The NHLBI Expert Panel has made similar recommendations but recommended the use of statins only in children who are 10 years or older [9].

Bile Acid-Binding Resins (Cholestyramine)

Bile acid-binding resins work by binding cholesterol in bile salts in the intestinal lumen, thus preventing enterohepatic reuptake in the terminal ileum. This results in depletion of bile salts in the liver and is the signal for increased bile salt production and the potential for increasing the excretion of cholesterol. In children and adolescents with familial hypercholesterolemia, LDL-C levels are reduced 10%–20% [49,50]. Bile acid-binding resins do not have systemic effects and adverse effects are limited to gastrointestinal discomfort. This discomfort coupled with the difficulty in taking either the pill or powder form of the resins limits their usefulness in young patients. They may also be used for patients whose statin use fails to meet LDL-C target levels with either medication alone. The efficacy of the two drugs was found to be additive in one pediatric study [42].

Cholesterol Absorption Inhibitors (Ezetimibe)

The dietary cholesterol absorption inhibitors represent the newest class of cholesterol-lowering agents and have not been extensively studied in children. They inhibit dietary cholesterol absorption at the level of the intestinal villus. However, unlike the bile acid-binding resins, they are systemically absorbed. One study has been published in children using ezetimibe for treatment of familial hypercholesterolemia in combination with statins, which resulted in a significantly greater reduction in LDL-C levels than did statin alone [51]. In 2009, the U.S. Food and Drug administration released a safety alert about the potential adverse effects of ezetimibe in adults; hence, these drugs should not be used in children without consultation with a lipid specialist. More information about the long-term effectiveness of this drug in children as well as potential adverse outcomes is needed.

Other Pharmacologic Agents

There has been very limited experience with the use of niacin and fibrates in children for the treatment of dyslipidemia, both of which have potential significant side effects. Neither of these drugs is recommended for routine use in children or adolescents for treatment of dyslipidemias and should only be prescribed by a lipid specialist.

SUMMARY AND RECOMMENDATIONS

There is accumulating evidence that lipid and lipoprotein abnormalities contribute to the development of atherosclerosis and that this process begins in childhood and is progressive across the life span. There are both genetic/metabolic and environmental (mostly dietary) influences on cholesterol levels in children. The genetic dyslipidemias are associated with the highest levels of LDL-C and TG as well as the lowest levels of HDL-C. In fact, the heterozygous form of familial hypercholesterolemia occurs in 1/500 individuals, making it a relatively common problem associated with increased risk of accelerated atherosclerosis and cardiovascular disease.

These lines of evidence suggest the need for two strategies to improve risk. The first strategy is a population-based approach, which seeks to improve diet and lifestyle factors in all children. This approach could lower population levels of lipids and lipoproteins and broadly reduce risk. This diet approach is also similar to that recommended for the prevention of obesity and hypertension and could have an important impact across a variety of risk factors for cardiovascular disease.

The second approach has been labeled the high-risk approach. It focuses on identifying those individuals who are at the highest risk, usually as a result of a genetic form of dyslipidemia. Universal screening with a non-fasting non-HDL-C is now recommended for children aged 9–11 years [9]. When children are identified with an elevated non-HDL-C, they should have repeat testing with a fasting lipid profile. They should also be evaluated for the presence of additional cardiovascular disease risk factors. Because this is a genetic abnormality, other family members, including the parents, should also be tested.

For children and adolescents with lipid and lipoprotein abnormalities, the first line of treatment is to improve diet and physical activity. This intervention may be sufficient for many children. For those age 10 years and older with persistently elevated LDL-C, despite diet therapy, pharmacologic management should be considered.

If these approaches are systematically implemented in primary pediatric practices, the lifelong risk of cardiovascular disease could be dramatically reduced across the population. Future research to evaluate the impact of treatment in childhood on adult cardiovascular outcomes would be very useful.

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95 Cardiovascular Risk Factors and Physical Activity in Children

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CONTENTS

Introduction 1171
Traditional CVD Risk Factors and Exercise 1172
Blood Pressure 1172
Blood Lipids 1172
Insulin Resistance and Type 2 Diabetes 1173
Other Cardiovascular Variables 1173
Key Mechanisms Linking Physical Activity to the Clustering of CVD Risk Factors 1174
Clustering of CVD Risk Factors and Its Relation to Physical Activity and Fitness 1175
Tracking of Physical Activity, Fitness, and CVD Risk Factors 1175
Tracking of Physical Activity 1175
Tracking of Physical Fitness 1176
Tracking of CVD Risk Factors 1176
Tracking of Clustered Risk 1176
How Can We Decrease Risk? 1176
Conclusions 1177
References 1177

INTRODUCTION

Atherosclerotic cardiovascular disease (CVD) and type 2 diabetes are associated with lifestyle and a number of biological risk factors such as hypertension, low high-density lipoprotein cholesterol (HDL-C), high triglyceride and low-density lipoprotein cholesterol (LDL-C) level, and insulin resistance in adults. These diseases are not usually manifested in children, but precursors of atherosclerosis such as fatty streaks in the arteries can be seen in children, and the degree of atherosclerotic precursors is related to the level of CVD risk factors [1,2]. However, type 2 diabetes, a disease which earlier typically was associated with adults, and its precursor insulin resistance, is becoming more common in children [3]. No studies have examined the progression of atherosclerosis from childhood until clinical manifestations in adults, and the exact importance of this early atherosclerosis is, therefore, not known.

Physical activity during childhood may protect against later CVD if certain assumptions are met. First of all, physical inactivity may exacerbate the atherosclerosis already present in childhood. This would be a problem if atherosclerosis progresses during the lifespan and tracks from childhood into adulthood. However, we have little knowledge about regression of atherosclerosis as a result of improved health behavior. There is some evidence of tracking of CVD risk factor profile and tracking of clustered CVD risk [4]. Second, physical activity and sports participation in childhood may influence physical activity levels in adulthood. Thus, changing to a more physically active lifestyle in later years may become increasingly difficult once an inactive pattern has been established. There is a rationale for primary prevention in children that can be summarized as follows: (1) a sedentary lifestyle causes increased levels in CVD risk factors, (2) a large percentage of children have a sedentary lifestyle to a degree that it may increase the risk of developing atherosclerosis, (3) CVD risk factors or sedentary behavior track during childhood and into adulthood, and (4) interventions including increased physical activity in children at risk are efficient in decreasing risk factor levels and changing behavior to a more physically active lifestyle.

Based on this rationale, this chapter focuses on (1) describing the association between physical activity/fitness and CVD risk factors, including clustered CVD risk in children; (2) key mechanisms, which link physical activity to the biological CVD risk factors including the atherosclerotic process; (3) tracking of physical activity, aerobic fitness, and CVD risk factors from childhood onward; and (4) the effect of interventions to promote physical activity and decrease CVD risk in children.

TRADITIONAL CVD RISK FACTORS AND EXERCISE

Numerous studies suggest a causal relationship between CVD and high levels in blood pressure (BP) and blood lipids in adults. Children are usually free of CVD, but BP, levels in cholesterol fractions, and triglyceride as risk factors of metabolic health track into adulthood [5]. Thus, these risk factors have been the focus of studies as they relate to exposures such as obesity, physical inactivity, and low aerobic fitness to health. Later, studies have added fasting insulin, glucose, and homeostasis model assessment for insulin resistance (HOMA-IR) to the list. Insulin resistance is probably the most important physiological factor in the development of metabolic syndrome, and some studies have, therefore, used a composite risk factor score based on the risk factors defined in metabolic syndrome. Finally, a new developing field in describing health status is inflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and hormonelike substances such as leptin and adiponectin.

Physical activity is generally considered a behavior. One can choose to be active or inactive. Conversely, aerobic or cardiorespiratory fitness is considered a trait since there is a genetic component. However, participation in large amount of moderate and vigorous physical activity can result in improvements in aerobic fitness. Thus, the two concepts are somewhat interrelated. In the following paragraphs, we will summarize how physical activity or fitness is associated with these different health markers.

BLOOD PRESSURE

The association between BP and exercise is still controversial in children. Cross-sectional studies have found an inverse association between physical activity or cardiorespiratory fitness and BP but no association between self-reported sports participation and BP [6,7]. In contrast to self-reported activity, another large-scale study using accelerometer-measured physical activity observed graded associations [8]. Since accelerometers measure all physical activity and self-reported sports activity mainly assess high-intensity physical activity, this could support the importance of total amount of physical activity and not just high-intensity sports-related activity, as beneficial for BP. Furthermore, these population-based studies include primarily normotensive children, and the effect of physical activity is greater in hypertensive children [9,10]. With respect to aerobic fitness, there is an inverse association between aerobic fitness and BP, which was stronger in overweight than normal-weight children [7]. Associations between aerobic fitness and hypertension were moderate in magnitude with odds ratios for hypertension of 1.5–3.0. In the study of Nielsen and Andersen, risk was only elevated in the least fit (first quintile) [7]; but in the study of Andersen, an inverse, graded association between aerobic fitness and BP was observed from a fitness level below 50 and 45 mL/min/kg in boys and girls, respectively [6].

Experimental studies on exercise training have almost entirely focused on children with hypertension [11–14] or obesity [15–17], and most studies had small sample sizes ($N < 100$). Hansen et al. studied the effects of 8 months of exercise training in both normotensive and hypertensive overweight children. They observed a reduction in systolic and diastolic BPs in the training subgroups of 6.5 and 4.1 mmHg, respectively, for the normotensive group and 4.9 and 3.8 mmHg, respectively, for the hypertensive group. Bell et al. studied obese children with a mean systolic/diastolic BP of 109/87 mmHg before training, and they found reductions of 5 and 4 mmHg in systolic and diastolic BP, respectively [15]. Another study found a training effect of 17 mmHg in systolic BP in children with essential hypertension [12]. This study also found an effect of resistance training and BP returned to pretraining levels after cessation of training.

In conclusion, physical activity and exercise training, both aerobic and resistance training, have a beneficial effect on BP in children. The size of the effect depends on baseline levels of BP, fatness, and aerobic fitness. Higher effect is found with higher BP level, lower fitness, and higher fat content at baseline.

BLOOD LIPIDS

Research reviewed by Strong et al. [18] suggests weak associations between physical activity and total cholesterol, HDL-C, LDL-C, and triglyceride levels. Some cross-sectional studies have found negative associations between total cholesterol and physical activity or aerobic fitness level and no association between HDL and physical activity [8]. This is in contrast to most intervention studies, which usually find an effect of aerobic training on HDL-C but no effect on total cholesterol [18]. In 2009, Dobbins et al. published a Cochrane review including seven school-based randomized controlled trials [19]. This review identified seven studies [20–26], and two further studies have been published since this review [27,28]. Overall, studies including clinical or school-based trials (randomized and non-randomized) show a weak beneficial effect on HDL-C and triglyceride levels but no effect on total cholesterol or LDL-C levels [29–31]. Thus, the effect of physical activity on blood lipids is difficult to determine in growing children. Lipids change concomitantly with the hormonal changes occurring during puberty [32], physical activity levels tend to decline during adolescence, and aerobic power (VO_{2max}) increase in boys with increased maturity and the opposite happens in girls [33]. These confounders could be controlled in randomized trials, but trials usually have quite short duration, and changes in lipids may take longer time. Some of the school-based trials lasting more than a year have found larger effects in blood lipids. Kriemler et al. found a 17% increase in HDL-C and a 15% decrease in triglyceride in a cluster randomized trial including a population-based sample of children [28]. Similarly, Resaland et al. found a 12% decrease in triglyceride and 6% decrease in ratio of total cholesterol/HDL-C ratio [27]. These improvements are quite large in view of the fact that they

studied populations with healthy lipid levels. In a post hoc analysis, Resaland et al. examined the effect of intervention in children with a high composite risk factor score and a low score separately. Substantially larger effects of the intervention were found in high-risk children [27].

In conclusion, physical activity has a beneficial effect on blood lipids in children. It is uncertain if total cholesterol is affected or it is mainly an increase in HDL-C that occurs; but in all studies, the ratio of total cholesterol and HDL-C improves. It seems likely that both aerobic and resistance exercise improves blood lipids.

INSULIN RESISTANCE AND TYPE 2 DIABETES

The development of insulin resistance may be the most important of all the risk factors. Insulin resistance and type 2 diabetes mellitus have been linked to BP, blood lipids, and other cardiovascular risk factors [34]. Several cross-sectional studies have shown that there is an inverse relationship between physical activity levels and aerobic fitness in children [35–37]. Also, improved fitness reduces insulin resistance [38–40]. Thus, the consensus is that exercise improves insulin resistance and, possibly, type 2 diabetes. The improvement in insulin sensitivity is caused by increased glucose transport mechanism and an increased number of glucose transporters. In addition, increases in physical activity can also result in lowering body fat, which has also been shown to improve insulin sensitivity and glucose transport.

OTHER CARDIOVASCULAR VARIABLES

Hotamisligil et al. observed that adipose tissue from obese mice produced TNF-α, a proinflammatory marker, and this cytokine was linked to insulin resistance [41]. This observation changed our view on adipose tissue, and it is now apparent that obesity is linked to a state of chronic low-grade inflammation [42]. Several cytokines, IL-6, TNF-α, and CRP, have been associated with the adipocyte and the CVD risk factors. In addition, the adipokines (substances secreted from the adipose tissue), namely, adiponectin, resistin, and monocyte chemoattractant protein-1 (MCP-1) have also been linked to the risk factors.

Research is accruing that these cytokines and adipokines are influenced by exercise. Thomas and Williams recently conducted a comprehensive review of studies of the effect of exercise on CRP, IL-6, and fibrinogen [43]. CRP is an acute phase reactant that increases significantly in response to trauma and inflammation. CRP is a sensitive marker of inflammation, and there is evidence of its causal role in inflammation [44]. Age, sex, body mass index (BMI), adiposity, physical inactivity, aerobic fitness, and smoking are associated with CRP levels [45]. There is evidence to suggest that regular physical activity protects against disease associated with chronic low-grade systemic inflammation, and physical activity has a role in the lowering of CRP [46].

The mechanisms responsible for the association between reduced CRP and increased physical activity are unknown, partly because physical activity is related to several confounders that are independently associated with CRP concentration. However, the discussion of causal pathways may be of more academic interest because if physical *activity* causes a decrease in fat tissue, which produces the cytokines that affect CRP, physical *inactivity* is still the cause of the production. Studies reporting the association between physical activity and CRP concentration in young people are relatively scant, with much of the research concentrating on overweight and obese individuals [43]. Observational studies have shown associations between physical activity and CRP [47–50].

Some of this effect may be mediated through the changes physical activity cause on fat tissue. Other studies using self-reported physical activity have failed to find association with CRP [51–54]. When aerobic fitness is evaluated, studies find much stronger associations to CRP. For example, Andersen et al. found an association between cardiorespiratory fitness and CRP with a correlation coefficient of –0.49 in 9-year-old children. They further found an 11.3 times higher risk for CVD risk factors to cluster in the upper quartile of CRP compared with the lower quartile [55]. The reason why physical activity shows weaker associations with CRP than aerobic fitness could be that only high-intensity aerobic exercise may have an effect, but it could also be the fact that the measure of physical activity has a higher level of error than the measure of fitness.

Most intervention studies only include obese children, and many of the studies are quite small. Meyer et al. found a reduction in CRP in a 6 month intervention in obese adolescents [56]. Balagopal et al. also found a reduction in CRP during a 4 month intervention in obese adolescents, but the intervention included diet changes as well as aerobic activity [57]. However, the change in CRP was independent of weight. A similar decrease was found in a school-based intervention of Rosenbaum et al. [58]. Conversely, Nassis et al. did not find reduction in CRP in a study of obese girls even if aerobic fitness increased 18.8% [59]. Lack of effect on CRP was also found in two studies of obese children by Barbeau et al. [49] and Kelly et al. [60], but the latter study only included nine subjects, and the small sample size may have caused a statistical type 2 error. Also, because CRP is a general inflammatory marker and highly sensible to infection, small studies may be confounded by a few subjects having low-grade infections.

The role of other inflammatory markers in CVD risk factors is controversial. IL-6 has a proinflammatory influence and it is elevated in obesity. Originally, IL-6 has a negative effect on metabolism [61]; however, it is now proven that muscle cells also act as an endocrine organ and among other substances produce IL-6 during contraction [62]. Myokines may be involved in mediating the health-beneficial effects of exercise and play important roles in the protection against diseases associated with low-grade inflammation, insulin resistance, hyperlipidemia, and diseases such as CVDs, type 2 diabetes, and cancer. The muscle-produced myokine IL-6 enhances glucose uptake in the muscle cells, the glucose production from the liver, and the lipolysis in the adipose tissue. Training studies have shown reductions in

resting concentrations of IL-6. However, even if plasma-IL-6 appears to be downregulated by training, the muscular expression of the IL-6 receptor appears to be upregulated [63]. How these observations apply to children is not known. Further, it is difficult to evaluate the role of IL-6 in observational studies because the acute response to exercise recedes fast [55]. A decrease in IL-6 has been found in obese children after an exercise intervention [57], but it has also been seen in normal-weight children [58]. There is no consensus of the effect of physical activity on inflammation in children.

Adiponectin and leptin are produced in adipose tissue. Adiponectin is anti-inflammatory and hypoadiponectinemia is associated with insulin resistance [63,64] and is also associated with low aerobic fitness. Whether the latter association is caused by the effect physical activity has on fat tissue is not known, but Kynde et al. found that low plasma adiponectin was associated independently with insulin resistance [63]. Leptin affects appetite regulation negatively, but it doesn't seem to be associated with insulin resistance. However, it is negatively associated with aerobic fitness [64]. Steene-Johannessen et al. found an association of $r = 0.84$ between directly measured VO_{2max} and serum leptin. Concomitantly, leptin was strongly associated with a composite CVD risk factor score [65]. There are few studies looking at leptin in children, and because of the strong association between fat mass and leptin, it is difficult to judge the independent effect of physical activity and the importance for CVD risk factors. Recently, Hosick et al. found no association between fitness and leptin when accounting for body fat [66]. However, we know little about the relationship between physical activity and leptin in children. The role of resistin, another adipokine, in CVD risk factors and insulin resistance, as well as the influence of exercise on resistin, has yet to be determined [67].

KEY MECHANISMS LINKING PHYSICAL ACTIVITY TO THE CLUSTERING OF CVD RISK FACTORS

It is shown that CVD risk factors cluster in some children [68]. This means that each risk factor is not independently distributed and levels of all the risk factors are more likely to be increased in the same individual [68]. Even if the clustering of CVD risk factors did not exist in children, it is not too difficult to speculate that it is an undesirable condition. Further, low aerobic fitness is strongly associated with this condition [69]. It is, therefore, relevant to discuss some of the physiological mechanisms leading to clustering of CVD risk factors and to discuss the role of exercise in relation to this clustering. Benefits of physical activity can be separated into acute changes caused by the activity itself and more long-term physiological changes caused by the training effects of physical activity on the muscle and fat tissues, the heart, and the action of enzymes and hormones. Most of the biological CVD risk factors are linked to the metabolism, which are regulated by enzymes and hormones, mainly the oxidative enzymes, insulin, and noradrenalin/adrenalin (catecholamines). Clustering of CVD risk factors are closely linked to high levels of fasting insulin, and the upper quartile of HOMA score was found to have >25 times increased risk of having clustered CVD risk than the lower quartile even in a normal healthy, young population [70]. It is, therefore, important to understand the relationship between physical activity and insulin sensitivity and level, and how insulin affects CVD levels, but it is also important to understand that physical activity has beneficial effects through different independent physiological mechanisms, which all change risk factor levels in a positive direction.

Acute physical activity cause different physiological changes, which influence CVD risk factors. Some of these mechanisms are shared with adiposity, while others are unique for physical activity, but may affect fat accumulation. The most important physiological changes are probably insulin and catecholamine (adrenalin) sensitivity, and both of these hormones can double their action after a few weeks or months of exercise training. Training improves insulin sensitivity specifically in the trained muscle. One study, utilizing a single leg training protocol, found increased glucose clearance limited to the trained leg, with the same amount of insulin causing the glucose clearance to double in the trained leg [71].

Training increases adrenaline sensitivity and decreases its release, leading to increased glucose clearance since adrenaline blocks insulin-mediated glucose uptake at a given exercise intensity [72]. Besides this effect of training, glucose uptake occur independent of insulin [72]. Moderate-to-vigorous exercise appears to activate a second "pool" of transporters independent of insulin [73]. Thus, the same glucose uptake requires less insulin after exercise. This adaptation may affect lipid storage in the fat cells and indirectly appetite regulation. The contraction-mediated glucose uptake in the muscle cell is increased when the stored glycogen is used during prolonged exercise. Further, the contraction-mediated glucose uptake is not blocked by adrenaline [74]. Even during periods of stress, physical activity may help to maintain low levels of insulin. Other acute effects are a lowering of triglyceride level and increased HDL [75].

In contrast to these mechanisms located in the muscle cells, fat tissue releases cytokines such as TNF-α into the circulation, which can decrease insulin sensitivity systemically [40]. Most of the common CVD risk factors are worsened by the action of insulin, which affects both metabolic pathways (blood lipids) and sympathetic nervous system (BP). The insulin sensitivity of the muscle cells is, therefore, extremely important because 80%–90% of the glucose will enter the muscle cell mainly mediated by insulin under normal resting conditions.

Other mechanisms related to prolonged training are increased lipoprotein lipase (LPL) activity and increased oxidative enzymes in the trained muscles. LPL is situated on the inner wall of the capillaries, and the number of capillaries increases in proportion to the training state of the muscle [76]. LPL catalyzes triglyceride transported from LDL or very low density lipoprotein (VLDL) cholesterol into the muscle cell, where it is metabolized, thereby improving the ratio of total

cholesterol/HDL. Changes in oxidative enzymes related to training are substantial. In untrained young subjects, 8 weeks of exercise training caused key oxidative enzymes such as succinate dehydrogenase and hydroxyacyl dehydrogenase to increase by 30%–40% [77]. This change improves the metabolism of triglycerides, which in turn improves glucose uptake. Exercise training also increases superoxide dismutase, catalase, and glutathione peroxidase, which reduces damage from free radicals. Thus, increases in these oxidative enzymes have the potential to reduce free radical formation, which has been associated with atherosclerotic plaque formation. However, the effect of training on oxidative enzyme levels disappear as fast as it develops after the cessation of training.

CLUSTERING OF CVD RISK FACTORS AND ITS RELATION TO PHYSICAL ACTIVITY AND FITNESS

High levels in many CVD risk factors simultaneously have been observed in children not more than 9 years of age [68]. A major problem related to research on the health effects of physical activity in children has been weak associations between physical activity (or aerobic fitness) and CVD risk factors. The weak relationships could be related to the fact that the disease processes are just starting and have not had time to mature. Also, the weakness may be partly caused by methodological problems because both physical activity and most CVD risk factors fluctuate widely from day to day. This fluctuation is caused by both measurement error and true changes. Analyzing a composite score of many CVD risk factors can solve part of this problem. We have recently analyzed such clustering of risk factors in relation to objectively measured physical activity [8], aerobic fitness [69], and combinations of physical activity, fitness, and obesity [78]. We found approximately 13 times increased risk for clustering of CVD risk factors for the lower quartile of fitness compared with the upper quartile and around 10 times increased risk for the upper quartile of fatness compared with the lower. Physical activity exhibited a protective effect even after adjustment for both fitness and fatness in the European Youth Heart Study.

Recently, we analyzed clustering of CVD risk factors in preschool children 6–7 years of age, and unexpectedly, we did not find any sign of clustering [79]. It was surprising because children included individuals who were unfit, fat, and showed low insulin sensitivity [80]. Also, there was no association between fatness, or fitness, and CVD risk factors. The children were tracked until the age of 9 years, and at this time, clustering had developed in around 14% of the children. Further, we found that the lowest quartile of fitness had a 35 times increased risk of having clustering of risk factors compared with the upper quartile. It would seem that the clustering of risk factors, also known as the metabolic syndrome, develops after the children start school, suggesting that the decrease in physical activity that occurs when children are seated could be important. Further studies are needed before conclusions can be drawn.

TRACKING OF PHYSICAL ACTIVITY, FITNESS, AND CVD RISK FACTORS

Tracking is a measure of how well subjects keep rank order within a variable. It can be expressed as a correlation calculated over the whole distribution or as an odds ratio of staying at risk from one point of time to another. A correlation coefficient is a good way to express stability in a variable if risk increases linearly, which it does in many CVD risk factors, and there is no well-defined cutoff point in the risk factor above which risk increases. Odds ratio of staying at risk or staying above a defined level in a risk factor may be a better way to analyze relationships if they are not linear. A subject changing from the lower part of the distribution to the middle may be of less importance than a change from the middle to the top.

Most CVD risk factors are linearly associated to CVD. A high tracking coefficient gives a high predictive value of the risk factor measured later in life, but a low value does not necessarily mean the opposite because it may be caused by measurement error or short time fluctuations, i.e., total cholesterol is very precisely measured in a particular blood sample, but day-to-day fluctuations are great. A tracking coefficient can never be better than the error variation in the risk factor, and it is, therefore, difficult to compare tracking coefficient between risk factors. Assessment of physical activity is difficult and both accelerometer measurements and self-reported activity have a low reproducibility, so tracking coefficients are always low, which does not necessarily mean that the activity level in childhood is not a determinant of adult activity. Aerobic fitness is more stable and changes gradually if physical activity is changed, and a precise assessment is possible. The tracking coefficient normally decreases with increasing time span between the measurements.

Tracking of Physical Activity

Although low tracking coefficients are reported in studies of physical activity, some studies have found that childhood participation in sports, educational level, other life experiences, and aerobic fitness level are predictors of adult physical activity level [81]. One large population study measured physical activity with accelerometers [82]. When analyses were corrected for seasonal variation, within-week variation, activity registration during night time sleep, within instrumental measurement error, and day-to-day variation, moderate tracking in physical activity from childhood to adolescence was found (stability coefficients of 0.53 and 0.48 for boys and girls, respectively). The Danish Youth and Sport Study used self-report and followed subjects for 8 years from adolescence to young adulthood and found correlations of 0.31 for men ($p < 0.01$) and 0.20 for women ($p > 0.05$) [83]. The risk for a sedentary man to stay inactive was 2.2 times higher than expected, but for women, more sedentary women than expected from a random distribution became active. Similar results were found in the Young Finns Study [84] and in the Amsterdam Growth and Health Study [85].

Tracking of Physical Fitness

Physical fitness can be assessed as aerobic fitness, or as different measures of strength, flexibility, and motor coordination. When tracking of aerobic fitness is analyzed, the results depend on the assessment method because indirect methods, such as a field test or submaximal test, include more measurement error than direct assessment such as measurement of aerobic fitness (VO_{2max}) during a graded exercise test. Only few studies have used direct measurements of VO_{2max}. Aerobic fitness relative to body size tracks moderately with a correlation coefficient around 0.5 [85,86]. Somewhat higher coefficients are found when isometric strength is assessed ($r = 0.7$), but if strength is expressed relative to body size values similar to aerobic fitness are found. Even higher coefficients were found in the Leuven Longitudinal study [87]. Tracking coefficient after 1 year of observation was around 0.9 for both static and dynamic strength and decreased to about 0.6 after 5 years.

Tracking of CVD Risk Factors

A few studies have measured tracking of CVD risk factors from adolescence to young adulthood, and they found similar results [88]. Both blood lipids and BP track in children, but higher correlation coefficients are usually found in cholesterol fractions (0.5–0.7) compared with BP or circulating triglyceride (0.3–0.4). Tracking of BP was assessed in an American study, which followed 211 subjects from childhood (3–11 years) to adulthood (30 and 50 years of age) [89]. Correlations between BP as a juvenile and adult (age 30 years) were low and still lower for measurements at age 50 years. Tracking of systolic BP was higher than in diastolic BP. However, more hypertensive subjects dropped out of the study, which could influence tracking coefficients. Also, many subjects at the age of 50 years use drugs for hypertension, which is an additional bias. Tracking correlations for BP vary between 0.2 and 0.5 with higher coefficients for shorter time span. Associations between BPs measured with year's interval are weakened by large intrasubject variability from day to day and even within minutes. Part of this variation could be eliminated by more measurements before the follow-up and after the follow-up, but such data are not available.

Blood lipids and lipoproteins are more stable than physical activity or BP as one ages [90]. Most correlations are between 0.5 and 0.7 for total cholesterol and LDL cholesterol and somewhat lower for triglyceride and other lipoproteins. This is quite high because big fluctuations occur from day to day in total cholesterol. Subjects in the highest quintile of total cholesterol as children have a two- to threefold increased risk of being in the highest quintile after 8 years of follow-up [83] and a doubled risk after 15 years of follow-up [91].

Tracking of Clustered Risk

In the Danish Youth and Sport Study, a total or clustered risk score was calculated as the sum of scores in the single risk factors (ranked into 1–6) [88]. A high correlation coefficient was found from adolescence to adulthood in men ($r = 0.67$, $p < 0.001$) but not in women ($r = 0.33$, $p < 0.01$). Recently, a report analyzing tracking of clustered risk was published from this cohort, and those who had clustered risk as teenagers had a sixfold increased risk of having clustered risk as young adults [4].

In conclusion, CVD risk factors and physical fitness track from childhood into adulthood. BP, triglyceride, and physical activity only show weak tracking, which, in part, could be due to difficulties in assessing these variables, but clustered risk tracks strongly.

HOW CAN WE DECREASE RISK?

Increase in physical activity may be achieved in different ways, and the most effective way in a specific population may depend on the culture. Most children are quite active, but a key issue is how to reach sedentary children. Increasing physical activity in the most active children may reveal limited health gain, while an increase among the sedentary children may be much more important in the prevention of future disease. Some arenas where sedentary children could be targeted are schools and in interventions targeting everyday living such as active transport. In many countries, there are strong associations promoting organized sport. These organizations may have the resources, but the main goals in these organizations are to improve performance and develop elite athletes. They very often lack initiatives to include children who are not successful in sports.

In countries where physical education is compulsory, school-based interventions are a possible way to reach sedentary children. Dobbins et al. recently reviewed the effects of school-based intervention to increase physical activity and improve health [19]. Two other studies have been published since [27,28]. Studies showed positive effects of interventions on physical activity behavior and a number of CVD risk factors. It is possible to improve physical fitness and blood lipid profile, but most studies do not find any effect on BP, and only few found an effect on BMI. An interesting analysis was performed in the study of Resaland et al., who performed a 2 year intervention in a rural city in Norway [92]. They found a substantial increase of 9% in aerobic fitness in the intervention group compared to the control group. However, in a post hoc analysis, where they stratified subjects into quartiles according to their baseline fitness level, they found a 13% increase in the least-fit quartile and a 3% increase in the most-fit quartile compared with the corresponding quartiles in the control group. This is interesting from a health perspective because metabolic risk factors tend to cluster in the least-fit children [69]. In general, it is necessary that the intervention includes a substantial increase in physical activity if health gains are to be achieved. Small effect sizes have been found with an increase from two to four physical education lessons, but studies including 60 min of

physical activity every school day have shown substantial health effects. The 60 min need not be physical education lessons but can be arranged as play in the school yard as long as some intensity is achieved.

Another setting, which may be promising, is active transport to school. There are no randomized trials looking at the effect of walking or cycling to school in children, but some observational studies have shown that cycling to school may result in improved health. The European Youth Heart Study analyzed changes in fitness from the age of 9 to 15 years in children who did not cycle at baseline. Some of these children changed to cycling, while others were non-cyclists at the age of 15 years. Children who starting cycling had a 9% higher fitness at the age of 15 years than those who did not cycle [93]. Beside improved fitness, an improvement was found in metabolic risk factors [94].

Potentially, interventions can be targeted at the general population of children or at children at risk such as overweight and obese children. Intervention studies in obese youths show that favorable changes in insulin sensitivity, lipid profile, indices of inflammation, endothelial function, cardiac parasympathetic activity, and carotid intima-media thickness (IMT) are produced by moderate-to-vigorous physical activity doses of 150–180 min/week [56,57,95]. However, for nonobese youths, intervention studies suggest that such doses are not effective; higher moderate-vigorous physical activity doses of 300 min/week seem necessary [96].

CONCLUSIONS

A sedentary lifestyle in children is associated with increased levels in disease risk factors, which are known to increase risk of premature death later in life, and the prevalence of clustered cardiovascular risk is more common in sedentary children. Further, a large percentage of European and American children have a lifestyle sedentary to a degree that it may increase the risk of developing premature atherosclerosis and lifestyle diseases such as CVD and type 2 diabetes. It has also been verified that both risk factors and sedentary behavior track during childhood and into adulthood. In addition, a recent study has shown that lifestyle prevention may be more important than treatment [97]. Therefore, there is a strong rationale for early prevention starting already in childhood. Interventions aiming at increasing physical activity in children are efficient in changing behavior to a more physically active lifestyle and have resulted in decreased CVD risk factor levels. An important setting for this may be the school. Physical education lessons, activities in breaks, active commuting to the school, as well as afterschool sports have the possibility to reach all children and also children at risk through specific activity programs. However, physical education programs have been more successful when educated teachers have run the lessons [19], and there may be a major job to do before expert teachers are available in many countries.

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96 Prenatal Influences on Future Health

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CONTENTS

Introduction 1181
Birth Weight and Future CVD 1181
Twin Studies and the Association of Birth Weight with CVD 1182
Sibling Studies and the Association of Birth Weight with CVD 1183
Intergenerational Studies of Offspring Birth Weight and Parental CVD Risk 1183
Maternal Pregnancy-Related Changes and Future Offspring CVD 1184
Prenatal Exposure to Hypertensive Disorders of Pregnancy 1184
Prenatal Exposure to Gestational Diabetes/Hyperglycemia 1185
Prenatal Exposure to Greater Maternal Adiposity and Weight Gain in Pregnancy 1185
Maternal Behaviors during Pregnancy and Future Offspring Health 1186
Maternal Smoking in Pregnancy 1186
Maternal Alcohol Consumption in Pregnancy 1187
Maternal Diet in Pregnancy 1188
Maternal Physical Activity in Pregnancy 1188
Conclusion and Implications for Health Policy and Future Research 1189
References 1190

INTRODUCTION

There is considerable epidemiological interest in the suggestion that exposures acting in early life have long-term consequences for health in adulthood. The early life factors include those acting during (or before) the period of fetal development, such as maternal diet, smoking, or alcohol use during pregnancy; those acting in infancy, such as breast or bottle feeding; and those acting in childhood, such as passive exposure to tobacco smoke. Nearly all domains of later health including cardiovascular disease (CVD), diabetes, various cancers, respiratory disease, mental health, and cognitive decline have been associated with early life exposures of one kind or another. In terms of public health policy, it is important to separate out causal associations, which offer the possibility of intervention and disease prevention, from noncausal associations.

In this chapter, we examine prenatal exposures only, and we pay particular attention to study designs that might shed light on whether or not the associations are causal, and if causal, what the likely underlying mechanisms might be. Many of the specific examples are related to CVD or its risk factors (including hypertension, diabetes, and obesity), though we do consider other health outcomes. The focus on CVD and its risk factors arises for a number of reasons.

First, CVD accounts for the majority of deaths in high-income countries and is an increasing cause of morbidity and mortality in low- and middle-income countries [1]. Second, much of the research on prenatal origins of disease has focused on CVD and its risk factors. Third, variation in normal pregnancy-related changes—such as increases in insulin resistance and blood pressure (BP)—are importantly related to CVD in later life in both mother and offspring. Lastly, the issues that arise in considering which prenatal risk factors might be importantly causally related to future CVD, or its risk factors, will equally apply to other disease/health outcomes.

We start by considering the relationship of birth weight to CVD and its risk factors, and then move on to the relationship of maternal pregnancy-related changes with future offspring health outcomes, before finally considering modifiable maternal behaviors during pregnancy that might be related to future offspring health. Our summary considers implications of current research findings for clinical and public health policy and also areas where further research should be directed.

BIRTH WEIGHT AND FUTURE CVD

Coronary heart disease (CHD) and stroke, the main manifestations of CVD, are rare until middle age, and over half of deaths due to these causes occur over the age of 70 years. Until recently, most of our knowledge concerning the etiology of CVD focused on adult risk factors focused on factors such as diet, smoking, physical activity, hypertension, and adult obesity [2]. There is indeed good evidence that these major adult risk factors explain most of the geographical and secular variations in CVD occurrence, and it has been

suggested that there is no need to seek further etiological risk factors [3,4]. Moreover, there are a range of drugs now available that are highly effective in secondary prevention (that work by reducing adult risk factors such as hypertension and total or low-density lipoprotein cholesterol), which, together with reductions in population levels of smoking, have contributed to the sharp decline in CVD in high-income countries in recent decades [5]. However, ultimately, primary prevention of the development of atherosclerosis and CVD risk factors in the first instance has to be better than treating risk factors in adults, and this is likely to require a better understanding of prenatal risk factors.

It has been known for decades that the pathophysiological process of atherosclerosis, which ultimately leads to CHD and ischemic strokes, begins in childhood and young adulthood [6–8]. Cardiovascular risk factors, such as high BP, obesity, dyslipidemia, and insulin resistance are present in childhood, associated with atherosclerosis and endothelial dysfunction, and track into adulthood [9–13]. Thus, understanding the determinants of variation in these risk factors from very early in life is likely to be important.

A large number of studies have demonstrated inverse (sometimes "J" shaped) associations of birth size (most commonly birth weight) with CVD endpoints [14] and risk factors, including BP [15], fasting glucose [16], insulin [16], total cholesterol and triglycerides [17,18], and positive associations with high-density lipoprotein cholesterol [17]. Conversely, birth weight is positively associated with body mass index (BMI) [19] and with both total fat mass and lean mass assessed by DXA scan [20]. The strength of associations of lower birth weight with adverse CVD events and risk factors is generally smaller, often considerably so, than those between risk factors measured in adult life and these outcomes. Furthermore, it is unclear what mechanisms underlie the associations of birth weight with later CVD outcomes.

Few investigators suggest that size at birth per se matters; rather this is a proxy marker for some other causal risk factor(s). The mechanisms that have been proposed for this association fall broadly into one of three areas:

- *Intrauterine programming.* The suggestion here is that factors affecting intrauterine nutrition/growth provide signals to the developing fetus about the environment in which they will grow up and develop and, as a result, "program" the developing fetus for an environment of thrift or plenty [21,22]. Poor intrauterine nutrition results in poor intrauterine growth, and hence low birth weight, and also programs the offspring for a life of thrift. If offspring subsequently experience a life of nutritional plenty, typified by high-fat energy-dense diets (common in many high-income countries and urban areas of low- and middle-income countries), they are at particular increased risk of future CVD. Epigenetic mechanisms are increasingly thought to mediate these processes [23].
- *Genetic mechanisms (the fetal insulin hypothesis).* The fetal insulin hypothesis suggests that associations are largely due to the effects of genetic variants that have pleiotropic effects influencing both fetal growth and later insulin resistance and hence CVD risk [24,25].
- *Confounding or bias.* It has been suggested that the associations of birth weight with CVD and its risk factors are largely due to confounding (e.g., by socioeconomic position or shared familial behaviors such as smoking, physical activity, and diet that could affect both perinatal outcomes and later disease risk in offspring), statistical artifact, and/or publication bias [26,27].

Family-based studies have been increasingly employed to try and distinguish between these possible different mechanisms, and these are summarized in the subsequent sections; a fuller discussion of these can be found elsewhere [28].

Twin Studies and the Association of Birth Weight with CVD

Twins, compared to singletons, experience intrauterine growth retardation and have on average birth weights that are 900 g lower than those of singletons. If the fetal growth impairment experienced by twins occurs through similar processes to that experienced by growth-impaired singletons, one would expect twins to be at greater risk of CVD. The salience of comparing twins with singletons (or the general population, which is largely made up of singletons) is reinforced by the fact that there is evidence that twins tend to exhibit upward growth centile crossing [29]. Thus, twins are, in general, naturally small for gestational age but rapidly regain weight to become similarly sized to age-matched singletons, the very pattern of intrauterine and postnatal growth that has been suggested in general populations to increase the risk of CVD. Despite this, large studies show that twins (whether monozygotic [MZ] or dizygotic [DZ]) are at no greater risk of CVD than are singletons or the general population [30,31], nor do they have higher levels of CVD risk factors [32,33].

An alternative use of data on twins is the more traditional twin comparison design. In this context, one can examine (1) whether variation in size at birth *within* MZ pairs (where there will be control for fetal and maternal genotype, intrauterine environment, and maternal size and behaviors during pregnancy and background family socioeconomic position) is associated with differences in adult CVD *within* these pairs, (2) whether variation in size at birth *within* DZ pairs (controlling for intrauterine environment, maternal genotype, size, and behaviors during pregnancy and background family socioeconomic position, but not for fetal genotype) is associated with differences in adult CVD *within* these pairs, and then (3) compare whether these within twin-pair associations differ from associations *between* unrelated pairs (representing

the general association without control for factors that are shared within twins) [34].

Twin studies comparing within and between pair associations have been used to explore the association of birth weight with BP [35], dyslipidemia [36], glucose intolerance [37], and CHD events [38,39]. There are more studies of BP (treated as a continuous variable) than of any other risk factors or of CVD events. A systematic review and meta-analysis of twin studies examining the association of birth weight with BP failed to provide conclusive evidence for a stronger role for either genetic or environmental factors [35]. This was attributed to small sample sizes and between-study variation in the way in which zygosity was defined and BP measured. In a subsequently published study using data from Sweden that included 594 DZ and 250 MZ pairs who were discordant for hypertension (a binary measure), within MZ pairs, a 500 g lower birth weight was associated with an odds ratio of hypertension of 1.74 (95%CI: 1.13, 2.70) and within DZ pairs of 1.34 (1.07, 1.69). The equivalent association in the whole cohort was 1.42 (1.25, 1.61). These results suggest that the inverse association of birth weight with hypertension is independent of genetic and environmental factors shared by twins, including maternal and fetal genotype (except mitochondrial DNA, which differs in MZ as well as DZ twins), maternal physiology and behaviors in pregnancy, and background familial socioeconomic position. However, in general, such twin studies have contributed relatively little to understanding the (causal) mechanisms linking birth size to CVD or its risk factors because few have adequate sample sizes and because an underlying assumption of these studies is that variation in birth size in twins represents similar pathophysiological processes as those that result in variation in birth size in the general population, the majority of whom are singleton; this assumption may not be correct.

Sibling Studies and the Association of Birth Weight with CVD

A natural extension of the within- and between-twins study is to examine associations within and between siblings. Factors that influence birth size can be broadly categorized into those that vary from one pregnancy to the next in the same mother (e.g., fetal genotype, placental implantation and function, maternal age, parity, and pregnancy complications) and factors that are shared by full siblings (e.g., family socioeconomic background, maternal genotype, maternal pelvic size, and maternal exposures across her life course up to the birth of her first child).

Sibling studies provide a useful method for distinguishing between the impact of shared maternal/family characteristics and those factors that vary between full siblings in explaining the associations between perinatal exposures and later outcomes. They have the advantage over twin studies that they are generalizable to the majority of the population, but the disadvantage that they cannot control for fetal genotype and hence cannot distinguish whether the fetal insulin hypothesis (genetic pleiotropy) or intrauterine mechanisms explain the association of birth weight with CVD and its risk factors.

To our knowledge, only three studies have employed a sibling design to explore the association of birth weight with CVD outcomes. The outcome examined in all three independent Swedish studies was BP [40–42], and their key findings were in broad agreement: in childhood and young adult life, there was an inverse association between birth weight and mean systolic BP within sibships having accounted for gestational length. In the largest of these studies, inverse associations of birth weight, and gestational age, with systolic BP were found both within and between sibships [41]. The authors concluded that the inverse associations of birth weight and gestational age with later BP were not explained by confounding due to family socioeconomic position, maternal skeletal size, or factors from across the earlier part of a mother's life course. Instead, the most likely alternative explanation for these associations involves differences between pregnancies (within the same mother) in maternal metabolic or vascular health during pregnancy and/or differences in placental implantation. Differences in maternal metabolic or vascular health during pregnancy might be related to her behaviors such as smoking, diet, and physical activity. However, in common with many of the general studies examining the association of birth size with CVD, these sibling studies did not have data to examine the role of these behaviors.

Intergenerational Studies of Offspring Birth Weight and Parental CVD Risk

Examining the association of offspring birth weight with CVD risk factors and events in their parents has been used as a means to determine whether genetic or intrauterine factors are the most likely explanation for the association of birth weight with CVD in individuals. If the birth weight–CVD association seen within individuals is due to a genetic mechanism from both maternal and paternal genes, then one would expect that offspring birth weight would be inversely associated with CVD in both mothers and fathers. Associations in fathers are of particular importance, since many factors that could influence maternal CVD risk (e.g., maternal diet and smoking) could also affect the intrauterine environment and thus the birth weight of her offspring. In contrast, paternal factors other than via fetal genotype cannot influence the intrauterine environment, so an association between offspring birth weight and father's CVD risk is more likely to be explained by genetic factors or shared familial lifestyles.

A meta-analysis of all published studies of the association of offspring birth weight with parental CVD endpoints found that among mothers, the pooled confounder adjusted hazard ratio of CVD mortality for a one standard deviation increase in offspring birth weight was 0.75 (95% CI: 0.67, 0.84), and among fathers, the equivalent association was 0.93 (95% CI: 0.91, 0.95), with statistical evidence of a difference between these two effects $p < 0.001$ [43].

The generally stronger associations of offspring birth weight with maternal CVD compared with paternal CVD can be explained by a number of different mechanisms, including paternal misclassification, fetal programming (possibly via epigenetic effects), and reverse causality with maternal predisposition to CVD resulting in intrauterine growth restriction, all of which could be operating simultaneously, and that have been discussed in detail elsewhere [28]. The implausibly high levels of non-paternity (30%) that would be required to explain the magnitude of the difference in maternal–paternal associations and the non-specificity of the association in fathers, with similar magnitudes of association for other outcomes that could be due to confounding, have lead to the suggestion that these intergenerational studies support a maternal specific (most likely intrauterine) explanation for the inverse association of birth weight with CVD risk seen in the general population [43].

This intergenerational design has also been used with the same rationale to explore the associations of size at birth with insulin resistance and type 2 diabetes [44–51]. These have reported contradictory results, with inverse [46,47,49], positive [45,50], and null [44] associations of offspring birth weight with insulin resistance/type 2 diabetes reported in mothers and inverse [45–47,50,51] or null [45,48] associations reported in fathers.

A key issue may explain these contradictions between using this design for CVD and using it for insulin resistance/type 2 diabetes. Gestational diabetes (and gestational hyperglycemia) is associated with increased risk of type 2 diabetes in the mother and with greater offspring birth weight and fat mass [52]. Thus, in mothers, a positive association of offspring birth weight and her risk of later type 2 diabetes and insulin resistance would be expected. Any effect of other mechanisms (intrauterine programming or genes with pleiotropic effects resulting in lower birth weight and insulin resistance) might be somewhat masked in these intergenerational studies. This line of reasoning in itself suggests that the intergenerational design may not be as helpful for studying insulin resistance/glucose intolerance/diabetes as it is for CVD itself [45].

MATERNAL PREGNANCY-RELATED CHANGES AND FUTURE OFFSPRING CVD

Normal physiological changes in pregnancy, including maternal increases in BP, fat deposition, and insulin resistance that are essential for normal growth and development of the fetus, may in extremis result in abnormal development that has long-term adverse health consequences in offspring. In the subsequent text, we consider evidence for the effect of prenatal exposure to hypertensive disorders of pregnancy (HDP), gestational diabetes/hyperglycemia, greater maternal adiposity, and greater maternal gestational weight gain (GWG) on future health outcomes. These exposures have largely been related to future risk of greater adiposity, CVD, and metabolic risk factors in offspring, and thus this section focuses on these outcomes.

Prenatal Exposure to Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy (HDP) (preeclampsia and gestational hypertension) are the most common complications of pregnancy and are associated with adverse health outcomes for both the mother and her offspring. Preeclampsia is defined as newly elevated BP and proteinuria after 20 weeks of gestation and occurs in about 2%–7% of otherwise healthy first pregnancies [53,54]. Gestational hypertension is defined as newly elevated BP after 20 weeks of gestation but without proteinuria and has been found to occur in 6%–17% of pregnancies [53,54].

Exposure prenatally to maternal preeclampsia and gestational hypertension is associated with higher BP in offspring [53,55–60]. The underlying mechanisms explaining the associations of HDP with offspring BP remain unclear and could include genetic, intrauterine mechanisms or shared familial risk factors [61]. Given the familial clustering of adiposity (either as a consequence of genetic predisposition or shared lifestyle) and the strong association of obesity with both HDP and elevated BP, in general (including in children; [11]), adiposity either as a consequence of genetic predisposition or shared lifestyle might be important in the mechanism linking maternal HDP to elevated offspring BP.

However, a recent analysis in the Avon Longitudinal Study of Parents and Children, a prospective U.K.-based pregnancy cohort, found that the associations of both preeclampsia and gestational hypertension with greater offspring diastolic and systolic BP assessed at mean age 9.9 years ($N = 6343$) were not explained by maternal/paternal BMI or offspring fat mass [53]. Results from that study did, however, suggest that the mechanisms linking preeclampsia to offspring BP may differ from those linking gestational hypertension to offspring BP. Preeclampsia was associated with lower birth weight and preterm birth (whereas gestational hypertension was not), and adjustment for these birth characteristics attenuated the preeclampsia–offspring BP associations to the null [53].

In a second study with smaller numbers but more detailed offspring vascular phenotype, preterm infants born of mothers with HDP ($N = 19$) had higher BP, thicker carotid intima, and lower flow-mediated dilatation in their mid-20s than a group who had been born preterm but whose mothers were normotensive throughout pregnancy ($N = 52$; [62]). By contrast, arterial stiffness was greater in those born preterm to normotensive mothers than those born preterm to hypertensive mothers. Since endothelial dysfunction is a defining feature of preeclampsia [63], the authors interpreted their findings as indicating that either genetic predisposition to endothelial dysfunction or the exposure in utero of the developing fetus to the same placenta-related factors (including inflammatory markers) that affect the mother may explain their findings.

Several studies have also examined the extent to which HDP are related to other CVD risk factors and other outcomes such as cognitive function in offspring but have generally reported null associations [57,59]. These null findings may reflect lack of statistical power in small studies.

Prenatal Exposure to Gestational Diabetes/Hyperglycemia

Gestational diabetes is associated with higher birth weight and greater fetal adiposity [52,64]. Among nondiabetic mothers, there is a linear association between fasting and post-challenge glucose and greater birth size [65]. Fuel-mediated teratogenesis, also known as developmental overnutrition, has been suggested as the most likely mechanism for these associations [66–68].

Developmental overnutrition, resulting from maternal hyperglycemia/diabetes, may also program offspring to lifelong increased adiposity and type 2 diabetes risk [69]. In studies of the Pima Indians of Arizona (a population with very high prevalences of obesity and type 2 diabetes), mean BMI, fasting glucose and insulin, and type 2 diabetes is greater in offspring (during childhood, adolescence, and early adulthood) born to mothers who had diabetes during their pregnancy compared with either the offspring of mothers who developed diabetes later in their lives or those who never developed diabetes [70–72]. In a sibling study (182 individuals from 52 families), also conducted in the Pimas, risk of obesity and type 2 diabetes was greater among offspring born after the mother had been diagnosed with diabetes than in their siblings born before their mother's diagnosis. Furthermore, within siblings, there was no association of paternal diabetes around the time of pregnancy with these offspring outcomes [73]. These findings suggest that, at least in a population at high risk for obesity and diabetes, intrauterine mechanisms make an important contribution to the link between gestational diabetes and offspring greater adiposity, insulin resistance, and type 2 diabetes [73].

More recently, the association of diabetes (type 1, type 2, or gestational) or hyperglycemia during pregnancy with offspring obesity and diabetes risk has been examined in European and North American populations, with the majority of such studies finding that offspring of mothers with gestational diabetes of hyperglycemia have greater BMI and fasting glucose and insulin [74–80]. These associations could be explained by genetic inheritance, shared familial lifestyles for risk factors increasing the risk of obesity and diabetes or intrauterine mechanisms.

A recent large sibling analyses of Swedish men (280,866 men from 248,293 families) found that the BMI of men whose mothers had diabetes during their pregnancy was on average 0.94 kg/m^2 greater (95% CI: 0.35, 1.52) than in their brothers born before their mother was diagnosed with diabetes [77]. This finding suggests that, as in the Pima Indians, intrauterine mechanisms contribute importantly to the link between maternal diabetes in pregnancy and later offspring adiposity.

Prenatal Exposure to Greater Maternal Adiposity and Weight Gain in Pregnancy

Since maternal obesity is a key risk factor for gestational diabetes and greater maternal fat deposition during pregnancy is related to greater levels of circulating glucose and free fatty acids, which freely cross the placenta resulting in increased fetal secretion of insulin and hence insulin-mediated growth, it has been suggested that greater maternal pre- or early-pregnancy adiposity and greater GWG will result in greater offspring obesity via intrauterine mechanisms. If this hypothesis is true, in particular, if greater maternal adiposity at the start of pregnancy programs offspring to greater adiposity later in their lives, the public health consequences would be extreme, as this could drive the obesity epidemic through subsequent generations irrespective of any improvements in key risk factors for obesity [81]. This is because women going into their pregnancy with greater adiposity would program their offspring to greater adiposity, and their daughters would go into their pregnancies with greater adiposity and so on.

Despite a number of studies demonstrating that maternal pre- or early-pregnancy BMI is positively associated with offspring BMI, there is little evidence that intrauterine mechanisms play a substantial role in these associations in general. In the larger epidemiological studies, the magnitudes of associations of maternal BMI with offspring adiposity are similar to those of paternal BMI with offspring adiposity [82–84], suggesting that these associations are driven by shared familial genetic or lifestyle characteristics. Where associations have been found to be stronger in mother–offspring compared with father–offspring associations, the differences are small and unlikely to be important drivers of the obesity epidemic [85]. Furthermore, when maternal genetic variation in *FTO*, conditional upon offspring *FTO,* was used as an instrumental variable for the causal effect of exposure to greater maternal adiposity in utero this did not support a strong effect [85].

The one exception to these general findings is with extreme maternal obesity in pregnancy. In an elegant sibling study, adiposity in the offspring of mothers with extreme obesity (BMI > 40) was lower in children born after their mother had undergone bariatric surgery and subsequent weight loss than those born before she had received this surgery [86]. Taken together with the findings relating to gestational diabetes, these studies suggest that developmental overnutrition resulting in long-term effects on offspring adiposity and associated metabolic disturbance via intrauterine mechanisms only occurs in the extremes of clinical obesity or where there exists metabolic disturbance such as diabetes in pregnancy. Variation at lower levels of maternal prepregnancy adiposity, and without diabetes, does not appear to have long-term effects of offspring risk.

On an average, healthy women gain 10–12 kg during pregnancy, with approximately 55% of this gain being maternal tissue related to fat deposition, blood volume expansion, and increases in breast and uterine tissue, a further 15%–20% is due to placenta and amniotic fluid and 25%–20% fetal tissue [87–89]. Rates of deposition of maternal fat parallel GWG with women gaining between 2–6 kg of fat during pregnancy [90]. Pregnancy is associated with maternal deposition of both subcutaneous and visceral fat, with most subcutaneous deposition being centrally located [90–94]. Maternal pregnancy-related fat accumulation is relatively constant from the start of pregnancy to the middle of the second trimester when

the rate of accumulation flattens [88,90]. Most maternal fat accumulation has occurred by the end of the second trimester [88,90]. In general, this fat accumulation is a normal physiological response to pregnancy and it together with women becoming temporarily more insulin resistant during pregnancy is important for providing the developing fetus with essential nutrients for normal growth and development.

Several studies have examined associations of GWG with offspring adiposity and have consistently (all but one) [95] reported positive associations with offspring mean BMI or obesity measured in childhood [96–99], adolescence [100], and adulthood [101]. Other studies have examined the association with offspring BP with conflicting results [96,98,101,102–104].

The three most recent and largest studies suggest positive associations of GWG with offspring BP in childhood [96,98] and adulthood [101] that may be mediated by the association of GWG with offspring adiposity [96,101]. In the Avon Longitudinal Study of Parents and Children, a U.K.-based prospective pregnancy cohort, GWG was also associated with other CVD risk factors in childhood, including adverse lipid and inflammatory profiles, with these associations largely mediated via associations with offspring adiposity [96]. It is difficult to determine whether these associations are causal and act via intrauterine mechanisms. The associations are independent of maternal pre- or early-pregnancy BMI, which suggests that they are unlikely to be solely driven by genetic and lifestyle characteristics related to greater adiposity in general.

A recent sibling comparison found that GWG within siblings was positively associated with birth weight, and the authors concluded that this suggested the association was unlikely to be confounded by background family socioeconomic position [105]. They also implied that these findings provided indirect evidence that the associations of GWG with later offspring adiposity was unlikely to be confounded by fixed family characteristics, such as background socioeconomic position, because of the positive association of birth weight with later adiposity. However, in general, studies examining the associations of GWG with later offspring adiposity have found that birth weight does not mediate this association [96,101]. Thus, sibling studies of the association of GWG with offspring adiposity measured in childhood or at older ages would be valuable.

MATERNAL BEHAVIORS DURING PREGNANCY AND FUTURE OFFSPRING HEALTH

Identifying modifiable prenatal exposures that importantly influence future disease is clearly important for public health. While potentially modifiable maternal behaviors during pregnancy such as maternal smoking, diet, and alcohol consumption have been related to a wide range of later offspring health outcomes, determining whether these are truly causal (which is essential for appropriate public health policy interventions) is difficult as randomized controlled trials of these behaviors in pregnancy are likely to be unethical or unfeasible [106]. In the subsequent sections, we consider four key potentially modifiable maternal pregnancy behaviors (smoking, alcohol, diet, and physical activity) and evidence for their association with later offspring health. As in previous sections, we pay particular attention to studies that might help with causal understanding, including parental comparisons, cross cohort comparisons, and Mendelian randomization studies.

Maternal Smoking in Pregnancy

Maternal smoking in pregnancy has been found to be associated with greater offspring obesity (and associated CVD and metabolic consequences), lower cognitive function, poor mental health, and reduced bone density in offspring. However, there are many confounding factors that could generate non-causal links between the smoking of mothers and the health of their children.

In the Avon Longitudinal Study of Parents and Children, maternal smoking during pregnancy is associated with lower offspring birth weight, whereas smoking by the father (at the time of their partner's pregnancy) is only weakly associated with birth weight (possibly because of confounding with maternal smoking, or through effects of environmental tobacco smoke), and when both maternal and paternal smoking during pregnancy are taken into account, the former shows a robust association that is little attenuated, whereas the latter association is essentially abolished [107]. These findings demonstrate the face validity of using such parental comparisons to determine whether maternal behaviors in pregnancy have a causal effect via intrauterine mechanisms on offspring outcomes since for birth weight, it is accepted that maternal smoking in pregnancy does indeed have this causal effect.

Maternal–paternal comparisons have suggested that the associations between maternal smoking in pregnancy and offspring greater adiposity [106], reduced bone density [108], lower child cognitive function [109], and higher BP [110] are all unlikely to be caused by specific intrauterine mechanisms, since similar associations are found for the association of maternal smoking with these offspring outcomes as for that of paternal smoking with the same outcomes. Thus, for these outcomes, shared familial socioeconomic position or genetic variations are more likely explanations for the association than are causal intrauterine mechanisms. However, stronger maternal associations are reported with respect to components of stature in childhood, particularly of leg length, suggesting that for offspring postnatal growth in stature there may be causal intrauterine effects of maternal smoking during pregnancy [111].

Another approach to addressing whether the association of smoking in pregnancy with offspring outcomes is via intrauterine mechanisms or confounded (particularly by socioeconomic position) is to use cross cohort comparisons [112]. If smoking in pregnancy is unrelated to (or less markedly related) confounding factors in one cohort compared

with another, this difference in confounding structures can be exploited to explore causality. This approach has been used to examine the relationship between maternal smoking in pregnancy and offspring behaviors. Associations were examined in the United Kingdom, Avon Longitudinal Study of Parents and Children and in the Brazilian, Pelotas 1993 pregnancy/birth cohorts [112]. Socioeconomic patterning of maternal prenatal smoking was stronger in the United Kingdom compared with the Brazilian cohort. Despite this difference in a key confounder, consistency in observed associations of maternal smoking with child psychological problems was found between these cohorts [112]. In both cohorts, after full adjustment for indicators of socioeconomic position, parental psychological factors, and paternal prenatal smoking, maternal smoking was associated with child externalizing/conduct problems in both cohorts. Furthermore, maternal smoking associations were much stronger than paternal smoking associations with externalizing/conduct problems in both cohorts [112]. Thus, for this adverse psychological outcome, there may be a causal intrauterine effect of exposure to maternal pregnancy smoking.

This is hypothesized to occur via adverse effects of exposure to smoking-related toxins in utero on early brain development: the fetal brain is particularly vulnerable to exogenous nicotine because it contains specific nicotine-sensitive receptors [113]. There is some concern, however, that in most studies, there are insufficient measures of parental psychological factors to adequately capture confounding by parental psychopathology and in parental antisocial behaviors (which were not available in the two cohorts from Brazil and the United Kingdom described earlier). Indeed, in two studies with more detailed measures of parental psychopathology [114] and measures of maternal and paternal antisocial behavior [115], associations of maternal smoking with offspring behavioral problems were essentially abolished when these parental characteristics were controlled for. These findings are consistent with those from a twin study and an assisted conception study, which suggest that shared genetic variation explains most of the association of maternal smoking with offspring antisocial behavior rather than this being due to intrauterine mechanisms [115,116].

In summary, the adverse effects of maternal smoking during pregnancy on prenatal and perinatal outcomes, such as increased risk of preterm birth and low birth weight, are now well established. However, the extent to which exposure to maternal smoking in utero translates into long-term effects on offspring health has been more difficult to determine. While, associations with many different offspring outcomes have been reported in the literature, it has since been found that the vast majority (including offspring adiposity, BP, cognitive function, and bone density) of these are not likely to be causal via intrauterine mechanisms. With child behavior problems, identifying whether or not associations with maternal smoking are causal remains a challenge, and studies using different methodological approaches are increasingly being explored in an attempt to resolve this. To date, these studies have yielded conflicting results, and thus, the extent to which associations of maternal smoking and child behavior are causal remains controversial.

Maternal Alcohol Consumption in Pregnancy

The fact that *heavy* alcohol use by pregnant women has adverse effects on health outcomes in their children, including effects on cognitive development, is well established [117,118]. Thankfully, few women drink heavily during pregnancy, so in most populations "fetal alcohol syndrome" is not a major public health issue. Many women, however, do drink some alcohol during pregnancy, generally at light or moderate levels, and there is conflicting evidence (and hence policy advice) regarding whether levels of light or moderate alcohol consumption are safe.

For example, two publications from the U.K. Millennium birth cohort suggest that light alcohol use during pregnancy (1–2 units/week maximum) is actually associated with *better* cognitive outcomes in children compared with abstention from alcohol in pregnancy [119,120]. These publications have led to suggestions in the media and by the eminent statistician Professor David Speigalhalter that advising women to abstain from alcohol use while pregnant is not "evidence based" (http://understandinguncertainty.org/node/890). However, the findings in this study might be due to residual confounding.

Women who drink small levels of alcohol during pregnancy tend, in most populations, to be relatively affluent compared with women who drink heavily and those who do not drink at all. The children of relatively affluent mothers are likely to have better cognitive outcomes, and thus socioeconomic position and maternal education may be important confounders in this association.

The metabolism of alcohol in the body is influenced by several genes, and the metabolic differences associated with particular genotypes are themselves associated with differences in alcohol consumption behavior between individuals carrying different genes [121]. These differences are generally small, but they are consistent, and importantly possession of the genes that underpin them is completely independent of the other factors that typically cluster with substance use [121]. For example, a particular rare variant of the alcohol dehydrogenase gene is consistently associated with abstinence from alcohol (compared with moderate use) with a particularly strong association with abstinence from alcohol use during pregnancy. But this genetic variant is not associated with mothers' education or other socioeconomic characteristics and nor is it associated with other lifestyle characteristics such as smoking.

This genetic instrument was used to investigate effects of maternal alcohol use on children's cognitive outcome in a large United Kingdom-based birth cohort study. In this study, in keeping with the results of the previous study, the children of mothers reporting light alcohol use during pregnancy had higher intelligence quotient (IQ) scores and did better in standard school tests than the children of mothers reporting abstinence from alcohol. Light alcohol-using

mothers, however, were also more affluent, more educated, less likely to smoke, more likely to take exercise, and to have a healthy diet, in other words, more likely to have a favorable profile with regard to a range of possible influences on their children's cognition. Adjusting for these factors in statistical models attenuated but did not abolish the apparently beneficial effects of alcohol on the cognitive outcomes studied. By contrast to these observational findings, children of women with the "abstinence gene" did better in school tests and had higher IQ scores than women with "light/moderate use" genes.

This is convincing evidence that maternal alcohol use actually exerts a damaging effect on children's cognitive development, an effect that only became apparent with use of a study design—Mendelian randomization [122,123]—able to adequately address the issue of residual confounding. A nice feature of this study is that the problem of residual confounding could not be addressed by an RCT as it would be unethical and very likely unfeasible to find a group of pregnant women who were happy to be randomized to either drink no alcohol or a light amount throughout their pregnancy.

Maternal Diet in Pregnancy

There are some extreme examples of how maternal diet during pregnancy can affect offspring development and long-term health such as inadequate periconceptual folate intake resulting in increased risk of neural tube defects in offspring [124] and exposure to famine in utero being associated with increased risk of CHD and glucose intolerance in adult offspring [125]. However, evidence of effects of less extreme variation in maternal diet during pregnancy, particularly in contemporary well-nourished populations, is less well established.

Although the influence of maternal diet on offspring size at birth has been investigated since the 1930s, the overall evidence for effects on birth weight remains inconclusive, with unresolved methodological challenges, inconsistent results among studies and only modest effects, where associations have been observed [126]. Beyond birth weight, several historical studies undertaken among women who were pregnant in the 1940s [127], 1950s [128], and 1960s [129] have reported that specific variations in dietary composition of pregnant women may alter long-term health in offspring; in particular, there is evidence that maternal diet in pregnancy may influence offspring BP.

High maternal animal protein intake [129] and both high and low maternal protein to carbohydrate ratios [127,128] have been associated with greater adult offspring BP at 30–50 years. While this might suggest that modifications to maternal protein or carbohydrate intake during pregnancy might influence long-term cardiovascular health of offspring, effects on offspring BP have not been observed in RCTs of protein or protein and energy supplementation for pregnant women in Guatemala [130], Gambia [131], and India [132] or in later observational studies of larger, more contemporary cohorts [133,134].

One of these RCTs—that of maternal protein and energy supplementation in India—while not finding an effect on offspring BP, did report beneficial effects of supplementation on other cardiovascular risk factors (lower insulin resistance and arterial stiffness) in adolescent offspring, however, as the intervention consisted of supplementation for both pregnant mothers and their offspring in infancy and childhood (up to 6 years of age) effects of prenatal and postnatal supplementation cannot be disentangled in that study [132]. Furthermore, a recent review found that there was no strong evidence of a wide variety of food groups, micronutrients, and macronutrients eaten by mothers during pregnancy being related to offspring BP [135]. The only exception was modest evidence that greater maternal calcium intake in pregnancy may be associated with lower offspring BP [135].

The impact of maternal prenatal diet on other components of offspring health has also been explored. For example, in contemporary, well-nourished women, greater maternal macronutrient intake in pregnancy was associated with greater intakes of the equivalent macronutrients in offspring at 10 years [136]. The stronger associations (with offspring intake) for maternal macronutrient intake prenatally, compared with both paternal macronutrient intake and maternal intake postnatally suggested that greater maternal macronutrient intake during pregnancy may have specific in utero effects on offspring macronutrient intake in later life. This could occur, for example, via programming effects on offspring appetite. However, this did not translate to effects of maternal prenatal macronutrient intake on offspring adiposity [136].

Finally, observational studies have reported that greater maternal intake of fish and seafood during pregnancy is associated with improved cognitive function in offspring [137,138]. It is believed that omega-3 fatty acids are responsible for these associations, and while several small trials of maternal omega-3 supplementation report some evidence of improved cognitive development in infants and children [139–142], there are concerns regarding these findings because of the small sample sizes and high attrition rates in these studies. Indeed, in a recently published large RCT maternal supplementation with omega-3 in pregnancy did not result in improved cognitive and language development in their offspring during early childhood [143].

In conclusion, based on the existing epidemiological evidence, there is little support for consistent effects of maternal diet in pregnancy on offspring health and development. As others have remarked [126], while this translates to limited options for nutritional intervention at present and few specific recommendations can be made, the prenatal period remains an ideal window of opportunity for clinical and health care practitioners to encourage overall healthy eating behavior in pregnant women.

Maternal Physical Activity in Pregnancy

Until several decades ago, physical activity during pregnancy was a cause for concern because of the perceived associated risk of maternal injury and of physiological changes

physical activity induces in blood flow, body temperature, and fetal oxygen delivery that could potentially have both short-term and lasting detrimental effects on the fetus [144]. More recently, several observational epidemiological studies have reported beneficial effects of greater levels of physical activity during pregnancy for the pregnant woman, such as a decreased risk of gestational diabetes [145] and preeclampsia [146,147]. Thus guidelines recommend that pregnant women maintain the same level of moderate physical activity as non-pregnant women [148].

However, current evidence is inconsistent on whether exercise during pregnancy is beneficial, harmful, or neutral for the health of the developing fetus [149]. These mixed findings are likely to reflect different methods of exposure and outcome assessment, different timing during the pregnancy for exposure and outcome assessments, differences in pre-pregnancy exercise habits between the study populations, and differences in the studies' abilities to control for potential confounding factors.

By far, the largest observational study to date, including over 90,000 participants in the Danish National Birth Cohort, found a strong and linear association between increasing levels of physical activity in early pregnancy and miscarriage before 18 weeks gestation [150]. As with other behaviors in pregnancy, RCTs in this area are difficult. However, a Cochrane systematic review of randomized controlled trials to promote aerobic exercise during pregnancy concluded that regular aerobic exercise during pregnancy (mostly swimming, static cycling, and floor exercises) appears to improve women's physical fitness, but that current evidence was insufficient to draw firm conclusions about its likely overall risks or benefits for the woman or baby [149]. The reviewers concluded that larger, better quality trials are needed before confident recommendations could be made about the benefits and risk of exercise during pregnancy.

The long-term effect of physical activity in pregnancy on offspring future health is even less well studied. Two small prospective studies assessed outcomes in offspring of women who exercised regularly throughout pregnancy compared with offspring of active women who did not exercise at 1 and 5 years of age. In the first study [151], which included 104 mother–offspring pairs, weight, length, and abdominal and head circumferences at mean age 1 year were similar in offspring of women who did or did not continue regular physical activity throughout pregnancy. In another study by the same group [152], which included just 40 mother–offspring pairs, at mean age 4 years, offspring of women who engaged in vigorous physical activity during pregnancy were lighter and had less subcutaneous fat but were of similar height as offspring of women who voluntarily stopped exercising in pregnancy. They also scored higher for oral language skills and general IQ (assessed by the Wechsler Preschool and Primary Scale Intelligence). Motor, integrative, and academic readiness skills were similar between groups. In both studies, women were matched for pre- and postnatal characteristics known to influence outcomes [151,152].

Thus, to date evidence suggests that maintaining moderate levels of physical activity during pregnancy may be beneficial to the health of the mothers, but it is unclear whether variation in levels of physical activity during pregnancy is causally (either beneficially or detrimentally) related to health outcomes in the developing fetus or longer term in offspring.

CONCLUSION AND IMPLICATIONS FOR HEALTH POLICY AND FUTURE RESEARCH

The inverse association of birth weight with CVD and risk factors is unlikely to be fully explained by residual confounding or genetic variants with pleiotropic effects on both fetal growth and later insulin resistance. However, birth weight per se is unlikely to be the key risk factor and it is relatively resistant to modification. Therefore, identifying modifiable prenatal risk factors that might have important impacts on future health is where future research should primarily focus. Current evidence supports a causal intrauterine effect of maternal diabetes and extreme obesity on increased risk of offspring obesity, but not of an important effect of variation in maternal early-pregnancy BMI across the distribution on offspring adiposity.

There is also evidence that physical activity both prenatally and during pregnancy reduces the risk of gestational diabetes [145]. Thus, interventions that promote healthy levels of physical activity in women of reproductive age and other means of preventing gestational diabetes are likely to be beneficial for both the mother and her future offspring.

Clinically, screening of women for gestational diabetes and treatment of this has been shown to be beneficial with respect to perinatal outcomes but effects on long-term maternal and offspring health are currently unknown. The mechanisms underlying the link between HDP and offspring elevated BP are unclear, but the reliability of these associations suggests that there may be some benefit in monitoring future BP of both mothers and offspring where the mother has experienced HDP.

There is increasing evidence that maternal consumption of alcohol during pregnancy, even at modest levels, results in lower cognitive function on offspring. This effect is modest, but nonetheless, women should be provided with this information so that they can make informed choices about drinking during pregnancy. For other modifiable behaviors such as smoking, diet, and physical activity, there are associations with a wide range of health outcomes in offspring but for most of these, currently it is unclear whether these are causal via intrauterine mechanisms or not.

Since RCTs in situations where timing of exposure/intervention (here, in mothers during pregnancy) is several years from assessment of outcome (here, in later childhood or adulthood), are expensive, and likely to be importantly affected by attrition and because RCTs of behavior change in pregnancy are difficult and in some cases unethical, it is likely that answers regarding causal effects of maternal behaviors during pregnancy on future offspring outcomes will largely rely on evidence from observational studies. Thus, investment in family-based studies such as sibling

comparisons and maternal–paternal offspring association comparisons, as well as cross cohort comparisons and Mendelian randomization studies (in which genetic variants that are robustly associated with the risk factor of interest, e.g., alcohol consumption), are important in this area. Such studies in general require large sample sizes and collaborative efforts.

There is a lot known generally about the adverse health effects of cigarette smoking, heavy alcohol consumption, consumption of a diet that is energy dense and low in fruit and vegetables, and low levels of physical activity, and therefore, women of reproductive age, as with the rest of the population should be encouraged to maintain healthy behaviors irrespective of any causal effects on their future offspring. However, there are a number of reasons why further research to determine whether different behaviors have causal effects via intrauterine mechanisms on offspring health is important.

First, pregnancy is perceived as a time when women are receptive to health advice, particularly, if it is likely to benefit their offspring, but such advice has to be correct and evidence based, otherwise there is the risk that all health-promoting advice will be discredited.

Second, if the mechanisms linking health behaviors to offspring health act via general family lifestyles then targeting pregnant women may achieve less benefit than interventions that are focused at all family members.

Third, for some behaviors during pregnancy, there may be both beneficial and detrimental effects. For example, increasing physical activity levels in pregnancy may have some benefit for mothers but may cause harm in terms of early fetal loss. It is key that a wide range of both maternal and fetal/offspring short- and long-term health outcomes are examined for these behaviors so that women are provided with clear information and relevant advice.

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Part XVII

Family Practice

Charles B. Eaton, MD, MS

97 Introduction to Family Medicine Section

Charles B. Eaton MD, MS

This part is written for generalist physicians (family physicians, internists, pediatricians, and general practitioners), nurse practitioners, and other health care providers to address the needs of lifestyle counseling (physical activity, weight loss, smoking cessation) in the context of a busy, primary care office setting. When necessary, it reiterates topics explored in more depth in other parts of the book, not from the viewpoint of an exercise physiologist, clinical psychologist, nutritionist, or medical specialist but from the perspective of a generalist.

Since the last printing of this book, the impact of the lack of regular physical activity and healthy eating in the U.S. population with the resultant epidemic of obesity and diabetes has become apparent. There has also been an explosion of the use of the e-health (Internet, cell phone, integrated voice response, electronic health record) in care of patients with chronic diseases and in lifestyle counseling in the research setting, and these channels of communication are beginning to be utilized in clinical practice.

In the first chapter, I review the literature on office-based physical activity counseling as well as more recent interventions done via the Internet and in the community setting and discuss how the results of this research may be used in daily office practice.

Dr. Carol Garber addresses exercise counseling in patients with chronic disease within the office setting in the next chapter. Safety and screening considerations to exercise prescription are reviewed, and the volume of exercise and estimating the intensity of exercise are discussed. Tips regarding resistance exercises, flexibility exercises, and neuromotor training are also reviewed in this chapter.

Drs. Kim Gans, Kelli Drenner, and colleague Gemma Gorham discuss nutritional counseling in a busy office practice in the next chapter. They discuss the importance of nutritional counseling and the potential role of primary care physicians and review effective patient-focused counseling strategies including motivational interviewing techniques and the 5As construct. Brief dietary assessment tools, such as Rate your Plate, Rapid Eating, and Activity Assessment for Patients, are discussed, and multiple resources for providers and practices are highlighted in this chapter.

Dr. Sean David describes the state of the art of using pharmacogenomic data, to tailor smoking cessation counseling particularly focusing on pharmacologic therapy for smoking cessation. While not quite ready for clinical practice at this time, the exciting potential of this personalized medicine approach is discussed.

In the last chapter of this part, Dr. David Ahern and colleague Judy Phalen review the e-health resources presently available to support Lifestyle Medicine. They review the evidence of e-health interventions aimed at improving rates of smoking cessation, healthy eating and weight loss, physical activity, and decreasing the morbidity of mental health problems such as anxiety and depression, which make up the majority of health behaviors attributable to preventable deaths and disability. They discuss the challenges in this behavioral medicine research including problems with adoption and implementation of these e-health tools by both providers and patients. They also review some of the proposed solutions needed to advance this field forward including tailoring of the behavioral messages, user-centered designs, and incorporating cultural values as well as behavioral economics into the e-health tools.

98 Office-Based Physical Activity Counseling in Healthy Adults

Charles B. Eaton, MD, MS, Arnold Goldberg, MD, and Emma Simmons, MD, MPH

CONTENTS

Guidelines for Physical Activity 1201
Physical Activity Counseling: The Role of Primary Care Providers 1202
Results of Studies on Physical Activity Counseling in Primary Care Settings 1203
Approach to Patient-Centered Physical Activity Counseling in Primary Care 1204
- Assess Present Level of Physical Activity 1204
- Assess Patients Willingness to Change Behavior 1204
- Assess Patient Safety to Exercise 1204
- Write Exercise Prescription 1205
- Encourage Behavioral Processes 1206
- Arrange Follow-Up 1206

Summary 1206
References 1206

Primary care providers in office-based practice have the potential to play an important role in reducing health risks related to their patients' physical inactivity. With the advent of the Patient-Centered Medical Home, electronic health records, patient portals, e-health tools, and practice redesign with group visits and care managers, primary care physicians now have the opportunity to go beyond time-consuming face-to-face encounters and provide more comprehensive lifestyle counseling using a team-based approach. This chapter will review the rationale for promoting physical activity counseling by primary care providers; results of studies on physical activity counseling in primary care and other relevant settings; and a recommended approach to patient-centered physical activity counseling in primary care settings both for the clinician and the health care team.

GUIDELINES FOR PHYSICAL ACTIVITY

Lack of physical activity has been identified as one of the leading preventable causes of death,[1] and regular physical activity demonstrates an inverse relationship exists between volume of physical activity and all-cause mortality.[2,3] In addition, regular physical activity decreases the risk of cardiovascular disease,[3] type 2 diabetes mellitus, osteoporosis, depression, obesity, breast cancer, colon cancer, and falls in older adults.[3] In addition, promoting physical activity has been shown to have large potential savings in cost-benefit analyses.[6,7]

Given the numerous health benefits of physical activity participation, various guidelines have been published on the recommended volume and intensity of physical activity for healthy adults over the past 35 years. In 2008, the Centers for Disease Control and Prevention (CDC) released the Physical Activity Guidelines for Americans, which are summarized in the subsequent sections.[8] For children and adolescents (aged 6–17 years), they recommended 1 h (60 min) or more of physical activity every day. Most of these should be either moderate- or vigorous-intensity aerobic physical activity. As part of their daily physical activity, children and adolescents should do vigorous-intensity activity on a minimum of 3 days per week. CDC also recommended muscle-strengthening and bone-strengthening activity on at least 3 days/week.

For adults (aged 18–64), recommend 2 h and 30 min a week of moderate-intensity, or 1 h and 15 min (75 min) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 min, preferably spread throughout the week. Additional health benefits are provided by increasing to 5 h (300 min) a week of moderate-intensity aerobic physical activity, or 2 h and 30 min a week of vigorous-intensity physical activity, or an equivalent combination of both. They also recommended that adults should do muscle-strengthening activities that involve all major muscle groups performed on ≥2 days/week.

For older adults (aged 65 and older), they recommended that older adults should follow the adult guidelines. If this is

not possible due to limiting chronic conditions, older adults should be as physically active as their abilities allow. Older adults should do exercises that maintain or improve balance if they are at risk of falling. For all individuals, some activity is better than none. Physical activity is safe for almost everyone, and the health benefits of physical activity far outweigh the risks. People without diagnosed chronic conditions (such as diabetes, heart disease, or osteoarthritis) and who do not have symptoms (e.g., chest pain or pressure, dizziness, or joint pain) do not need to consult with a health care provider about physical activity.

For adults with disabilities, it is recommended that they follow the adult guidelines. If this is not possible, these persons should be as physically active as their abilities allow. They should avoid inactivity. For children and adolescents with disabilities, they suggest, when possible, to meet the guidelines for children and adolescents—or as much activity as their condition allows. Children and adolescents should avoid being inactive.

For pregnant and postpartum women, regardless of trimester, it is suggested that healthy women who are not already doing vigorous-intensity physical activity should get at least 2 h and 30 min (150 min) of moderate-intensity aerobic activity a week. Preferably, this activity should be spread throughout the week. Women who regularly engage in vigorous-intensity aerobic activity or high amounts of activity can continue their activity provided that their condition remains unchanged and they talk to their health care provider about their activity level throughout their pregnancy.

Despite the numerous benefits of physical activity and the recent federal guidelines, only 48.8% of U.S. adults meet recommended levels of moderate to vigorous physical activity, 37.7% have suboptimal levels of activity, and 14.2% are inactive by self-report.[9] Accelerometer data suggest an overreporting bias with 42% of children aged 6–11 years meeting the current 60 min/day recommendation but only of 8% of adolescents meeting this goal and fewer than 5% of adults meeting the ≥30 min/day recommendation.[10]

PHYSICAL ACTIVITY COUNSELING: THE ROLE OF PRIMARY CARE PROVIDERS

Health care settings offer a potentially attractive vehicle for making changes in the levels of physical activity of inactive individuals because patients visit physicians and other health care providers frequently. Approximately 76% of the U.S. population visits a physician in the course of a year, with an average of 5.3 visits per year.[9] Moreover, patients look to physicians for advice regarding preventive behavior.

The U.S. Preventive Task Force (USPTF) previously in 1996 recommended physical activity counseling based upon the proven efficacy of regular physical activity in reducing the risk for coronary heart disease, diabetes, hypertension, and obesity, and the potential impact of physician counseling on patients' levels of physical activity.[11] However, the more recent USPTF recommendations concluded that evidence was insufficient to recommend for or against behavioral counseling in primary care settings to promote physical activity.[12] This conclusion was based upon the mixed results of physician-based counseling studies on sustained behavior change but fails to include more recent studies and the lessons learned from the research done from other settings such as workplaces, community, and Internet-based studies. In the next section, we review the research done over the past decade in relevant settings and recommend physical activity counseling in physician office based upon expanded primary care office setting using the Care Model proposed by Wagner et al.[13]

The Care Model proposes that improved patient outcomes such as regular physical activity will be fostered in a primary care office setting when an informed, activated patient and family interact with a prepared proactive team approach focusing on such a behavioral change. This requires the synergistic interaction of community resources (safe walking paths, YMCAs, schools, worksites, exercise facilities); self-management support (setting goals, tools for monitoring); delivery system design (previsit motivational assessment, physical activity vital sign, exercise prescriptions, referrals to exercise specialists where applicable, care managers, telephone follow-up); clinical information systems (reports detailing the percentage of patient who are sedentary, overweight, or obese); decision support (pop-ups reminding the provider that patient needs exercise prescription and is motivated to make change, metabolic equivalent (MET) levels of activity choices, injury prevention); the motivated patient, family, and social support (chat rooms, group activities); and the provider and office team (medical assistants, nurses, care managers, community health workers, pharmacists, exercise physiologists, health coaches) trained to perform a role in this system of care.

While not all elements of the care model may be feasible in a given practice, many aspects have been studied and shown to have promise and are discussed in the next section. Indeed, this idealized model of care is a far cry of present primary care practice. Podl et al. observed 4215 office visits in primary care in Ohio and found that only 23% of visits were documented exercise counseling being performed, and on average, this counseling lasted about 47 s.[14] A Canadian survey found that only 11.8% of family physicians routinely counseled about exercise. A total of 58% of the physicians felt less than 25% of their patients would respond to such counseling, less than half felt knowledgeable about exercise counseling, and two-thirds said they didn't have enough time to perform this counseling.[15] These barriers to face-to-face counseling by primary care physicians, namely, lack of physician education, lack of time, and lack of effectiveness of counseling, have been consistently found and suggest a new approach focusing on the team-based model as found in the care model (decision support tools, referral to community resources, exercise specialists, health coaches, and care managers) might overcome these barriers.

RESULTS OF STUDIES ON PHYSICAL ACTIVITY COUNSELING IN PRIMARY CARE SETTINGS

A review of the literature by the American Heart Association Council on nutrition, physical activity, and metabolism in 2006, found that interventions in primary care health care settings can increase physical activity, at least in short-term follow-up.[16] They concluded that some research has shown that even brief (3–10 min) interventions can increase physical activity, and although physicians typically delivered the advice, effective interventions often involved other members of the health care team, such as nurses and health educators. Written prescriptions, provided in addition to verbal advice, may enhance the effectiveness of interventions. Multiple-component interventions that include behavioral strategies such as goal setting, problem solving, self-monitoring, and feedback, as well as supervised exercise and provision of equipment, have generally been more effective than advice only, although these findings have not been entirely consistent across studies. Technological innovations such as using the Internet or making automated phone calls may reduce the effort and cost of interventions, although further research is needed to clarify this.[16]

Walking is the most prevalent and preferred method of physical activity for both work and leisure purposes, thus making it a prime target for physical activity promotion interventions. Williams et al. reviewed 14 randomized controlled trials, which tested interventions assessing walking behavior and found that intensive interventions can increase walking behavior relative to controls.[17] Brief telephone prompts seem to be as effective as more substantial telephone counseling. They found preliminary evidence that prescriptions to walk 5–7 days/week did better than those that recommended 3–5 days/week and that moderate-intensity pace did better than vigorous-intensity pace. They found no differences in benefit in the volume of physical activity, measured as total walking minutes, when single or multiple daily walking bouts were prescribed. Interventions delivering physical activity promotion through non face-to-face channels showed efficacy in promoting overall physical activity, especially when theory-based and individually tailored. Mass media campaigns targeting broader audiences did not increase walking behavior.

Since these reviews several more recent trials inform recommendations for physical activity counseling in primary care. The Activity Counseling Trial was a 24 month trial in 11 primary care practices that tested social-cognitive theory-based interventions to increase self-efficacy, social support, and environmental resources as a means to increase physical activity in primary care practice.[18] They compared 2–4 min of brief physician counseling including assessing present level of activity, providing advice to increase activity, and setting long-term goals of physical activity using a target of ≥5 days/week of ≥30 min of moderate activity or ≥3 days of 30 min of intense vigorous activity. In addition, the providers referred patients to an on-site health educator for further health education and counseling. A second group received a more intense intervention including the same brief counseling plus a 30–40-minute behavioral counseling session with the health educator, a motivational videotape, confirmation of physical activity goals, plus an individualized activity plan. Telephone calls were made 1 week after intervention for advice and support, and this second group also received monthly newsletters, weekly mail-back cards for reporting weekly physical activity, current goals, etc. This group was also given a step-counter. A third more intense intervention group received all aspects of the first two groups plus biweekly counseling calls and monthly calls after the first 6 weeks and during the second year, telephone calls were made on a mutually negotiated basis. In addition, participants received weekly classes at centers by the health educators on enhancing behavioral skills. The investigators found that all three groups increased physical activity (PA) at 6 months: in the brief advice group, 14.3% (from a baseline of 1.5%) were at the PA goal for women and 16.4% (from a baseline of 0.6%) were at the PA goal among men; in the second group, 9.9% (from a baseline of 0.8%) were at PA goal in women and 29.9% (from a baseline of 2.5%) were at the PA goal in men; and in the third group, 25.7% (from a baseline of 0.8%) were at the PA goal in women and 18.5% (from a baseline of 1.3%) were at the PA goal in men. *This study suggests that even a brief physician intervention of 2–4 min resulted in significant improvement in physical activity, with only modest increased benefit for more intensive interventions.*

Looking at psychosocial mediators of physical activity changes in the Activity Counseling Trial, Baruth et al. found that behavioral processes seemed more important than cognitive processes with some sexual dimorphism in this trend.[19]

Behavioral processes such as self-commitment, substituting alternatives, rewarding oneself for being physically active, and increased self-efficacy played the most important role in predicting increased in physical activity. *The authors suggested that physical activity interventions should incorporate strategies that specifically aim to increase participant's use of behavioral processes, such as encouraging participants to enlist social support, reward themselves for being active, or substitute alternatives for being active instead of sedentary.*

Petrella et al. compared exercise prescription alone vs. stage-based exercise counseling program in older sedentary adults in family practice in Canada.[20] Similar to the activity counseling trial (ACT), they found that the both groups increased physical activity and cardiovascular fitness, suggesting that a brief intervention may be quite effective, especially if it accounts for the patient's level of cardiovascular fitness.

Van Sluijs et al., in a Dutch general practice cohort, compared brief physician advice with a trans-theoretical model of physical activity intervention using the PACE protocol.[21,22] After 1 year, both groups increased physical activity to greater than 300 min of leisure time physical activity at least moderate-intensity. *This study again suggests that tying a patient's medical condition to the need to increase regular*

physical activity and performing brief exercise counseling appear to be helpful.

Morey et al.,[23] using a multicomponent physical activity counseling protocol involving clinical endorsement of the need for more physical activity, frequent telephone counseling, and quarterly tailored mailing in elderly veterans in primary care in North Carolina, found a significant increase in physical activity from 57 to 127 min of weekly physical activity in the intervention group but no change in the usual care group. *This study demonstrates that even in elderly patients with multiple comorbidities, unsupervised physical activity is safe and an intensive physical activity counseling protocol was effective in a primary care setting.*

Use of the Internet to increase physical activity has been tested in several clinical trials with mixed results. Marcus et al. compared tailored Internet, to tailored print to standard Internet from overweight, sedentary community participants. All three groups had less than 10 min of moderate to vigorous PA per week, and by 6 months, the tailored groups did slightly better than the standard Internet, but this finding was not statistically significant (120, 112, 90 min, $p = 0.15$, respectively). By 12 months, all three groups sustained their increased physical activity (90, 90, 80 min; $p = 0.74$, respectively) but with no superiority of the tailored interventions. The most commonly used standard Internet site was the American Heart Association website, http://www.startwalkingnow.org/.[24]

APPROACH TO PATIENT-CENTERED PHYSICAL ACTIVITY COUNSELING IN PRIMARY CARE

Based on the barriers to physical activity counseling including the lack of education and confidence in exercise counseling by primary care physicians, the lack of time during a 12–15 min office visit in primary care and the lack of perceived efficacy of the interventions available to primary care physicians, and the body of evidence from clinical trials regarding physical activity interventions, the following approach is recommended.

Assess Present Level of Physical Activity

Most primary care physicians assess physical activity in selected patients using no standardized approach such as during new patient visits, during health maintenance exams, and during assessment of patient visits regarding obesity, diabetes, hypertension, dyslipidemic, osteoarthritis, and other musculoskeletal problems. However, many primary care physicians do not document these assessments at all and few perform them routinely unless they have a systems-based approach. One relatively successful technique is to incorporate physical activity into the vital sign assessment.[25] With the increasing use of electronic medical records, the physical activity vital sign assessment can be easily added to body mass index assessments. Two relatively simple questions, one assessing sedentary behavior, i.e., how many hours of sitting, including commuting time, TV watching, and computer use, and the second, asking about moderate to vigorous physical activity. The questions used by the Behavioral Risk Factor Survey are appropriate, i.e.,—During the past month, other than your regular job, did you participate in any physical activities or exercises such as running, calisthenics, golf, gardening, or walking for exercise? If yes, how many hours per week. Alternatively, the following question has been used in successful clinical trials.[26]

> As a rule, do you do at least half an hour or moderate or vigorous exercise (such as walking or a sport) on five or more days of the week?

After reviewing a patient's level of physical activity in more depth to determine if the screening question truly defines patients who are in need of exercise counseling, link the patient's physical inactivity to an important medical problem that the patient has or to a future health concern.

That is, as you are probably aware, your lack of exercise is associated with you _____ (being overweight, having high cholesterol, having diabetes, having high blood pressure, being at risk for having thin bones and breaking a hip, etc). This risk can be helped with a change in your physical activity levels.

Assess Patients Willingness to Change Behavior

How willing are you to increase your physical activity over the next 2 weeks? If the patient is willing, then proceed with exercise prescription. If they are not willing, ask them why not?

Assess Patient Safety to Exercise

Physical activity, while known to increase longevity, reduce cardiovascular risk, promote weight loss, cease smoking, improve mood, lower blood pressure, and increase bone density over the long term, may also be associated with increased risk of injury, accidents, and sudden cardiac death during exercise bouts. Exercise stress testing and supervised exercise programs are rarely needed even for elderly patients with multiple comorbidities. Other chapters in this textbook review the indications for exercise testing and medical evaluations of at risk patients. However, multiple studies have shown that gradual exercise at a mild to moderate pace for patients is safe without the need for formal exercise testing even in deconditioned, high-risk patients such as those postmyocardial infarction.[27] Reviewing any history of prior injuries with exercise and suggesting corrective action is appropriate. Most injuries occur due to overuse injuries from a rapid escalation of physical activity or improper equipment such as shoe wear without appropriate insoles, heel counters. A rule of thumb is to not increase activity by more than 10% per week in terms of total minutes.

Write Exercise Prescription

Multiple studies have shown writing a written exercise prescription is more effective than simply giving advice. Each prescription should specify four components of the physical activity plan: Frequency, Intensity, Type, and Time (or duration). These four components can be easily remembered by both providers and patients when the mnemonic FITT is used.[27]

Determining the appropriate level of intensity of physical activity is usually the first step in completing the prescription. Physical activity has been defined as "any bodily movement produced by skeletal muscles that results in energy expenditure,"[27] while moderate physical activity refers to any activity performed at an intensity of 3–6 METS (work metabolic rate/resting metabolic rate) or 4–7 kcal/min.[26] This level of physical activity can be achieved by most healthy adults by walking briskly (3 mph), cycling for pleasure (<10 mph), swimming with moderate *effort,* pulling a golf cart, mowing the lawn with a power mower, painting, or performing general cleaning at home.[26] Moderate activities have also been defined as activity at 50%–70% of maximum heart rate (220 – age) (Table 98.1).[28]

In contrast, vigorous activity has been defined as more than 6.0 METS, more than 7 kcal/min, or more than 70% maximum heart rate. For most sedentary patients, a moderate level of physical activity is an appropriate initial goal, especially if they have not engaged in vigorous physical activity in the recent past or if they have a medical condition that would preclude their participation in vigorous activity or require formal exercise testing.[27] For individuals already engaged in moderate activity, advancement to vigorous activity may be an appropriate goal, while those individuals who have been totally sedentary might be best off starting out with a goal of activity that falls below the level of moderate intensity (e.g., walking slowly, light stationary cycling, or light stretching).

Patients can be taught to monitor the level of intensity of physical activity in several ways, including determining their desired heart rate zone and instructing them to take their pulse rate while exercising using a perceived exertion scale, such as the Borg Perceived Exertion Scale.[28] (Figure 98.1).

If patients are able to talk comfortably but get a little sweaty while exercising, this usually indicates that they are within 50%–75% of their maximum heart rate.

Once the level of intensity of physical activity is decided upon, the other elements of the FITT exercise prescription can be completed. To meet the national physical activity recommendations, the goal for moderate-intensity activity should be ≥5 days a week, and the duration of activity each day should be 30 min; for vigorous levels of activity, the goals are three sessions of ≥20 min.[27,29] However, as noted previously, for patients who are not willing to meet the goal for moderate-intensity activity, an appropriate initial goal might be to engage in very short bouts (e.g., 5–10 min) of activity a few times per week. Such patients might be encouraged to gradually increase the time spent during each session of activity so that they eventually accumulate at least 30 min/day. Patients who choose to engage in activities meeting criteria for moderate or vigorous intensity should also be encouraged to spend a few minutes to warm up with stretching exercises or light activity, especially if they are older adults or have been very sedentary. Finally, the type of activity chosen for the exercise prescription should be based on several criteria: something the patient enjoys, an activity that was previously engaged in on a regular basis, an activity that can be easily integrated into daily routine

TABLE 98.1
Exercise Prescription

Suggested Program (FITT)		
Frequency	Times per week	
Intensity	Moderate	Vigorous
Type	Activity type	
Time	Minutes per session	
Comments		
Signature		Date

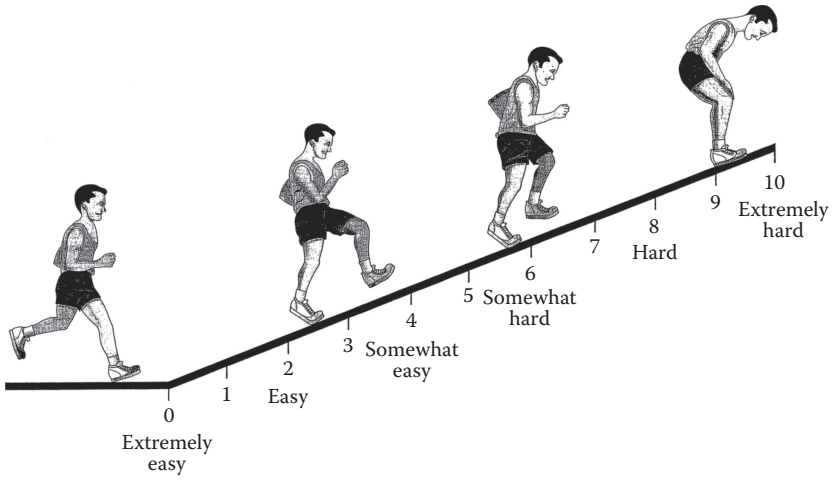


FIGURE 98.1 Borg perceived exertion scale.

(e.g., walking during lunch break, housework, yard work), an activity that meets social or recreational needs or goals (e.g., sports, dancing), and an activity that can be performed safely or under supervision (e.g., walking clubs, use of a fitness facility). The prescription plan may also specify a variety of activities that can be combined to meet the overall goal for frequency and duration.

The use of an exercise or physical activity prescription facilitates the behavior change process in a number of ways. First, it sets a specific physical activity goal for the patient. Second, like other prescriptions written by the health provider, it conveys the importance of physical activity to the patient and builds on the influence and authority of the health care provided. Third, it gives the health care provider something concrete and tangible to do to address the problem of sedentary behavior. Fourth, the process of completing the prescription facilitates the development of a mutually agreed-upon plan for addressing physical activity. The prescription, if also signed by the patient, serves as a written contract between patient and provider that may enhance the patient's adherence to the plan. Finally, if a copy of the prescription is saved in the chart, it can be used during subsequent visits to review the patient's progress.

Encourage Behavioral Processes

Behavioral medicine research has shown that patients that track their behavior are more likely to accomplish a behavioral change compared with those who do not. Asking patients to fill out a physical activity log is a helpful way to accomplish this. Social support such as exercising with a buddy or support person, joining a walking club or gym, and training for an event can lead to increased physical activity.

While regular walking is the most common form of exercise by most Americans, finding safe, walking paths can be an issue. Recently, there has been much work by communities, states, the CDC, and the American Heart Association to develop access to safe walking paths. Primary Care Practices should investigate or be aware of walking paths in their patient's neighborhoods.

While multiple websites are available, the American Heart Association's website, http://www.startwalkingnow.org/, provides tips about starting a walking program, nutrition and physical activity logs, walking paths near patients who have a job and a social networking site to find other community members starting a walking program, and providing emotional support via a monitored chat room.

Another helpful web-based resource is a wellness programs supported by the patients health plan or employer. Shape UP the Nation, http://www.shapeupthenation.com/, provides programs for physical activity as well as programs related to weight loss, healthy eating, and smoking cessation. Additional websites and e-health tools are described in Chapter 101.

Arrange Follow-Up

The last step of exercise counseling is to arrange follow-up. This can be either by a face-to-face office visit with either the provider or other member of the care team, i.e., team nurse, health coach, care manager, or by remote contact such as by telephone, e-visit, or some combination of office visit and remote contact. Most studies suggest that follow-up contact should be within several weeks of the initial exercise counseling session.

SUMMARY

Physical inactivity and sedentary behavior are reversible risk factors for multiple chronic diseases. Primary care physicians, particularly in the setting of a Patient-Centered Medical Home, have the opportunity to use the "teachable moments" within patient's visits to provide exercise counseling in the context of a comprehensive system of care and thus are able to mimic clinical trials that have shown to be effective in improving physical activity. This office system of care in conjunction with public health and policy initiatives in changing the physical activity environment (safe walking and cycling paths, take the stairs campaigns) and social media campaigns provide new opportunities for incorporating exercise counseling in primary care.

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99 Exercise Prescription for Patients with Chronic Health Problems

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CONTENTS

Introduction 1209
Safety Considerations and Screening 1209
Recommendations for Exercise Prescription 1209
The Exercise Training Session 1211
Cardiorespiratory (Aerobic) Exercise 1211
Estimating Exercise Intensity 1211
Estimating Exercise Volume 1211
Resistance Exercise 1211
Flexibility Exercise 1212
Neuromotor Exercise Training 1212
References 1212

INTRODUCTION

The purpose of this chapter is to provide advice for physicians prescribing exercise for their patients during an office visit. A goal of increasing intentional exercise, while concurrently reducing sedentary time by interspersing short periods of physical activity and standing between periods of sedentary activity throughout the day is a goal for most adults, including persons with chronic disease or disability [1–5]. Because of the complexities of exercise training in individuals with chronic diseases and the considerable benefits of an individualized exercise program, referral to a certified advanced fitness professional with training experience working with people with chronic diseases is recommended [1].

SAFETY CONSIDERATIONS AND SCREENING

For most people, the risks of exercise are greatly exceeded by the benefits of exercise [1,5]. A very low risk of musculoskeletal and cardiovascular disease (CVD) complications is associated with walking and moderate-intensity physical activities, and these activities are recommended for most adults to achieve improved health [1]. The risks of adverse CVD and musculoskeletal sequelae increase when an inactive individual engages in *unaccustomed* vigorous exercise [1,6], so it is important to gradually progress to vigorous exercise in those insufficiently active or sedentary.

Nonetheless, there are individuals in whom exercise may be hazardous, and the reader is referred to current clinical guidelines for exercise for contraindications to exercise [1,5,7–9]. Preexercise screening is helpful for those beginning exercise for the first time or after a long hiatus, regular exercisers who plan to substantially increase or change their exercise program, and anyone with a change in health status or new onset signs or symptoms. It is important *not* to assume that people who regularly exercise do not need regular evaluation for signs and symptoms of CVD, as these are often overlooked by both the individual and the health care provider [1,10]. Diagnostic exercise testing may be useful in persons who have suspected or known coronary heart disease (CHD) [1,8,11–13]. The evidence is less clear in asymptomatic persons with diabetes or with multiple CVD risk factors, but there may be value of diagnostic testing particularly in individuals at moderate or high risk [12]. Diagnostic exercise testing is of questionable value as a routine screening in asymptomatic low risk adults [1].

Prescreening for exercise should generally include

- Physical examination and review of the current and past medical history to identify contraindications to exercise
- Screening for and educating about prodromal signs and symptoms of CVD
- Diagnostic exercise testing as indicated according to clinical practice guidelines

RECOMMENDATIONS FOR EXERCISE PRESCRIPTION

A program of regular exercise *beyond physical* activities of daily living is *essential* for most adults to improve and maintain physical fitness and health [1–5]. Optimally, an individual exercise program will include several types of exercise: cardiorespiratory, resistance, flexibility, and neuromotor exercise training [1–3,5]. It is important to individualize the exercise prescription according to an individual's habitual

TABLE 99.1
Recommendations for the Individualized Exercise Prescription

Cardiorespiratory ("Aerobic") Exercise	Recommendation
Frequency	• ≥5 days · week^{-1} of moderate exercise
	• Or ≥3 days · week^{-1} of vigorous exercise
	• Or a combination of moderate and vigorous exercise on ≥3–5 days · week^{-1}
Intensity	• Moderate and/or vigorous intensity
	• Less intense exercise may be beneficial in deconditioned persons.
Time	• 30–60 min · day^{-1} of purposeful moderate exercise
	• Or 20–60 min · day^{-1} of vigorous exercise
	• Or a combination of moderate and vigorous exercise per day
Type	• Regular, purposeful exercise that involves major muscle groups and is continuous and rhythmic in nature
Volume	• A target volume of ≥500–1000 MET · min · week^{-1}
	• Or >1000–1500 kcal · week^{-1}
	• Or increasing pedometer step counts by ≥ 2000 steps · day^{-1} to reach a daily step count ≥7000 steps · day^{-1}
Pattern	• One (continuous) session per day
	• Or multiple sessions of ≥10 min
Progression	• A gradual progression of exercise volume by adjusting exercise duration, frequency, and/or intensity as tolerated
Resistance Exercise	
Frequency	• 2–3 days · week^{-1}
Intensity	• Moderate to hard intensity for novice to intermediate exercisers
	• Very light to light intensity for older or sedentary persons
Time	• Duration to complete exercises
Type	• Resistance exercises using each major muscle group
Repetitions	• 8–15 repetitions
Sets	• 1–4 sets
Pattern	• 2–3 min rest between each set of repetitions
	• A rest of ≥48 h between sessions
Progression	• A gradual progression of greater resistance, and/or more repetitions per set, and/or increasing frequency as tolerated
Flexibility Exercise	
Frequency	• ≥2–3 days · week^{-1}
Intensity	• Stretch to the point of feeling tightness or slight discomfort
Time	• Hold for 10–30 s
Type	• Exercises for each of the major muscle-tendon units
Volume	• 60 s of total stretching time for each flexibility exercise
Pattern	• Repeat of each exercise 2–4 times
Progression	• Gradual progression as tolerated
Neuromotor Exercise Training	
Frequency	• ≥2–3 days · week^{-1}
Time	• ≥20–30 min · day^{-1}
Type	• Exercises involving motor skills such as balance, agility, coordination, and gait, and multifaceted activities such as tai chi and yoga
Volume	• ≥60–150 min per week
Pattern	• Single or multiple shorter sessions per day
Progression	• Gradual progression as tolerated

Source: Adapted from Haskell, W.L. et al., *Med. Sci. Sports Exerc*., 39, 1423, 2007; Garber, C.E. et al., *Med. Sci. Sports Exerc*., 43, 1334, 2011, 2010, 2008a; Nelson, M.E. et al. *Med. Sci. Sports Exerc*, 39, 1435, 2007.

physical activity, physical function, health status, individual exercise responses, and stated goals [1]. Warming up, cooling down, employing a gradual progression of exercise volume and intensity, attention to proper training technique, and avoiding exercise under extreme heat or cold may be effective in reducing the risks of exercise [1,10].

Current recommendations for exercise are presented in Table 99.1. These volumes of exercise should be considered as targets for optimal exercise behavior, exercise less than these amounts is beneficial due to the dose response nature of exercise [1,5]. Therefore, an effective approach is to develop an exercise program that is feasible and enjoyable according to the individual patient's physical capabilities, personal goals and preferences, and limitations imposed by factors such as time and the physical and social environment [1]. The goal is to progress the exercise program gradually over time as tolerated to attain levels of exercise at or above the recommended targets and to enhance health benefits [1].

THE EXERCISE TRAINING SESSION

The exercise training session optimally includes several phases [1,7]:

- Warm-up: ≥5–10 min of low- to moderate-intensity cardiovascular and muscular endurance activities
- Conditioning: ≥20–60 min of aerobic, resistance, neuromotor, and/or sports activities
- Cooldown: ≥5–10 min of low to moderate-intensity cardiovascular and muscular endurance activities
- Stretching: At least 10 min of stretching exercises performed after the warm-up or cooldown phase

CARDIORESPIRATORY (AEROBIC) EXERCISE

Cardiorespiratory or aerobic exercise is sustained endurance exercise such as walking, cycling, aerobic group exercise classes, and "cardio" equipment found in gyms (e.g., elliptical trainer, treadmill, and stair stepper). These exercises do not require much skill to perform and so can be recommended for most adults [7]. Adequate levels of physical fitness and some skill are needed to engage in other cardiorespiratory exercises such as jogging, running swimming, rowing, kayaking, cross country skiing, sports, and some group exercise classes, so these can be part of the exercise program for more advanced exercisers [7]. Table 99.1 shows the recommended quantity and quality of aerobic exercise.

Estimating Exercise Intensity

Cardiorespiratory exercise intensity can be measured in absolute or relative terms. The metabolic equivalent (MET) is an index that represents the rate energy expenditure, so that 1 MET is the rate of energy expenditure at rest and 10 METs represents an energy expenditure 10 times greater than resting energy expenditure [1,13]. Tables of the METs for a wide range of physical activities and exercise are available [14,15]. Absolute measures of energy expenditure can result in misclassification of exercise intensity (e.g., moderate, vigorous), so *relative* measures of exercise intensity (energy expenditure of an activity relative to the individual's maximal capacity) are preferred for exercise prescription [1,3]. The most practical methods for clinical use is percent of the estimated or measured maximum heart rate ($\%HR_{max}$) or heart rate reserve ([Maximal heart rate – resting heart rate] + resting heart rate) or the maximal oxygen uptake ($\%VO_{2max}$) [7]. Direct measurements of heart rate and oxygen uptake as gained by exercise testing are recommended for greater accuracy, but when not feasible, estimation of exercise intensity is acceptable [1]. Table 99.2 shows the approximate absolute and exercise intensity ranges for various levels of exercise intensity. Self-rating scales that measure perceived effort and the pleasantness of exercise can be used to monitor or refine the prescribed exercise intensity of exercise in conjunction with the absolute or relative measures described earlier.

Estimating Exercise Volume

It is helpful to estimate exercise volume as part of the exercise prescription because of the important role of exercise volume in the attainment of beneficial health and fitness outcomes, particularly weight management [1]. Pedometers are effective for promoting physical activity, and they can provide an approximation of exercise volume [16]. The $MET \cdot min \cdot week^{-1}$ and $kcal \cdot min \cdot week^{-1}$ can be used to more precisely estimate exercise volume for individuals. The $MET \cdot min^{-1}$ and $kcal \cdot min^{-1}$ for many of physical activities can be estimated using published tables [14,15].

RESISTANCE EXERCISE

There is increasing evidence for the health benefits resulting from participation in resistance exercise and with improvements in muscular fitness [1–3,5]. Resistance training each major muscle group (i.e., the muscle groups of the chest, shoulders, upper and lower back, abdomen, hips, and legs) using weight machines, free weights, stretchy resistance bands, or other resistance equipment is recommended. A program that includes multijoint exercises (more than one muscle group) and single joint exercise can be recommended. This might include multijoint exercises such as the chest press, shoulder press, pull-down, dips, lower-back extension, abdominal crunch/curl-up, leg press, and squats, and single joint exercises such as biceps curls, triceps extensions, quadriceps extensions, leg curls, and calf raises target single muscle groups.

Resistance training should be performed with at least 48 h separating the exercise training sessions for the same muscle group [1,17]. To improve muscular strength, a resistance level that allows a person to complete about 8–15 repetitions (up to 20 repetitions) per set should be selected. Each set should be performed to the point of muscle fatigue but not failure.

TABLE 99.2
Relative and Absolute Exercise Intensity for Cardiorespiratory Endurance and Resistance Exercise

	Relative Intensity				Absolute Intensity (MET) by Age		
Intensity	%HRR or %VO_2R	%HR_{max}	%VO_{2max}	Perceived Exertion (Rating on 6–20 RPE Scale)	Young (20–39 Years)	Middle Aged (40–64 Years)	Older (≥65 Years)
Very light	≤30	≤57	≤37	≤ Very light (RPE ≤ 9)	≤2.4	≤2.0	≤1.6
Light	30–40	57–64	37–45	Very light–fairly light (RPE 9–11)	<4.8	<4.0	<3.2
Moderate	40–59	64–76	46–63	Fairly light to somewhat hard (RPE 12–13)	4.8–7.1	4.0–5.9	3.2–4.7
Vigorous	60–89	77–95	64–90	Somewhat hard to very hard (RPE 14–17)	7.2–10.1	6.0–8.4	4.8–6.7
Near maximal to maximal	≥90	≥96	≥91	≥Very hard (RPE ≥ 18)	≥10.2	≥8.5	≥6.8

Source: Adapted from Garber, C.E. et al., *Med. Sci. Sports Exerc*., 43, 1334, 2011, 2008a; Swain, D.P., *Sports Med*., 30, 17, 2000; Nelson, M.E. et al., *Med. Sci. Sports Exerc*, 39, 1435, 2007.

VO_{2max}, maximal oxygen uptake; HR_{max}, maximal heart rate; VO_2R, oxygen uptake reserve; HRR, heart rate reserve; (% HR_{max}, percent of maximal heart rate; %VO_{2max}, percent of maximal oxygen uptake; RPE, ratings of perceived exertion; MET, metabolic equivalent.

FLEXIBILITY EXERCISE

Joint range of motion can be improved by flexibility exercises, and these may also enhance postural stability and balance—more so when combined with resistance exercise [1]. Flexibility exercises are most effective when preceded by a warm-up with light-to-moderate cardiorespiratory or muscular endurance exercise. The stretch position is best held for 10–30 s at the point of tightness or slight discomfort. Attaining 60 s of total stretching time is the goal for each exercise [1]. Many types of stretching exercises can be effective, but for most adults, the most appropriate types are as follows:

- Active static stretching entails holding a position using the strength of the agonist muscle, typical of many forms of yoga.
- Passive static stretching in which a body position is held by another part of the body, or employing a device such as elastic bands or a barre.
- Dynamic slow movement stretching encompasses a gradual transition from one body position to another.

NEUROMOTOR EXERCISE TRAINING

Neuromotor exercise, or functional fitness training, focuses on motor skills such as balance, coordination, and agility. Neuromotor exercise training improves balance, agility, and muscle strength and reduces the fear of falling and the risk of falls in older people [1,3]. Tai chi, qigong, and yoga are multifaceted activities that involve varying combinations of neuromotor, flexibility, or resistance exercise, and so can be particularly helpful when included in a program of exercise for adults.

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100 Nutrition Counseling in a Busy Office Practice

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CONTENTS

Nutrition and Health 1215
Dietary Guidelines 1215
Nutrition Counseling: The Role of Primary Care Physicians 1215
How to Do It? 1216
Assess Dietary Practices in the Context of Health Risks 1217
Rate Your Plate 1217
Rapid Eating and Activity Assessment for Patients 1219
Advise: Give Clear, Specific, and Personalized Behavior Change Advice 1219
Agree: Collaborate with Patient to Select Treatment Focus 1219
Assist Patient in Setting Goals, Addressing Barriers, and Securing Support 1220
Arrange Schedule Follow-Up 1220
Resources to Help Physicians Do Nutrition Counseling 1220
References 1222

NUTRITION AND HEALTH

Consuming a healthy diet is associated with lower risks for chronic disease morbidity and mortality.[1] It has been estimated that 400,000 to more than 500,000 deaths/year are attributable to poor diet and physical inactivity.[2] If the increasing trend of overweight is not reversed, poor diet and physical inactivity will likely overtake tobacco as the leading preventable cause of mortality in the near future.[2] The most recent data indicate that 72% of men and 64% of women are overweight or obese, with about one-third of adults being obese.[3] Even in the absence of overweight, poor diet is associated with major causes of morbidity and mortality. These include coronary heart disease, stroke, hypertension, type 2 diabetes, osteoporosis, and some types of cancer.[1,4,5]

DIETARY GUIDELINES

Nutritional problems are prevalent in the United States. Adults and children eat inadequate quantities and varieties of fruits, vegetables, and whole grains and consume insufficient amounts of calcium and iron, too much saturated fat and sodium, and too many calories from solid fats, added sugars, and refined grains.[1,6] The U.S. Department of Agriculture recently released the 2010 Dietary Guidelines for Americans.[1] By law, these guidelines are reviewed and updated every 5 years by a committee of scientific experts. The 2010 Dietary Guidelines recommendations encompass two overarching concepts:

- Maintain calorie balance over time to achieve and sustain a healthy weight by balancing calories consumed through food and calories expended through physical activity.
- Focus on consuming nutrient-dense foods and beverages. Limit intake of sodium, solid fats, added sugars, and refined grains and emphasize nutrient-dense foods and beverages (vegetables, fruits, whole grains, fat-free or low-fat milk and milk products, seafood, lean meats and poultry, eggs, beans and peas, and nuts and seeds).

Specific dietary guidelines are shown in Table 100.1. To meet these guidelines, many would need to make significant changes in their eating habits and lifestyles. To facilitate these changes, individuals will need support from all sectors of society, including health professionals, educators, other individuals and families, communities, organizations, businesses, and policymakers.[6]

NUTRITION COUNSELING: THE ROLE OF PRIMARY CARE PHYSICIANS

Nutrition counseling is effective in changing dietary habits and has been shown to reduce medication costs.[7–12] National guidelines stress the importance of physician involvement

TABLE 100.1
Specific Dietary Guidelines, 2010

- Reduce daily sodium intake to less than 2300 mg (1500 mg among persons 51+ and those of any age who are African American or have hypertension, diabetes, or chronic kidney disease)
- Consume less than 10% of calories from saturated fatty acids by replacing with monounsaturated and polyunsaturated fatty acids
- Consume less than 300 mg/day of dietary cholesterol
- Keep trans fatty acid consumption as low as possible
- Reduce intake of calories from solid fats and added sugars
- Limit consumption of foods that contain refined grains, especially refined grain foods that contain solid fats, added sugars, and sodium
- If alcohol is consumed, consume in moderation—up to one drink per day for women and two drinks per day for men
- Increase vegetable and fruit intake
- Eat a variety of vegetables, especially dark-green and red and orange vegetables and beans and peas
- Consume at least half of all grains as whole grains. Replacing refined grains with whole grains
- Increase intake of fat-free or low-fat milk and milk products
- Choose a variety of protein foods, which include seafood, lean meat and poultry, eggs, beans and peas, soy products, and unsalted nuts and seeds
- Increase the amount and variety of seafood consumed by choosing seafood in place of some meat and poultry
- Replace protein foods that are higher in solid fats with choices that are lower in solid fats and calories and/or are sources of oils
- Use oils to replace solid fats where possible
- Choose foods that provide more potassium, dietary fiber, calcium, and vitamin D. These foods include vegetables, fruits, whole grains, and milk and milk products

Source: U.S. Department of Health and Human Services, U.S. Department of Agriculture. *Dietary Guidelines Advisory Committee. Dietary guidelines for Americans, 2010,* U.S. Department of Health and Human Services, U.S. Department of Agriculture, Washington, DC, 2010, http://www.cnpp.usda.gov/DGAs2010-PolicyDocument.htm, accessed April 26, 2011.

in nutrition counseling.[5,6,13] Healthy People 2020 includes objectives to (1) increase the proportion of physician office visits made by patients with a diagnosis of cardiovascular disease, diabetes, or hyperlipidemia that include counseling or education related to diet and nutrition (target: 22.9%); (2) increase the proportion of physician office visits made by adult patients who are obese that include counseling or education related to weight reduction, nutrition, or physical activity (target: 31.8%); and (3) increase the proportion of physician visits made by all child or adult patients that include counseling about nutrition or diet (target: 15.2%).[6] Specific clinical guidelines regarding hypertension, hypercholesterolemia, and diabetes mellitus also contain specific nutrition counseling recommendations.[14–17] In addition, the need for primary care physicians to provide counseling on nutrition and physical activity has been highlighted by both the 2010 *Surgeon General's Vision for a Healthy and Fit Nation*[18] and First Lady Obama's "Let's Move Campaign."[19]

Most Americans have a primary care physician whom they see at least once in every 2 years.[20] Experts suggest that there is a nutrition-related reason for more than 25% of all visits to primary care physicians[21] and patients want their physicians to provide nutrition counseling.[22–25] Despite this, however, most primary care physicians do not adequately deliver nutrition counseling to their patients.[5,21,26–39] For example, a study that directly observed physicians' counseling on dietary habits in private medical practices found that physicians counseled adult patients on dietary habits in only 25% of visits.[28] Healthy People 2020 reports even lower rates for adults and children combined: 12.2% of physician office visits of all child or adult patients included counseling about nutrition or diet in 2007 (Healthy People 2020 report). Furthermore, when dietary counseling does occur, the time spent is usually less than 5 min per patient, with the average time being 1 min.[27] Other studies have shown varying rates, but all are low.[25,40]

Barriers to nutrition counseling in the physician's office include time limitations; inadequate reimbursement; lack of financial incentives; inadequate nutrition training in medical schools and residencies; lack of confidence in counseling skills; uncertainty of the effectiveness of nutrition counseling; working in an acute care environment; lack of a systematic, organized approach within the practice structure; and lack of resources, tools, and support systems to facilitate nutritional counseling.[21,39,41–44] Primary care physicians do think nutrition counseling is important[21,38] and when they provide nutrition counseling to patients, they can be effective.[45–47] However, the current, time-pressured care process makes it difficult to accommodate this type of intensive lifestyle counseling into usual practice.[21]

Thus, nutrition counseling in the primary care office setting needs to be performed more frequently; but it is unlikely that this will happen unless it can be accomplished in a short period of time with little additional training. Evidence is growing that brief counseling strategies by the physician can be effective.[5,48–55] Results from less intensive, minimal-contact interventions to supplement brief primary care physician advice/counseling appear similar to results achieved through medium-intensity, routine face-to-face counseling from nutritionists, dietitians, or specially trained primary care physicians.[5] However, translation to practice of brief physician interventions is less than optimal, and more effectiveness and translational research is needed.[5,21] In the meantime, what is a primary care physician to do? Something is better than nothing. Providing 5 min or less of nutrition counseling during a patient visit is feasible and can be effective as discussed earlier, and if physicians do not discuss nutrition, patients may take this as a sign that they don't need to make any dietary changes.[56]

HOW TO DO IT?

The following principles of patient-focused behavioral counseling can help physicians improve the effectiveness of their communications with patients regarding lifestyle changes,

including dietary changes: (1) accept the patient as he or she is, (2) acknowledge that the patient has some answers, (3) build the patient's confidence, (4) set realistic expectations for self and patient, and (5) share responsibility.[56] Effective interventions combine nutrition education with behaviorally oriented counseling to help patients gain the motivation, skills, and support needed to change their eating patterns and food preparation practices.[5] In general, these interventions can be described by the 5A behavioral counseling framework.[5,57] In addition to the 5As model, patient-centeredness is an important quality of the physician–patient interaction. Patient-centeredness can be defined as being responsive to a patient's needs, beliefs, values, and preferences.[58,59] An effective technique for ensuring that the patient–provider interaction is patient-centered is motivational interviewing (MI), which can be woven into the 5As.

The primary "spirit" of MI is that it takes a *collaborative* approach to motivating an individual toward behavior change by eliciting the individual's own internal resources for change in an *evocative* manner and supporting the *autonomy* to make his/her own decision about change.[60] MI focuses on behavior change as identified by the patient rather than the physician. In this collaboration, the physician takes on a guiding role as a resource for patient-guided change.[60] Physician advice can be incorporated into these encounters but only after eliciting the patient's permission.[60,61] MI helps patients identify behaviors that they may be willing or ready to consider changing, and therefore, the counseling is less likely to be frustrating for both physician and patient. The goal of MI is to elicit "Change Talk" (desire, ability, reasons, or need for change [DARN]), which, in turn, leads to commitment language from the patient. MI is especially useful for individuals who are less ready to change,[60–62] making it especially useful in the primary care setting where physicians may be raising previously unaddressed health issues or sensitive issues like overweight and obesity. MI has been used effectively in a brief format for many health and lifestyle issues including diet, exercise, and weight.[60,61,63–65]

The 5As construct (ask, assess, advise, assist, and arrange) has been promoted as an approach to brief health behavior counseling, including nutrition and weight management.[57] Following the 5As protocol has been associated with greater patient motivation to lose weight and intentions to change behavior.[58] The 5As construct has been reinterpreted in several ways[56,58,66] but is often organized as shown in the following text for nutrition counseling and weight management. The interpretation in the following text integrates MI communication techniques into the 5As construct to increase patient motivation for dietary change:

1. *Assess* dietary practices in the context of health risks.
2. *Advise* to change dietary practices with clear, specific, and personalized advice for behavior change.
3. *Agree* on focus of counseling and treatment based on the patient's interest and willingness to change.
4. *Assist* the patient in setting and achieving goals to change dietary practices. Address motivational barriers by using counseling and self-help techniques. Determine whether the patient needs additional information or help; refer to dietitian or other resources as needed.
5. *Arrange* regular follow-up and support.

Each of these 5A steps will now be discussed in more detail with an inclusion of MI concepts. In Table 100.2, see an example of a brief counseling encounter using these principles that can be accomplished by a physician in 5 min.

Assess Dietary Practices in the Context of Health Risks

The first step in nutrition counseling is to assess patients' current dietary behaviors. Most physicians who do not have formal training in nutrition need user-friendly tools that can rapidly and accurately assess diet and monitor change among adult patients in primary care settings. There are a variety of such tools available. They can be self-administered, are easily scored, and take 10 min or less to complete. Some of these tools focus on specific health problems (like high cholesterol or heart disease),[67–70] while others focus on the total diet.[71,72] In addition, some of the tools not only assess patients dietary behaviors but also provide information to aid physicians in discussing patients' answers and counseling them appropriately. Two such tools are highlighted in the subsequent sections. These were chosen because they are brief and user-friendly and enable physicians not only to rapidly and accurately assess patients' diets but also to immediately facilitate discussion and goal-setting. Both of these tools can be self-administered by the patient at home, in the waiting room, or in examining room prior to meeting with the physician. The physician then can quickly review the completed questionnaire and use it to advise the patient.

Rate Your Plate

This semi-quantitative questionnaire directs a patient to record his or her eating patterns and provides an assessment of the nutritional quality of the food choices.[69] This tool has been validated and shown to be an effective part of a program to lower patient's cholesterol in primary care practice, worksites, and other community settings.[73] Questions are focused on food choices and preparation methods with responses separated into three columns (A, B, C) with column C having the most healthful response choices. Several different versions (a heart disease prevention version and a total diet version) are available by contacting Dr. Gans. The Rate Your Plate tool can be easily self-scored or scored by the physician. Physicians can quickly interpret the patient's score and responses, praise the patient for positive eating habits (Column C), help the patient determine which nutrition issues are most problematic (Column A), and determine whether the patient would like to change these eating habits. There is also an area for goal-setting, which can be self-administered or done jointly with the physician.

TABLE 100.2
5 Min Nutrition Counseling for Dietary Change

Steps (5As)	Action[a]
ASSESS: Eating habits	Have patient complete a dietary assessment tool such as REAP, Rate Your Plate, or web-based resources at home or in the waiting room. Review their responses
ADVISE: Give clear, specific, and personalized behavior change advice	You might say: "May I give you some advice that I give other patients with your health concerns?" Examples of what to say: "As we discussed, your blood cholesterol is too high. An important way to lower cholesterol is to reduce the saturated fat that you eat" For patients taking medication for high cholesterol: "What you eat is important even if you are taking medication because eating better helps the medicine work better. By changing your eating habits, you may be able to save money by cutting down on the amount of medicine you take"
AGREE: Collaborate with patient to select treatment focus	Offer a menu of options for discussion instead of just one idea. Patients are less likely to be resistant if they have choices "Based on what I see from your Rate Your Plate, it looks like there are some food choices that could be changed to lower the saturated fat you eat. These include eating more chicken and fish instead of red meat, eating fewer fried foods, or using different fats for cooking" "Which of these ideas would you like to discuss?"
Readiness to change negotiated behavior	"Picture a scale from 0 to 10 with 0 meaning *not at all* and 10 meaning *very*. How *ready are you* to make this change?" Why are you a _____ (insert number) and not a 0?" Reflect patient statements that indicate DARN (desire, ability, reason, and need) For patients NOT ready to change behavior, add: "I'd like to help you when you are ready to make changes in your diet." "Is it okay if I ask you again at our next visit?"
Confidence to change behavior	"How *confident* are you that you can make this change? If the patient says "5," then ask: "What would it take for you to go from a 5 to a 6 or 7?" This gives the patient the opportunity to reflect on why dietary change is important and how they might overcome barriers to change
ASSIST: Assist patient in setting goals, addressing barriers, and securing support	Problem-solve barriers to change. Ask "What might you do to overcome these barriers?"
Note: Can be done by physician, support staff or external resources	Focus more on how the patient can change than on the barriers that get in the way. Reflect DARN and offer suggestions if they ask
Set goal	"What do you think you will do now?" Help patient set a reasonable goal for change "You are going to substitute more chicken and fish for red meat. How many times a week will you make this substitution?" "You are going to use a different fat for cooking. What will you use instead of (butter, shortening, stick margarine)?" "How many fewer fried foods will you eat each week?" "What will you eat instead?" Ask "How can I help you achieve your goal?" • Provide handouts and web resources according to patient interest and need • Provide lists and recommendations for community resources (nutrition classes). • Refer to registered dietitian if there is a need and patient is interested.
Ask: "What other changes might you want to make to your eating habits?	Repeat the confidence exercise, problem-solving barriers, and goal-setting
ARRANGE: Schedule follow-up	For those who set goals: "Would you be willing to come back in about a month weeks to discuss your progress?" or "At your next visit, would you be willing to talk about your progress?" For those who did not set goals: "Would you be willing to come back in about a month and talk about this again?" or "At your next visit, can we talk about this again?"

[a] These steps can also be used by providers treating children. For younger children, these steps would address the parents. Older children could be addressed directly involving both the child and parent.

Rapid Eating and Activity Assessment for Patients

Rapid Eating and Activity Assessment for Patients (REAP) was developed to help physicians evaluate and counsel for healthy eating.[71,72] REAP has been designed to assess diet related to the Food Guide Pyramid and the U.S. Dietary Guidelines. REAP includes questions to assess intake of whole grains, calcium-rich foods, fruits and vegetables, fat, saturated fat and cholesterol, sugary beverages and foods, sodium, and alcoholic beverages and physical activity. REAP also includes questions regarding whether the patient shops and prepares his or her own food, ever has trouble being able to shop or cook, follows a special diet, eats or limits certain foods for health or other reasons, and how willing he or she is to make changes to eat healthier. REAP has an accompanying provider key, which provides guidelines for counseling advice to give for specific patient's dietary issues.

Another option is to use an online tool, such as the My Pyramid Tracker, which allows patients to enter their food intake and receive a printout with recommendations (http://www.cnpp.usda.gov/or http://www.mypyramidtracker.gov) that could be discussed with the provider.

Advise: Give Clear, Specific, and Personalized Behavior Change Advice

The purpose of this step is for the physician to establish dietary behavior as an important part of health care and enhance the patient's motivation to change. Such advice is most powerful when it is personalized by linking dietary behavior change to the patient's specific health concerns, past experiences, or family or social situation.[57] For example, this could be tied to medical conditions such as diabetes or high cholesterol, to developing a disease linked to the patient's family history or even to a spouse's health. Asking permission first and using advice messages with wording such as "As your physician, I feel I should tell you" rather than "You should" are a powerful, yet respectful way to avoid undermining patient autonomy.[57] "As your doctor, I need you to know that reducing the amount of saturated fat you eat is important for your health because it will help you lower your blood cholesterol." Strong, clear, and personalized advice is best. Personalizing the message plays to the strengths of the physician who knows the patient and his/her medical history well. [56] Most patients in adult practice will have a specific health-related reason for changing their diet. Advice messages can be compactly constructed and brief (30–60 s).[5]

Agree: Collaborate with Patient to Select Treatment Focus

Here the patient and physician "come to common ground" on whether dietary change is to be undertaken and which area(s) should be the focus.[57] To prevent resistance, physicians should actively engage the patient's agreement before proceeding with further counseling.[57] When both patient and physician agree that change is warranted, they then collaborate to define dietary change targets. For example, "Based on what I see from your Rate Your Plate, it looks like there are some food choices that could be changed to decrease the amount of saturated fat you eat. Which of these approaches (substitute chicken and fish for meat, eating fewer fried foods, or using different fats in cooking) would you like to discuss?" If the patient is ready to make specific dietary changes, the physician and patient together should identify acceptable goals. For patients with multiple areas of necessary dietary change, the physician and patient should come to agreement regarding which change(s) to address first.[57] After considering a variety of options and based on patient preference, the physician and patient together set specific goals for dietary change.

Physicians can assess readiness and motivation to make dietary changes by using a method developed by Rollnick et al.[60] To determine readiness, ask: "On a scale of 0–10, how ready are you to make this change (i.e., using different fats in cooking)?" If the patient says 5 or less, he or she is probably not yet ready to make a change. Ask: "Why are you a XX (i.e., 4) and not a 0?" to get a sense of what might be motivators of change for the patient. Listen for motivators of change (DARN) and reflect these back to the patient. Reflecting this Change Talk is empathy in action.

A warm, empathetic, and nonjudgmental style by the physician elicits greater cooperation and less resistance from patients, particularly those not yet interested in changing their dietary behaviors.[57] If the patient is not ready to change, the physician provides a motivational intervention to boost readiness and confidence and to address patient-specific barriers to change.[57] In this case, the physician would express empathy, e.g., "It is understandable that you might not want to take steps to change right now" or "Changing your diet can be difficult." Empathy for the difficulty of behavior change is an important component of successful behavior counseling. One of the most powerful predictors of patient compliance is the feeling that "my doctor cares about me as a person."[56] The physician should also emphasize his/her confidence in the patient's ability to change the behavior (building self-efficacy) and reassure the patient that there are multiple ways to approach successful dietary change.[57]

Self-efficacy (confidence) is another important factor in behavior change. To determine confidence, ask the patient: "How confident are you that you can make this change?" If the patient says "5," one could then ask: "What would it take for you to go from a 5 to a 6 or 7?" The patient's answers will give an idea of what his or her barriers and facilitators might be. These issues can be addressed later in the counseling session and be reassessed in later visits to help move a patient along the continuum of readiness to change.

Assist Patient in Setting Goals, Addressing Barriers, and Securing Support

In this step, the primary care physician (or other office staff) offers additional assistance to the patient in addressing barriers to change, setting goals, and/or securing needed supports and provides motivational interventions to increase motivation and/or skills. Those not ready to set a goal or commit to making a specific behavior change can benefit from MI strategies that explore ambivalence and enhance motivation.[57] Problem solving is a critical aspect of behavior change. First, identify the patient's barriers to making dietary changes. There are typically two types of barriers: (1) attitudes that maintain the problem behavior (e.g., "I don't like vegetables") and (2) triggers—situations or feelings that lead to the problem behavior (e.g., "When I go out to dinner, I always eat too much"). To assess barriers, physicians can ask a question like: "What might make it difficult for you to eat less meat?" After identifying the specific barriers, the physician would then discuss possible ways in which the patient could overcome them. Again a focus on overcoming the barriers gives the physician the opportunity to elicit DARN. Physicians need not have all the answers—the patient has many of them. In this capacity, the physician serves as a "facilitator" rather than a "lecturer." The patient argues for behavior change rather than the physician.

The next step is to mutually set goals for dietary behavior change. Specific, measurable goals are best. For example, goals such as "I will eat fruit at breakfast and as an afternoon snack every day" is better than "I will eat more fruits and vegetables" and "I will only eat red meat two times each week" or "I will use only olive oil or canola oil for cooking" are specific. Write the goals down in the patient's chart and on paper for the patient to take home. Then the physician and patient should discuss the options available to help the patient achieve the dietary change goals including self-help materials, nutrition programs to join, and/or more intensive counseling by a dietitian or nutritionist.[57] Additional assistance is likely to produce better outcomes than minimal-contact, advice-only treatment[57] and does not need to be provided directly or solely by the primary care physician.

Effective assistance techniques could include problem-solving skills training, guidance in obtaining social support from friends and family, modeling and behavioral rehearsal, written contracts, stimulus control (removing environmental or social cues that trigger unhealthy eating and adding cues that trigger healthy eating), the use of self-monitoring and self-rewards, and the provision of self-help materials including print, video, or computerized or web-based resources.[57] Some patient education resources are included in the resources described in the subsequent sections.

Physicians can also provide assistance through referral to other health care staff within the clinic or health care system or to community dietitians/nutritionists or nutrition education programs in the community. Physicians should ask patients if they are interested in referrals; for example, "A nutritionist can help you make the changes in your eating habits that we discussed. Do you think you would be interested in seeing a nutritionist?" Internal Revenue Service tax laws allow patients to include in medical expenses the cost of a weight-loss or dietary counseling program undertaken at a physician's direction to treat an existing disease. These costs can also be reimbursed using medical flex accounts at many worksites.

Arrange Schedule Follow-Up

Routine follow-up assessment and support through repeat visits, telephone calls, or other contact is important. If the patient has agreed to make dietary changes and set a goal, scheduling a return visit will encourage the patient to follow through. Even if the patient isn't quite ready to make changes, setting the stage for future discussions is critical to maintaining a therapeutic doctor–patient relationship.[56] Keep the door open for further dialogue. Repeated "doses" of counseling are often necessary over months or years. Simply notifying patients that follow-up will occur is a powerful motivator, communicating that dietary change is important and that follow-up assistance will be available if needed.[57] Follow-up should be scheduled within a relatively short time period (e.g., a month)[57] and should refer back to the goals set at the previous visit. "When I last saw you, you agreed to work on substituting chicken and fish for meat 5 times a week and switching to canola oil and olive oil for cooking. How did that go?" Clinical staff can arrange patient follow-up assessment and support through repeat clinical visits, telephone calls, e-mail, or other methods of contact.[57] This step can also include referrals as discussed earlier.

In summary, the 5A's combined with MI techniques have promise for helping health care physicians talk with patients about dietary behaviors. These approaches have been incorporated into primary care practice successfully; however, it has been observed that the last two steps of Assist and Arrange are rarely completed by physicians.[21,29] These steps can be achieved better by involving other office staff, using quality patient education materials, and referring to community programs or dietitians in the community. Office-level systems supports (prompts, reminders, and counseling algorithms) have also been found to significantly improve the delivery of appropriate dietary counseling by primary care physicians.[57]

RESOURCES TO HELP PHYSICIANS DO NUTRITION COUNSELING

- *The Roadmaps for Clinical Practice Series: Assessment and Management of Adult Obesity Primer.* In 2003, the American Medical Association and the U.S. Department of Health and Human Services released this primer,[13] which offers practical recommendations for addressing adult obesity in the primary care setting. It includes 10 booklets plus clinical tools and patient handouts and offers

practical advice on evaluating patients for current and potential health risks related to weight, beginning with a measure of the body mass index (BMI); understanding medication and surgical options; improving communication and counseling; and making office environments more accommodating to obese patients.

- American Academy of Family Physicians (AAFP) *Americans In Motion-Healthy Interventions* (AIM-HI)[74]: AIM-HI resources are downloadable and available on the AAFP website. They include AIM-HI PracticeManual[75] for physicians to learn to use the AIM-HI tools to integrate fitness strategies in their practices; AIM-to-Change toolkit, which contains an array of patient educational materials and office resources to help physicians create a fitness culture and encourage patients to live healthy lives; *AIM-HI Fitness Inventory* for patients to complete prior to their visit to gauge their current level of fitness and their readiness to change; *AIM-HI Food & Activity Journal* for patients to use to record their behavior patterns related to physical activity, nutrition, and emotional well-being; *AIM-HI Prescription Pads* to use with patients to set goals and create a plan; *AIM-HI Children's Books* to share easy-to-understand health messages with young patients and their families; *Make a Change for Family Fitness DVDs* that promote a non-diet approach to healthy living and encourage families to be physically active, eat healthy foods, and strengthen their emotional well-being (English and Spanish in one DVD); *AIM-HI Tips for Healthy Children and Families*, a packet of free posters and patient education handouts that offers tips on small changes to improve health; and *AIM-HI Group Visits Guide*, a step-by-step guide to conducting and getting paid for group visits for patients with chronic conditions affected by overweight and obesity.

  AIM-HI also offers a series of free online continuing medical education (CME) program podcasts (webinars and audio seminars) to train physicians in nutrition counseling and treatment. Podcasts include the following: Putting Nutrition Science to Work in Family Medicine, a series of three webinars presenting evidence-based guidelines and practical approaches to integrating nutrition into family medicine offices; Healthy Steps to Treating Childhood Obesity, discussing recent data on childhood obesity, early intervention, and optimal ways to overcome barriers; Foods That Foster Healthy Hearts, a webinar that describes small dietary changes patients can make to significantly reduce the risk of coronary heart disease; Patient-Centered Approaches to Better Fitness, a 20 min audio podcast offers new strategies for effectively talking to patients about nutrition, physical activity, and emotional well-being; and Motivating Healthy Behaviors, a 10 min audio podcast provides tips for motivating patients to make and sustain lifestyle changes.
- *AMA Healthier Life Steps*™ provides information and resources for physicians and patients on four key health behaviors including poor diet and physical inactivity. These resources include the *Physicians' Guide*,[76] which includes patient screening, intervention, and motivation tools and techniques, and the AMA Healthier Life Steps Physician's Guide to Personal Health toolkit, which is designed to help physicians support their personal efforts to live a healthier lifestyle and serve as role models to their patients.[77,78]
- *Bright Futures Nutrition and Pocket Guide (2011, 3rd Edition)*[79–81] is the most thorough and current health care physician reference regarding nutrition assessment, counseling, and referral for children. Each chapter provides an overview of the developmental period, interview questions, screening and assessment tools, counseling topics and approaches, desired health and nutrition outcomes, and frequently asked questions and suggested responses. It also includes the latest thinking on prevention, early identification, and ongoing monitoring of nutrition-related health issues in children.
- *The Childhood Obesity Action Network Implementation Guide* was created to accelerate improvement in the prevention and treatment of childhood obesity. The guide defines three key steps to the implementation of the 2007 Expert Committee Recommendations Regarding the Prevention, Assessment and Treatment of Child and Adolescent Overweight and Obesity: Summary Report.[82] The guide includes the following: Step 1, Obesity Prevention at Well Care Visits (Assessment & Prevention); Step 2, Prevention Plus Visits (Treatment); and Step 3, Going Beyond Your Practice (Prevention & Treatment) and provides detailed guidelines for health care providers regarding assessment, prevention, counseling, and treatment.[83]
- *North Carolina Eat Smart, Move* developed and disseminated their own toolkit, which includes a physician reference guide, color-coded BMI charts, blood pressure charts, and prescription pads promoting the "5-4-3-2-1–Almost None" prevention message (five or more servings of fruits and vegetables daily, three structured meals daily—eat breakfast, less fast food, and more meals prepared at home, 2 h or less of TV or video games daily, 1 h or more of moderate to vigorous physical activity daily, limit sugar-sweetened drinks to "almost none").[21]
- *Let's Move in the Clinic*: In 2010, First Lady Michelle Obama launched "Let's Move in the Clinic," an initiative to encourage health care providers to make a clinical commitment to measuring

BMI and counseling patients about optimal nutrition and physical activity. The five-step program includes (1) a Health Care Provider Pledge to measure BMI and counsel patients about optimal nutrition and physical activity, (2) a tool to assess quality of services provided in their practice, (3) a commitment to make BMI screening a part of quality care, (4) the use of the Rx for Healthier Living prescription pad (which uses the 5, 2, 1, 0 rubric—eat at least five fruits and vegetables every day, limit screen time to 2 h or less per day, get 1 h or more of physical activity every day, and drink fewer sugar-sweetened drinks),[84] and (5) the provider's commitment to be a leader in the community. *Let's Move* provider tools are available on letsmove.gov or the aap.org website.

- *The American Academy of Pediatrics obesity prevention and counseling tools and toolkits*. These materials include the following: Connecting With a Provider: How to find a PCP or RD in your area for coordination of care; Suggested Pediatric Weight Management Protocols; visual reference charts for pediatricians and RDs to coordinate the process and scheduling of pediatric weight management care office visits[85]; Pediatric Weight Management–Medical Summary: A form for primary care providers to guide the assessment component of the child's first office visit; Pediatric Weight Management–Ongoing Care Coordination and Information Sharing: A form for PCPs and registered dieticians to summarize and document key information from each office visit[86]; *Healthy Active Living Prescriptions*, developed in concert with the "Let's Move" initiative to provide health care practitioners with tools to use in counseling families about healthy nutrition and physical activity; The Pediatric Obesity Clinical Decision Support Chart to provide child health care professionals practical support and guidance to help improve care and outcomes for overweight youth and is consistent with the 2007 Expert Panel Recommendations [82].
- Many state and local health departments and obesity prevention programs have also developed their own health care provider toolkits for nutrition and/or weight control. These include Iowa,[87] Minnesota,[88] Missouri,[89,90] Washington,[91] California,[92,93] Maryland,[94] Texas,[95] and Ohio.[96] These resources include various tools including prescription pads, posters, patient education materials, reimbursement information, and more.

In summary, primary care physicians can provide effective nutrition counseling in a busy office environment. Physician advice primarily gives the cue to action and acts as a catalyst for patient dietary change, while other health professionals or take-home resources provide the details.[57] Providers should look for and take advantage of opportunities to receive further training in nutrition counseling and weight management and download resources to help create office systems and counseling protocols that support nutrition counseling.

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101 e-Health Resources to Support Lifestyle Medicine and Management

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CONTENTS

Introduction 1227
e-Health Tools, Platforms, and Programs 1228
The Evidence 1228
Tobacco Use 1228
Diet, Nutrition, Physical Activity, and Weight Management 1229
Mental Health 1229
Challenges of e-Health Resource Implementation 1229
Generalizability 1229
Adoption, Integration, and Sustained Use 1230
Quality 1230
Traditionally Underserved Populations 1230
Overcoming Obstacles to the Use of e-Health Resources 1230
Tailoring, User-Centered Design, and Cultural Relevance 1230
Research Methods 1230
Discussion 1231
References 1231

INTRODUCTION

In 2009, health care spending in the United States amounted to nearly $2.5 trillion, making up 17.6% of the country's gross domestic product [1]. Some of the most costly, but often preventable, chronic medical conditions among Medicare beneficiaries include hypertension, heart disease, pulmonary conditions, diabetes, and mental disorders, with overall Medicare expenditures projected to reach $879 billion annually by 2018 [2]. Total U.S. health care costs attributed to smoking and obesity were calculated at $193 billion [3] and $147 billion [4], respectively. Concomitantly, physicians and other health care professionals are under increasing pressure to focus on prevention and health outcomes as Patient-Centered Medical Home (PCMH) efforts [5], payment reform [6], meaningful use [7], and consumers [8,9] press for improved patient care and better health outcomes over the current status quo in the United States of incenting health care professionals primarily for acute and chronic illness care.

One promising strategy for improving health outcomes involves engaging patients and consumers to become active participants in their own lifestyle management jointly with their health care providers. Several studies have noted the substantial role that prevention can play in reducing morbidity and mortality. Fine et al. [10] found that four risk factors (cigarette smoking, risky drinking of alcoholic beverages, limited physical activity, and being overweight) were attributable to 39% of the total deaths in the United States. Other research estimated that 50% of the preventable deaths in this country were associated with behavioral risk factors such as alcohol, tobacco, and illicit drug use; sexual behaviors; and diet and physical activity [11]. Mokdad et al. [12] found that 38.2% of the actual causes of death in the United States in 2000 were attributable to tobacco use (18.1%), physical inactivity/poor diet (16.6%), and alcohol consumption (3.5%), with sexual behaviors and illicit drug use accounting for another 1.5%. The National Cancer Institute estimated that 50%–75% of cancer deaths may be attributable to tobacco use, poor nutrition, and physical inactivity [13]. Finally, the link to mental health issues such as depression cannot be ignored as potential contributing factors to deaths from smoking, substance abuse, firearms, and the like.

In addition to their singular impact on a host of health conditions, unhealthy lifestyle choices often occur in combination with one another and are concentrated among nonrandom segments of the population. For example, traditionally underserved communities are most likely to have multiple behavioral risk factors but often have limited or no access to high-quality care on a regular basis [14]. However, the synergistic effects of multiple risk behaviors may be mitigated by small changes in one behavior which may, in turn, positively

influence other healthier actions (i.e., an increase in exercise patterns may motivate a change in eating behaviors) [15]. Others have also noted promising research efforts that target simultaneous multiple lifestyle behavior changes [16,17], though [18] suggest that further investigation into this approach is needed.

Despite all this, patient lifestyle management and monitoring are time-consuming and difficult for health care providers to do consistently. Given the estimate that primary care physicians have only 1 min for prevention within a clinical encounter [19], even when the desire exists to engage in face-to-face, ongoing health promotion endeavors with patients on a large scale, the capacity to do so within the confines of a practitioner's schedule may not. Indeed, the U.S. Preventive Services Task Force lists 45 preventative interventions that it believes should be conducted as part of the Patient Protection and Affordable Care Act [20]. In addition, truly integrated care coordination still eludes most clinicians [21]. Clearly, alternative models of patient-centered lifestyle management must be investigated [22].

Over the last decade, a wide range of consumer-facing e-Health tools, platforms, and programs (hereafter referred to as e-Health resources) have been developed for health behavior change and lifestyle management to prevent the onset of disease and improve overall health. Evidence-based e-Health resources can be scalable, cost-effective, tailored to reach traditionally underserved populations, and potentially act to both engage consumers and reduce the burden on health care providers in achieving optimal care coordination and patient health outcomes [23–26].

The purpose of this chapter is to provide a high-level, though not exhaustive, overview of existing e-Health resources and their current and potential use for supporting patient-centered adult lifestyle management (including within PCMH); how e-Health resources may enable and enhance clinical care and health outcomes via patient engagement, activation, and adherence to treatment recommendations; and the capacity for e-Health resources to bridge the digital divide and improve health equity for all groups. While numerous evidence-based e-Health resources have been created for chronic disease management, we will not focus on those platforms here.

e-HEALTH TOOLS, PLATFORMS, AND PROGRAMS

e-Health, as we define it, is the use of emerging interactive technologies (e.g., Internet, social media, mobile platforms and computing, CD- and DVD-ROMs, interactive television and voice response systems, computer kiosks, web portals, computerized tailored interventions) to enable health improvement and health care services [27]. A Cochrane Review on interactive health information communications found that these applications improved health behaviors and clinical outcomes [28]. Mounting research also indicates that consumers and patients (as well as their doctors) are increasingly interested in and expecting to use e-Health resources to connect with their practitioners, gather health information for themselves or a family member, and use these tools to improve their own health [9,29–32].

THE EVIDENCE

As they evolve, e-Health resources are being tested for efficacy, including both process (how the application is used) and outcome (what effect the program had on users' knowledge, attitudes, behaviors or clinical states) measures. Health care providers, purchasers (i.e., health care organizations interested in investing in population management tools), and increasingly, consumers are looking to the results of these evaluations for assurance of their quality and effectiveness.

Here, we provide a brief synopsis highlighting the evidence base for the use of consumer-facing e-Health resources to engage patients in their own lifestyle management. We focus on those behaviors with the greatest potential to improve patient health outcomes and reduce the burden (poor health, financial costs) of chronic disease management related to unhealthy lifestyle choices.

Tobacco Use

As the leading preventable cause of death in the United States [12], tobacco use (more specifically smoking) is an ideal target for lifestyle management. A host of recent research studies have indicated positive smoking/tobacco cessation results via the use of e-Health resources, including e-mail, the Internet, integrated phone/Internet, interactive voice response, and text messaging [33–36]. Norman et al. [37] also wrote about the importance of using e-Health resources on a global level to improve population health as it relates to smoking. Rabius et al. [38] noted higher quit rates with interactive, tailored Internet sites, though results were stronger for participants who did not report an indicator of depression. Two other studies found that components of an online site—interactive quitting tools/one-on-one messaging [39] and higher-depth tailoring [40]—were associated with higher cessation rates. Other topics raised included short- versus long-term cessation and the need to support long-term participant engagement [41], as well as the use of social support tools [33]. One literature review of available online sites highlighted the "underutilization of the interactive capabilities of the Internet to personalize treatment, to connect users with a virtual support system and to provide follow-up treatment contacts" [42], while another's review of randomized controlled trials (RCTs) for smoking cessation found mixed results, especially for younger adults, though pointed to the methodological and other learnings that will improve future efforts [43].

Mobile health ("mHealth"), perhaps the most nascent frontier in e-Health resources, has shown little success with regard to tobacco cessation efforts to date [44,45], despite the platform's feasibility and participant interest in multiple components [46]. This may be a result of the newness of this tool for lifestyle management, targeting a younger audience not yet ready to quit smoking, or the fact that some tools

are poorly designed with no underlying theoretical basis or actual resource provision [47].

Diet, Nutrition, Physical Activity, and Weight Management

Numerous e-Health resources have been developed for diet, nutrition, physical activity, and/or weight management, either as individual targets for lifestyle management or via multiple lifestyle behavior change programs.

With regard to diet and nutrition, the use of tailored and personalized e-Health resources influenced fruit/vegetable and/or fat intake [48–50] and other nutrition patterns [51], including among low-income families [52]. E-mail prompts supported more sustained use of a website along with a positive increase in fruit/vegetable intake, though changes were short-lived [53]. Webber and Lee found that an Internet-based program both improved the diet quality and reduced the caloric intake of women in an online weight loss program [54].

Recent studies for weight reduction and/or increased physical activity (with or without diet and nutrition components) have met with mixed results. Blanson Henkemans et al. [55] observed that the use of an online lifestyle diary supported increased motivation for self-management and lowered reported body mass index. A pilot study that explored the impact of an Internet-based exercise versus exercise and dietary advice weight loss program noted that the combined group (exercise plus dietary info) reduced its caloric intake, but there was no significant increase in weight loss in either the group [56]. Two tailored interventions for physical activity, both among ethnically diverse populations, observed conflicting results: one which used computerized tailored reports that were printed and mailed to participants found no significant differences between experimental subjects and controls [57]; the other determined that an Internet-based program, which also included e-mail support, had a positive effect on walking and moderate-to-vigorous activity [58]. A 2010 review of second-generation tailored health communications also uncovered stronger links to nutrition efforts than those for increasing physical activity [51]. As with smoking cessation efforts, the capacity to access social support to achieve behavior change for nutrition, physical activity, or weight management seems paramount [59–60].

Mental Health

Evidence-based e-Health resources for patient lifestyle management have also been created for improving mental health and psychological well-being. Given the strained availability of behavioral and mental health clinicians, the financial costs borne by consumers to receive this care, as well as the stigma felt by some patients regarding accessing these resources in-person [61,62], e-Health resources may bring care to those unwilling or unable to seek it out via other outlets [63,64]. Here, we focus on depression and insomnia.

Two depression studies that augmented usual treatment with online programs, the first with various informational components/questionnaires and e-consultations [65] and the second, which included multiple psychotherapeutic approaches [66], reduced depression severity/improved patient–clinician relationships and decreased symptoms of depression, respectively. Warmerdam et al. [61] showed that both an online cognitive behavioral therapy (CBT) intervention and an online problem-solving therapy program were successful in lowering depressive symptoms. A pilot study using web- and mobile phone-based interventions noted the feasibility of increasing depression medication adherence in the participants, as well as greater patient engagement in care, both of which hold the potential for decreasing depression severity [67]. Self-help websites for depression have also shown a reduction in depression severity among those using the programs [68,69]. Finally, a multilingual informational website for immigrants not only increased depression awareness and comprehension but also decreased the stigma felt by participants toward those with mental illness [70].

Roughly, one-third of U.S. adults experience secondary (or temporary) insomnia at some point with another 10% reporting this as a chronic condition [71]. This lack of sleep impacts overall health and well-being and can lead to more chronic health problems. Most e-Health-related insomnia treatments utilize components of CBT (which is the "usual care" standard), for which there is evidence of its effectiveness and capacity for tailoring [72,73]. An early online CBT intervention study noted improvements in total sleep time and sleep efficiency with similar improvements in the control group [74]. More recent web- and CBT-based RCTs for insomnia have shown improvements in sleep quality, with decreases in insomnia severity and daytime fatigue [75], as well as increases in sleep efficiency and decreases in both waking after sleep onset and scores on the Insomnia Severity Index [76,77]. Another RCT, which used an online self-help model targeting workers in Japan, increased sleep quality and other sleep-related behaviors while reducing sleep-onset latency [78].

CHALLENGES OF e-HEALTH RESOURCE IMPLEMENTATION

Many of the e-Health resources created to date show promise of being efficacious, whether it be for improved nutrition, smoking cessation, or increased physical activity. The functionality of the applications themselves and how they are actually used in the "real world" are understood to be paramount to achieving successful behavioral change. However, significant barriers and challenges continue to exist in realizing the full potential of these tools, platforms, and programs for coordinated patient–provider lifestyle management efforts.

Generalizability

The importance of developing an evidence-base for e-Health resources cannot be understated. However, what works in

a controlled research study may be difficult to replicate in an actual physician practice. Enwald and others remarked on the challenges of methodology (study design, selection bias, control groups, retention, self-reports, etc.) as barriers to truly assessing the efficacy of these platforms for physical activity (and, by extension, other behavior change efforts) [51,79]. Differences between study participants and providers' patients—gender, ethnicity, age, race, sexual orientation, socioeconomic status, primary spoken/read language, patients' health/technological literacy, and/or access to the Internet or mobile platforms—can all influence the capacity to reproduce encouraging results in real time or to reach those in greatest need of these programs [80,81].

Adoption, Integration, and Sustained Use

Often, e-Health solutions have been created as "stand alone" interventions or designed specifically for a particular research study. For example, evidence-based interventions that exist online may provide benefit to patients, but often run parallel to, and are not easily accessible by, that patient's provider. Those researchers who have received grants to develop and evaluate the efficacy of an e-Health resource often see the program stagnate once the grant funding ends.

Additionally, while many clinicians would appreciate the capacity to refer their patients to effective e-Health Resources for lifestyle management, their ability to vet and stay abreast of the "best of breed" in this arena is virtually nonexistent. Most e-Health tools, platforms, and programs are not designed or easily integrated into a physician's workflow [82] or/and electronic health record (EHR) system (when one exists) nor a consumer's activities of daily living.

There are also barriers to adoption with regard to patients and consumers. Beyond the issues of access and health/technological literacy (addressed in Section 4.4), many of the studies cited earlier in which lifestyle changes were realized also found that they were short-lived (often due to a decline in patient use of the e-Health resource over time) and pointed to the need for more ongoing lifestyle management support. As with health care providers, the use of many e-Health resources is not easily integrated into a patient's activities of daily living; rather, it is a separate endeavor that is not routinized into their lifestyle.

Quality

While not the focus of this chapter, a significant amount has been written about the quality (or lack thereof) of online information and e-Health tools, platforms, and programs for various health topics and disease states [83,84]. The key relevance for lifestyle management is the need for a trusted and timely vetting process for use by providers (and patients), which would allow for integrated, "just-in-time" referrals to appropriate and evidence-based e-Health resources. Currently, this capability is sorely lacking, with the exception of a few large, integrated delivery systems (e.g., Kaiser Permanente, Group Health Cooperative).

Traditionally Underserved Populations

Given the current lack of equity in health care access and outcomes for traditionally underserved populations [105], legitimate concerns have been raised about the "digital divide" in that e-Health resources may exacerbate disparities which already exist. Demographics such as gender, ethnicity, age, race, sexual orientation, socioeconomic status, primary spoken/read language, and health/technological literacy have been well documented in numerous scholarly writings (more than addressed here) as often having a negative impact on a patient's access to and utilization of computers, the Internet, and/or mobile platforms [85–89]. These issues add one more challenge for certain populations to effectively utilize e-Health tools, platforms, and programs.

OVERCOMING OBSTACLES TO THE USE OF e-HEALTH RESOURCES

Despite the challenges described earlier, e-Health resources are being used more and more to engage patients in their own care. While the current state of the art is imperfect, research and creative designers are producing new knowledge that will help to "build a better mouse trap."

Tailoring, User-Centered Design, and Cultural Relevance

Technology-based tools have the capacity to integrate large amounts of personal and demographic information quickly and over prolonged periods of time to provide patients and consumers with specific feedback regarding deeply relevant lifestyle management actions they can take. Indeed, many of the e-Health resources mentioned earlier showed greater efficacy through the use of tailoring or personalization. Kreps and Neuhauser [90] site this capacity as an opportunity to develop more engaging, accessible, and easily used e-Health resources for diverse populations. Kreuter et al. [91] outline how "cultural tailoring" can expand the ability of lifestyle management platforms to reach broader cultural groups.

Finally, the concept of user-centered design (UCD) must be central to the development of e-Health resources. UCD's basic principles are that the patients' and consumers' wants, desires, and limitations are the focus of and highly important to the entire design process. UCD "tries to optimize the product around how users can, want or need to use the product, rather than forcing the users to change their behavior to accommodate the product" Wikipedia 2011—quite the converse to, "If you build it, they will come."

Research Methods

In a special section of *Evaluation and Program Planning* on the methodological challenges in e-Health research, [92], as well as the other authors, highlighted areas of specific

concern to e-Health researchers. These include, for example, privacy/security, electronic informed consent, appropriate control groups/conditions, and other more generic issues that many grapple with across all behavioral health research (e.g., recruitment, retention, incentives, theory-based design).

Fortunately, efforts abound seeking novel approaches and models to create stronger and more generalizable e-Health tools, platforms, and programs. Ritterband and Tate [93] underscore the need for further development of methodological paradigms to guide the expansion of Internet research science. Ritterband et al. [76,77] go on to propose a scientific-based behavior change model for web-based interventions, the hope of which is to firmly strengthen the creation and use of Internet-based platforms.

There are also efforts to apply non-technology-based research frameworks to bolster e-Health research methodology. For example, the Reach, Efficacy, Adoption, Implementation and Maintenance model [94] may have applicable lessons for the evaluation of e-Health resources [95]. In addition, it has been noted that the Consolidated Standards of Reporting Trials recommendations hold great potential to better the quality of e-Health research [96].

DISCUSSION

In this chapter, we have reviewed targeted e-Health resources and the promise and potential for them to enable and support lifestyle medicine and management [97]. Overall, the available evidence indicates that many of these e-Health resources are effective and can be used by providers to activate and support collaborative self-care. Indeed, these e-Health tools, platforms, and programs are consistent with health care transformation to a more patient-centered, equitable, and efficient system as recommended by the Institute of Medicine [98]. As health care transformation proceeds, e-Health resources will become increasingly necessary to engage patients, including traditionally underserved populations [99], in lifestyle management.

e-Health resources for lifestyle management integrated with primary care will improve health outcomes through enhanced patient–provider communication, patient activation, reduced clinical inertia, and improved adherence to medication regimens. To meet this ambitious goal will require a UCD approach to development and implementation, working in collaboration with primary care and patients together [100–103]. There are a myriad ways that patients use e-Health resources currently; however, they are often disconnected from provider referral and documentation systems (e.g., EHRs), which makes them difficult to recommend and track.

Patient experience is emerging as an important measure of quality, as indicated by the requirement for measurement of patient experience in the context of Accountable Care Organizations (ACOs). e-Health resources that support patients' wants and needs are likely to enhance patient experience, (i.e., a strong desire for secure messaging with providers and use of social media/networks).

Future research is needed to evolve and extend these e-Health resources to further enhance impact and integration into clinical care. The future e-Health-enabled PCMH and ACO will likely incorporate a wide range of e-Health resources to fulfill the vision of a truly patient-centered health care system [104].

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102 Pharmacogenomic Tailored Therapy for Smoking Cessation

The Promise of Personalized Medicine

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CONTENTS

Introduction 1235
Neurobiology of Nicotine Dependence 1235
Pharmacogenetic and Pharmacogenomic Investigations of Smoking Cessation 1236
Future Directions and Clinical Applications 1236
  Research 1236
  Practical Issues and Best Practices 1236
Summary 1236
Acknowledgments 1237
References 1237

INTRODUCTION

The National Institutes of Health (NIH) Director, Francis Collins, defined personalized medicine as the use of "an individual's genetic profile and individual information about environmental exposures to guide decisions made in regard to the prevention, diagnosis, and treatment of disease" [1]. While there are many emerging applications of personalized medicine in lifestyle medicine, none have any greater potential impact on public health than smoking cessation. Tobacco use is responsible for approximately 5 million deaths annually, and current projections indicate that tobacco-related mortality will top 10 million deaths per year by the 2030s and 1 billion deaths throughout the twenty-first century [2,3]. Yet quitting smoking well into middle age eliminates most of the risk of dying prematurely from cancer or vascular disease [4].

Even for the most efficacious pharmacological and behavioral therapies, the majority of smokers are unsuccessful in sustaining abstinence for any given quit attempt [5,6]. Twin studies established that nicotine metabolism, smoking initiation, smoking persistence, and smoking cessation are heritable and under the influences of genetic and environmental factors [7,8]. Thus, the "one-size-fits-all" approach to treatment has substantial room for improvement, and identification of specific genetic factors affecting nicotine neurobiology has the potential to advance the state of the science and improve clinical smoking cessation outcomes.

NEUROBIOLOGY OF NICOTINE DEPENDENCE

The neurobiology of nicotine dependence is complex and involves multiple neurotransmitters and metabolic enzymes. Once tobacco smoke is inhaled, nicotine is readily absorbed in alveolar capillaries and crosses the blood–brain barrier within seconds. Nicotine binds to its nicotinic acetylcholine receptors in the midbrain and elsewhere [9], which stimulates increased release of dopamine in the brain's reward centers and a complex interplay of multiple neurotransmitters responsible for the reinforcing properties of nicotine and conditioned smoking behavior [10–14].

Therefore, multiple investigations have explored associations among genes encoding neurotransmitter receptors and transporters within pathways implicated in nicotine dependence (e.g., dopamine, serotonin, norepinephrine, acetylcholine, gamma-aminobutynic acid (GABA), opioid, beta-endorphin) [15], the hepatic enzymes that metabolize nicotine (e.g., cytochrome p450 2A6/*CYP2A6*) [16], and smoking cessation drugs such as bupropion (*CYP2B6*) [17]. The goals of these investigations are to identify subgroups of patients most likely to be efficacious for smoking cessation, screen for individuals likely to develop side effects that limit treatment adherence, choose drug doses that are appropriate for each patient based on hypothesis-testing studies of pharmacologically selected "candidate genes" (pharmacogenetics), and to identify novel molecular targets for smoking cessation treatment based on hypothesis-generating genome-wide association studies (pharmacogenomics).

PHARMACOGENETIC AND PHARMACOGENOMIC INVESTIGATIONS OF SMOKING CESSATION

Most pharmacogenetic investigations of smoking cessation have evaluated associations between candidate genes in nicotine-associated pharmacodynamic and pharmacokinetic pathways using genotyping of samples from smoking cessation clinical trials post hoc—rather than prior to treatment to prospectively tailor therapy—in studies of nicotine replacement therapy (NRT) [18–33] and sustained-release bupropion [26,34–42]. In addition to NRT and bupropion, befloxatone, fenfluramine, and venlafaxine [43–46] as well as patient choice between NRT or bupropion [47] have been evaluated.

To date, there have been very few examples of replication of associations between candidate genes and drug response. Some candidate genotypes have shown opposite effects in different trials, such as the mu-opioid receptor 1 (*OPRM1*) rs1799971 A allele [25,30]; others have been associated with opposite effects in bupropion and NRT such as the *DRD2* rs1799732 Ins allele [26,48]; some are associated with treatment response to one drug but not another such as the *DRD4* L allele [21,27]; and others simply have not been replicated, such as the Beta 2 subunit gene for nicotinic acetylcholine receptors (*CHRNB2*) [35]. However, there are some examples of replication. For example, a gene that affects dopamine D2 receptor expression in brain reward regions (Ankyrin and Kinase Domain Containing 1 [*ANKK1* rs1800497 A2 allele]) [49] has been associated with improved smoking cessation outcomes with bupropion in three clinical trials [37,38,41], and the gene for Catechol-*O*-methyl Transferase (*COMT* rs4680 A allele) has been associated with improved response to NRT patches in two clinical trials [22,24,31]. There are also a growing number of studies showing associations between emerging *CYP2A6* genotypes, associated with rate of nicotine metabolism, and dose of NRT nasal spray used [28] and efficacy of NRT for smoking cessation [48,50,51].

Genome-wide association investigations have been published using samples from two clinical trials of bupropion [52] and three trials of NRT [52,53]. These studies have identified several hundred novel genotype associations predictive of the efficacy of these medications, which include some candidate genes with known associations with nicotine dependence and many newly identified candidate genes, such as cell adhesion molecules and solute transporters.

FUTURE DIRECTIONS AND CLINICAL APPLICATIONS

There are several important research questions and practical challenges that must be overcome for smoking cessation to be ready for widespread clinical use.

Research

More replication of associations between specific candidate genes and drug response are needed to establish the predictive value of genetic testing. Moreover, additional research is needed in different ethnic groups, as most published studies have examined only European-ancestry populations and in the interactions between genes and gender because there is limited evidence suggesting ethnic and sex subgroups are likely to moderate pharmacogenetic outcomes [33,39,50]. Prospective studies examining the use and impact of genetic tests to tailor treatment are needed to confirm that their use in real-world settings improves smoking cessation outcomes without unintended psychological or behavioral consequences. At the time of this writing, only one such trial has been published with promising results, but more prospective studies are in the pipeline [54]. Even if genetic testing improves clinical outcomes, its cost-effectiveness needs to be better demonstrated in order to convince health care organizations to offer genetic testing for smoking cessation; to persuade payers, policy makers, and opinion leaders that funding specific genetic testing for nicotine dependence treatment is a high priority public investment; and to compel industry to develop novel genetically tailored therapies. Cost-effectiveness studies of several pharmacogenetic smoking cessation investigations suggest that depending on the specific drug or combination of drugs, genetic testing is likely to be cost-effective, but data from prospective studies are needed [55,56].

Practical Issues and Best Practices

Evidence-based treatment guidelines—based on the analytic and clinical standards of validity—have been published for treatments other than tobacco dependence—and are likely to provide clinical annotations in the future [57]. Clinical information systems and protocols that support clinician decision making and processes of care for personalized medicine are needed [58]. The clinician workforce needs to be trained in both communication skills and medical indications for genetic testing in the treatment of nicotine dependence, and personalized smoking cessation treatment must be patient-centered, culturally sensitive, and utilize a shared decision-making model [59] to maximize the potential for positive health outcomes and minimize the risk of harm. Furthermore, patients and physicians should be aware of federal protections against genetic discrimination, such as the Genetic Information Nondiscrimination Act of 2008 [60]. Patients' genetic literacy should be assessed and appropriate education provided such that true informed consent in genetic tailoring of treatment is possible [61].

SUMMARY

Table 102.1 summarizes the important clinical take-home messages from this chapter. Research, to date, has provided encouraging evidence suggesting that genetic testing has the potential to transform the way we presently

TABLE 102.1
Personalized Medicine for Smoking Cessation—Clinical Take-Home Messages

Nicotine dependence and smoking cessation are under the influence of genetic and environmental factors and current "one-size-fits-all" pharmacotherapies have room for improvement
Some polymorphisms in genes affecting dopamine neurotransmission and nicotine metabolism have been associated with drug response for sustained-release bupropion and nicotine replacement therapy in multiple studies, but there are many examples of other candidate genes in the dopamine, serotonin, and other pathways lacking either not associated with smoking cessation or lacking replication. Pharmacogenetic studies of varenicline have not as yet been published
Hundreds of genetic variants spanning multiple pharmacological pathways have been associated with drug response for smoking cessation, but these associations have yet to be replicated
Cost-effectiveness studies have been inconclusive but suggest that based on some scenarios of cost of genetic testing and treatment selection, genetically tailored treatment may be cost-effective
Results from prospective, genetically tailored smoking cessation treatments have not as yet been published
Multiple research and practical implementation milestones need to be reached before personalized medicine will be ready for widespread clinical implementation
Tobacco treatments guidelines are available at http://www.surgeongeneral.gov/tobacco/ and clinical annotations for genetic testing to guide smoking cessation and other treatments will be available at http://www.pharmgkb.org/

care for treatment-seeking smokers. However, until multiple research and practical translational milestones have been reached, physicians and other practitioners of lifestyle medicine should combine the individualized, patient-centered smoking cessation care they are well trained to offer, informed by the *Agency for Health Research and Quality* Tobacco Dependence Treatment Guidelines (available at: http://www.surgeongeneral.gov/tobacco/). Interested readers are referred to the *Pharmacogenomics Knowledge Base* (PharmGKB; http://www.pharmgkb.org/), where clinical annotations for genetic tests guiding smoking cessation and other treatments are being released and updated regularly.

ACKNOWLEDGMENTS

Personal funding to A.M. by NIH/NCCR CTSA grant number TLI RR025742. Personal funding to S.P.D. by R21DA027331 and R24GM61374.

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Part XVIII

Lifestyle Medicine in Geriatrics

Charlotte A. Tate, PhD

103 Lifestyle Medicine and the Older Population

Introductory Framework

Charlotte A. Tate, PhD

CONTENT

References 1245

On a population basis, people are living longer with increased average life expectancies becoming a global phenomenon. Not only are people living longer but they are also living healthier. In recent decades, on average, older people live with fewer disabilities and less loss of functioning than in generations past. Many live with more chronic diseases and postponement of disability [1,2]. As Crimmins [1, p. 94] notes, "The key to continued improvement in health is to delay the onset of risk factors, disease, and disability in older-aged individuals."

My purpose in this brief introduction is to provide a context for encouraging the agenda for the continued enrichment of the health of people living in the latter decades of their lives. Despite the nuances in interpretation, I use the less offensive (hopefully) generic expression, "older people," as an identity phrase for people living in their sixth decade and beyond. Moreover, the enrichment of health is often called healthy living, healthy lifestyle, healthy aging, and successful aging. Our preference is to use successful aging, which often is associated with the older population when in reality it is a descriptor for the entire human life course [3]. The conceptual framework of successful aging encompasses the depth and breadth of the human experience, as discussed by Rose [4] in the next chapter of this section. Following Rose, Chodzko-Zajko and Schwingel [5] discuss a major criterion for successful aging, that is, physical activity. They present a unique approach to actualize a regular program of increased physical activity in older persons. Then, I briefly discuss the impact of the stereotypes of old age and end with what I believe to be at the crux of lifestyle medicine: assisting people to live lives of meaning.

Because the older population is a heterogeneous group, dividing the later decades of the life span into apparently discrete, but continuous, chronological age ranges has facilitated investigating and developing the ways and means for improving the health of older adults. In 1974, Neugarten [6] coined the phrases, young-old and old-old, to distinguish those people between the ages of 55–75 years from those over the age of 75 years, respectively. Since then, her idea has been expanded to include other age ranges—from the young-old, the old-old, to the oldest-old. Although each respective "age group" is demarked by an age range that may differ among investigators or reporting agencies, each has a number of average distinguishing health-related descriptors, characteristics, and demographics (e.g., see entries in [7]). These age ranges are useful for comparisons on a population basis; however, individually, people may (or may not) transition to the next phase at any chronological age. Thus, the use of chronological age is arbitrary at best.

For our purposes here, Baltes and Smith [8], in capitalizing on the earlier work of Neugarten and their own extensive research findings, provide a framework for us to consider the importance of successful aging. They describe suitable descriptors for what they call the Third Age (or young-old) and the Fourth Age (or oldest-old), as shown in Table 103.1. They distinguish the two ages, not by chronological age, but by the major characteristics, from successful aging of the young-old to the tribulations of the oldest-old. In their view, optimization of the life course is possible in the Third Age but difficult in the Fourth Age. It, therefore, behooves older individuals to remain in the Third Age as long as possible by adopting or maintaining strategies and activities that delay the transition into the Fourth Age. As one example, Freedman et al. [9] looked at three possible candidates for intervening in the transition toward frailty, a Fourth Age descriptor: increasing physical activity, treating depression, and preventing falls. Of the three, they concluded that, while the other two were certainly effective, the prevention of falls might be the most efficacious in delaying the progression to the frailty associated with the Fourth Age.

We recognize that the growing knowledge base from life course research models increasingly supports the notion that aging-related diseases and functioning in adults have their origins in early life experiences and perhaps even fetal life [10]. Among a multitude of factors including heritability, epigenetic mechanisms linking the genotypes to the various environments produces a phenotypic matrix of characteristics and behaviors of health and disease. While some

TABLE 103.1
Later Years of the Human Life Course: The Good and the Bad News

Good news: The Third Age or the young-old
- Increase in life expectancy: more older people live longer
- Substantial latent potential for better fitness (physical and mental) in old age
- Successive cohorts (generations) show gains in physical and mental fitness
- Evidence of cognitive-emotional reserves of the aging mind
- More and more people who age successfully
- High levels of emotional and personal well-being (self-plasticity)
- Effective strategies to master the gains and losses of late life

Bad news: The Fourth Age or the oldest-old
- Sizeable losses in cognitive potential and ability to learn
- Increase in chronic stress syndrome
- Sizeable prevalence of dementia (about 50% in 90-year-olds)
- High levels of frailty, dysfunctionality, and multimorbidity
- Dying at older ages: with human dignity?

Source: Modified from Baltes, P.B. and Smith, J., *Gerontology*, 49, 125, 2003.

behaviors and characteristics resist modification, many lifestyle behaviors can indeed be modified by older persons resulting in a shift toward healthy aging or staying in the Third Age. Although earlier life experiences may point toward taking an unhealthy pathway, older persons can enter (or reenter) the pathway toward successful aging, *albeit* with requisite persistence.

To address that question, Rose [4] proposes entry points into the pathway of successful aging through changes in lifestyle. First, she explores the development of Successful Aging as a construct and its determinants, as we understand them today. As she rightfully points out, as we advance in age, many environmental and lifestyle factors mitigate or enhance the negative or positive impacts that our early life experiences and genetic makeup may have on our functioning as adults. She then points to a number of lifestyle modifications that can enhance the health, sense of wellbeing, and function of older people. She emphasizes the importance of a regular program of physical activity, a major determinant for the prevention or delay of lifestyle diseases. She then gives a few hints to health professionals to assist them in developing interventions that have lasting impact.

Indeed, a regular program of physical activity is vital to staying in the Third Age for as long as possible. Chodzko-Zajko and Schwingel [5] focus on the benefits of physical activity, or exercise, and some of the models used to assist older persons in adopting and maintaining a physically active lifestyle. They present, in a novel way, the answers to questions an older person might have about physical activity and its benefits. They then discuss a few strategies for helping older people adopt and stay on the active aging pathway. Importantly, they emphasize that frail older persons can reap the rewards of physical activity as well.

Encouraging previously sedentary older people to be physically active is a daunting task, but not impossible to achieve, in older people whose generation did not grow up in a society that supported and encouraged physical activity. In particular, older women who grew up in the United States before Title IX experienced the negative influences of gender stereotypes that supported sedentary behavior. Like all stereotypes, old-age stereotypes profoundly impact people as they advance through the life course.

Influenced by culture, ethnicity, socioeconomic status, and gender, the spectrum of the old-age stereotypes is multidimensional, crossing numerous domains of society. At its heart, the stereotype of old age is ageism, a social construct that embodies societal views and attitudes that have evolved over the decades [11].

Like many stereotypes, the internalization of the old-age stereotype is subconscious, probably begins at an early age, and may subsequently lead to changes in perception and projection, thereby impacting cognitive and physical performance, view of self, and so on [12]. Based on her own body of work and others, Levy [13] proposes that the stereotype embodiment through assimilation results in self-definitions that influence function and health in the latter decades of the human life span. She identifies three pathways of stereotype embodiment that exert their influence: psychological through expectations, behavioral through healthy practices, and physiological through the autonomic nervous system.

These internalized stereotypes can and do influence the outcomes of interventions aimed at assisting individuals in adopting lifestyle behaviors that keep them on the pathway of healthy living, or healthy aging in this case [14]. Perhaps, it is safe to say that most people, at the very least in North America and Europe, know that regular physical activity and a nutritious diet are important. Acting, though, requires overcoming lifelong patterns of living and reformulating many of the internalized stereotypes developed over the life course. As Tumosa [15, p. 540] states, "Knowing what needs to be done [adopting healthy eating habits] is one thing, but deciding to act, regardless of the barriers, is quite another." Moreover, extrinsic factors have profound influences. O'Brien Cousins [16, p. 361] notes "…it was not simply a lack of social support that explained older people's sedentary living patterns… but rather strong, negative, and discouraging remarks and behaviors by an individual's immediate family and network of friends."

Hope springs eternal for a gradual shift in the society's view toward people living in the late decades of life. Naturally, the old-age stereotype is not necessarily negative but may be quite positive depending on the culture, ethnicity, gender, and economic circumstances. A full exposition of the topic, however, is beyond our scope and purpose. We encourage health professionals to be sensitive to the negative and positive influences of old-age stereotypes and the impact that their own behaviors and attitudes have on the health and well-being of the older people they serve.

In conclusion, as we grow older, we wish to remain healthy and robust and lead independent lives of meaning. Indeed,

the Harvard geriatrician Gillick [17] states, "The ultimate determinant of a good old age is the ability to derive meaning from life, with all the other factors (health, emotional well-being, housing, and so on) serving to facilitate a sense of purpose, belonging, and continuity." Thus, our challenge, as individuals and as a society, is to create, develop, and live in an environment, however defined, that promotes and supports a healthy lifestyle regardless of a person's age.

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104 Aging Successfully
Predictors and Pathways

Debra J. Rose, PhD

CONTENTS

Defining Successful Aging 1247
Models of Successful Aging 1248
Life-Course Approach to the Study of Aging 1248
Determinants of Successful Aging 1249
Building Pathways to Successful Aging: The Results of Intervention Research 1249
Exercise or Physical Activity 1249
Cognitive Training and Stimulation 1250
Dietary Influences 1251
Social Engagement and Volunteerism 1251
It's Never Too Late: Fact or Fiction? 1251
Role of Health care Practitioners in the Promotion of Successful Aging 1252
Summary 1253
References 1253

According to the Centers for Disease Control and Prevention,[1] the United States is on the "brink of a longevity revolution." This prediction is supported by statistics showing that by 2030, one in every five Americans will be 65 years or older. Mortality rates and longevity are also expected to improve with global life expectancy at birth projected to increase by at least 10 years, reaching approximately 76 years by 2050. As a consequence of this disproportionate growth in the older adult segment of the population, health care spending is also projected to increase by as much as 25% unless the health of the older adult population can be preserved or improved substantially.[2] Indeed, current estimates of the number of older adults (65 years and older) in the United States who are considered to be aging "successfully" are alarmingly low.[3] Based on data derived from a national sample of older adults enrolled in the Health and Retirement Study, only 11.9% of older adults were categorized as aging "successfully" in any one year according to a similar set of criteria first established by Rowe and Kahn.[4,5] Moreover, the odds of successful aging (SA) declined by as much as 25% over the 6 year measurement period (1998–2004) with the adjusted odds of SA being lower for adults 75 years and older, males, and those at a lower socioeconomic level.[3]

In this chapter, I will briefly explore the construct of SA, the many definitions and methods used to test various SA models, some of the predictors of SA as currently supported by research across multiple disciplines, and the results of intervention research focused on building pathways to SA. Finally, the role of the health care professional in promoting SA will be discussed and recommendations for implementing intervention strategies that have been shown to be effective in primary and secondary health care settings will be provided in the final section of this chapter.

DEFINING SUCCESSFUL AGING

Both the concept of SA and the term itself is not universally accepted as noted in a review article by Depp and Jeste[6] who identified as many as 29 different definitions of SA during the course of reviewing 28 quantitative studies of SA. By far, the most often included component of SA in more than half of the studies reviewed was physical functioning/disability. Other components included, albeit in fewer study definitions, were cognitive ability, social functioning, life satisfaction, and absence of disease. As a result of the variability in how SA was defined, vastly different proportions of study participants were categorized as aging successfully (1%–94%, median 35%).

In other studies that have explored the construct of SA using qualitative methods of inquiry[7] (i.e., older adult perceptions of SA) or mixed-method approaches that combine objective and subjective criteria of SA,[8–10] the proportion of older adults categorized as aging successfully has again varied widely. Using the objective criteria set forth by Rowe and Kahn in their model of SA, Strawbridge et al.[9] found that only 18.8% of the 867 older adults (65–99 years) who comprised their sample would be categorized as successfully aging. In contrast, 50.3% of the same sample was similarly categorized on the basis of a single question that asked them to rate the extent to which they thought they were aging successfully.

Moreover, when researcher-based criteria was compared with the perceptions of older adults as to what attributes they thought defined SA, a more encompassing definition emerged.[7] While the majority of older adults who responded to a mailed survey considered two-thirds (13/20) of the already listed attributes to be important to SA, additional attributes were identified that could be broadly divided into four larger dimensions of health—physical, functional, psychological (mental), and social health.

On the basis of these divergent findings, a number of researchers have argued that the perceptions of older adults need to be included in any definition of SA.[7,11,12] McLaughlin et al.[3] have also called for a broader definition of SA, particularly if the concept is to be used as a benchmark for assessing the health and functional status of the older adult population. The authors argue that if the term continues to be narrowly defined, "we are likely to classify many older adults with good health and functioning as being in an unhealthy state for what might be relatively minor reasons" (p. 225). By way of a compromise to the current controversy over how best to define SA, Depp et al.[13] suggest that future research endeavors "focus on the determinants of success as independent components and investigate the extent to which risk factors and interventions impact these components" (p. 532).

MODELS OF SUCCESSFUL AGING

To date, the most popular model of SA that has been used to guide gerontology research is one first conceptualized and collaboratively investigated by an interdisciplinary team of scholars assembled by the MacArthur Foundation and chaired by Dr. John Rowe,[4,5] a geriatrician and physiologist at Mt. Sinai Medical Center. The development of this model was to herald a dramatic paradigm shift in aging research from one that focused on the negative aspects of aging such as disease and disability to one that emphasized the positive aspects of aging and the important role that lifestyle and other psychosocial factors play in helping older adults retain and/or enhance their ability to function well into their later years.

The ability to maintain three key characteristics formed the basis of Rowe and Kahn's SA model: a low risk of disease and disease-related disability, high mental and physical function, and active engagement with life.[4] In order to be categorized as aging successfully, however, older adults needed to display high levels of all three of the aforementioned characteristics. A sample of 1189 older adults aged between 70 and 79 years who met the objective criteria established for SA (i.e., top 33rd percentile across all three domains) were subsequently followed for the next 8 years.[4,5] In all, the many related studies that followed produced close to 100 scientific publications and a best-selling lay publication,[5] in which a number of myths previously associated with the aging process were successfully debunked.

Baltes and Baltes[14] developed a complimentary model of SA known as the Selective Optimization with Compensation (SOC) model. The SOC model was based on findings emerging from the original Berlin Aging Study[15] that followed a sample of 516 persons aged between 70 and 100 years between 1993 and 1998. In contrast to the Rowe and Kahn model of SA, the SOC model focuses more on describing the behavioral and psychological processes involved in adapting to age-associated reductions in physiological reserve and breadth of neural plasticity. The basic assumption of the SOC model is that individuals engage in behaviors that are aimed at optimizing their general reserves as they age while also compensating for restricted plasticity or adaptive potential. Subsequent research demonstrated that different combinations of the SOC mechanisms are used by adults of different ages to regulate their lives and that higher engagement in SOC-relevant strategies is associated with indicators of SA such as positive psychological functioning, life satisfaction, and emotional well-being, irrespective of age.[16]

More recently, Pruchno et al.[17] have begun testing a two-factor model of SA. Central to their conceptual model of SA is the contention that adults can experience chronic disease and disability and still believe that they are aging successfully and that SA is a characteristic that should not be delimited by age. Unlike the two previous models of SA described, the assumptions of the two-factor model proposed by Pruchno et al. were tested in a large sample of middle-aged adults (50–74 years). Using a mixed-method approach, wherein SA was defined using both objective and subjective criteria, the authors sought to understand how and to what extent the objective and subjective aspects of SA were related to each other, as well as the role of age and gender. Their preliminary results provide support for a model of SA that includes both objective and subjective criteria. Moreover, their findings further suggest that certain factors such as cognitive function, social engagement, and psychological well-being, previously identified as components of SA, might be better viewed as predictors or antecedents of SA, respectively.

LIFE-COURSE APPROACH TO THE STUDY OF AGING

In recent years, a major shift toward the adoption of a life-course approach to studying aging has begun that capitalizes on data derived from historical and birth-cohort studies. The life-course approach,[18] as it is called, is being driven by a growing consensus that adult function has its roots in early life experiences and that aging is "driven by the rate of accumulation of molecular and cellular damage" (p. 717).

According to Kuh et al.,[18] addressing two fundamental questions is central to a life-course research approach to aging. The first (question) seeks "to identify what factors across the life course, from the molecular to the societal level, independently, cumulatively, or interactively influence whether people as they age maintain their physical and cognitive capability and stay intellectually and socially connected," whereas the second addresses the question of how best to "transfer this knowledge to people themselves and the institutions that exist to improve human health" (p. 720). It is worthy to note here that the first question being addressed

specifically identifies two of the three components that Rowe and Kahn[4,5] identified in their model of SA. Preliminary findings suggest that early movement experiences in childhood can predict changes in motor and cognitive abilities in mid- and later life as well as the risk of mortality.[18,19]

DETERMINANTS OF SUCCESSFUL AGING

Key determinants of SA that have been described in a number of review articles on the topic can be broadly divided into the following categories: genetic, biological, psychological, and social/environmental. As Depp and Jeste[6] noted in their review, the predictors of SA appeared to vary as a function of the definition of SA used in each study. The strongest and most consistent predictor emerging was younger age (closer to 60 years) with other strong predictors being health related (e.g., absence of arthritis, higher Activity of Daily Living levels, hearing problems, abstinence from smoking). Engaging in higher levels of physical activity, having fewer medical conditions, global cognitive function, absence of depression, and lower systolic pressure were moderately supported as predictors of SA with only minimal support being provided for higher levels of education, income, being married, and white.

Although the once prevalent belief that the secret to SA was to choose your parents wisely has since been found wanting as a result of the MacArthur studies of SA[5] and more recently published molecular genetic studies,[20] one's genetic makeup does play a role in the onset of disease[21–23] and changes in mental function,[24] two important components of the Rowe and Kahn SA model. The good news is that as we age, the influence of genetics appears to become less influential, while environment and lifestyle factors become much more important. The aging process also results in a number of changes occurring at the cellular level that affect the rate at which cells multiply and how they function. These changes can result in compromised immune system responses, the onset of certain diseases (Alzheimer's disease and cancer), and an inability to regulate important body functions. Age-related dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, which can result in the secretion of glucocorticoids (e.g., cortisol) and the subsequent damage to important brain structures such as the hippocampus, has also been reported.[25] This dysregulation of the HPA axis has been associated with decreased cognitive function and increased depression.[25] The influence of allostatic load[26] (AL) on indices of SA was first investigated during the course of the MacArthur studies of SA and conceptualized as an index of wear and tear on the body resulting from environmental challenges, both internal and external, that are repeatedly placed on the physiological systems of the body across the lifespan. Seeman et al.[27] found higher AL scores to be associated with poor physical and cognitive function as well as an increased risk for cardiovascular disease in a sample of older men and women.

Cross-sectional and longitudinal studies have identified a number of psychological attributes that have been associated with SA. These include such things as intelligence and cognitive capacity or reserve, self-efficacy, affect (positive or negative), and attitudes toward the aging process.[28] Although less well studied, there is some evidence to support a role for positive spirituality in SA,[29–31] particularly as it relates to one's physical and mental health. Spirituality has been shown to be positively related to measures of physical and mental health, psychological well-being, and life satisfaction in older adulthood.[31]

Important social and environmental factors that have been cited in the literature as important for SA include such things as the physical environment and the level of social support available. Living in an environment that is safe, clean, and affords access to both desired and essential services is believed to be fundamental to aging successfully. Socioeconomic disparities also influence how well an older adult ages. Older adults with fewer financial resources available to them have less access to health care, healthy foods, opportunities for continued education, and a host of other services and/or resources required for aging successfully.[32]

While each of the variables described in this section have been shown to correlate, to a greater or lesser extent, with how well an older adult functions, it is likely that the complex interplay that occurs among these many variables, combined with the influence of individual lifestyle factors (e.g., physical and cognitive activity, nutrition, social engagement), best determines how older adults are and/or perceive that they are aging successfully.

BUILDING PATHWAYS TO SUCCESSFUL AGING: THE RESULTS OF INTERVENTION RESEARCH

Exercise or Physical Activity

A mounting body of empirical evidence has demonstrated that exercise or physical activity plays an important role in shaping many of the physical, psychological, and cognitive changes that occur across the lifespan. Certainly, structured exercise- or physical activity-based interventions are at the core of most, if not all, attempts to prevent the onset of disability, slow the progression of disease or system impairments, or restore function to a level that optimizes independence following a traumatic event. Pope and Tarlov[33] refer to these as the primary, secondary, and tertiary roles played by physical activity in promoting health.

For each of the components identified in the SA model developed by Rowe and Kahn, physical activity has the potential to serve as the primary vehicle for enhancing and/or maintaining each of the three key characteristics identified. Indeed, a substantial amount of research has demonstrated an important primary role for physical activity in the prevention of a number of chronic diseases[34] (e.g., cardiovascular disease, type II diabetes, osteoporosis, certain types of cancer), functional limitations,[35,36] and premature disability.[37–39] Moreover, regular engagement in physical activity is associated with the retention of substantially higher levels of cognitive health as characterized by preserved executive control function well into later adulthood.[40–42] Finally, regular

engagement in physical activity, particularly in socially supportive group environments, facilitates "active" engagement in life.[43] This is particularly true for older women who are just beginning an exercise program.[44,45]

Despite the wealth of research evidence that has identified physical inactivity as a key risk factor for a number of chronic medical conditions that result in premature disability and/or mortality in the older adult years, only 51.2% of older adults (≥65 years) reported participating in the currently recommended level of physical activity (i.e., at least 150 min of moderate-intensity aerobic activity per week or 75 min of vigorous-intensity activity per week).[46] Older adults aging with a disability are even less likely to engage in any type of leisure-time activity when compared with older adults without disability. This is a particularly troublesome finding given that individuals with disability who regularly engage in physical activity derive similar health benefits. A reduction in the level of functional impairment and improvements in perceived quality of life have also been demonstrated for individuals with disability who participate in physical activity, even at different levels of intensity.[47,48]

A review of the research investigating the efficacy of different types of physical activity interventions as they influence health in the older adult population, suggest that a "one type suits all" physical activity intervention is not effective.[49–51] As the different roles for physical activity identified earlier in this chapter suggest, relatively healthy older adults can derive significant health benefits and/or a reduced risk for disability by participating in many different types of physical activity interventions (e.g., walking, cycling, structured exercise classes), whereas older adults living with one or more chronic diseases and/or system impairments that adversely affect their health and restrict their mobility appear to benefit more from a physical activity intervention that is more individually tailored to their needs and specifically addresses the impairments that are contributing to a more rapid decline in their health. While the overall intensity of the designed intervention may not differ between these two groups, how the major exercise principles (i.e., overload and specificity) and related exercise variables (i.e., frequency, intensity, time, and type) are manipulated may be very different. Finally, for older adults who are frail or transitioning into frailty, individualized physical activity interventions that manipulate the major exercise principles and variables in yet another way and are delivered in combination with other intervention strategies (e.g., medication management, environmental modifications to living environment) appear to be a more effective intervention approach.[52] Growing evidence also suggests the need for including a behavioral counseling or social-cognitive component within a physical activity intervention as a means of developing self-regulation skills and better long-term compliance with a physical activity intervention.[45,52,53]

The benefits of exercise on cognitive function among older adults, considered as important as maintaining physical capacity by Rowe and Kahn, have also been explored in a number of clinical trials over the past decade. Using meta-analytic techniques, Colcombe and Kramer[54] evaluated the effects of 18 clinical trials that investigated the impact of different fitness interventions on cognitive function in healthy older adults ranging in age from 55 to 80 years. The benefits of exercise were most apparent for higher order executive functions such as planning, abstraction, and the selection of relevant sensory information. Larger and more reliable improvements in cognitive function were noted for those fitness interventions that combined aerobic exercise with resistance training and were longer in duration (6+ months). Of further note was the finding that clinical populations showed similar improvements with exercise as did the non-clinical populations studied. It is presumed that the mechanisms by which exercise exerts its primary influence on brain function lies in its promotion of neurotrophic factors and reduced oxidative stress and inflammation.[55,56]

Cognitive Training and Stimulation

Intervention strategies that specifically target higher order cognitive processes have also demonstrated significant improvements in the cognitive function of both healthy older adults and those already experiencing mild cognitive impairment.[57–60] The Advanced Cognitive Training for Independent and Vital Elderly trial[61] investigated both the short- and long-term benefits of a cognitive training program that targeted specific cognitive skills in a sample of 2000 healthy, community-dwelling older adults. Participants were randomly assigned to one of three different training groups (i.e., verbal episodic memory, inductive reasoning, or processing speed) or a no-contact control group. Immediate posttraining improvements in the specifically targeted cognitive skills were observed after only 10 training sessions and continued 2 years after completion of the initial training.[57]

Cognitive training interventions have also been shown to be effective in reversing intellectual decline with age. This was nicely demonstrated in the Seattle Longitudinal Study.[62] Approximately two-thirds of study participants identified with declining cognitive function demonstrated significant improvements in multiple indices of executive function, with approximately 40% of those who had experienced significant declines over the course of the 14 year period they were monitored, returned to predecline levels of function.[58] Moreover, the positive training effects continued to be observed 14 years posttraining.[59]

Other innovative cognitive training programs that have been tested include Senior Odyssey,[63] a cognitive enrichment program that engages older adults in complex problem-solving activities in a team-like atmosphere that also promotes social connectedness. Participation in the program has been shown to enhance cognitive functions such as verbal fluency, speed of processing, and mindfulness.[63–65] Studies investigating the benefits of computer-based cognitive training programs have also demonstrated positive effects on a number of important domains of executive function (e.g., processing speed, memory, selective attention) as well as improved performance in their everyday lives.[66,67] Many of these programs are now commercially available and being widely used in rehabilitation, community, and retirement settings.

Dietary Influences

Both the adequacy and quality of food consumed by the older adult will influence their ability to age successfully. Numerous studies have demonstrated the impact of an inadequate diet on physical health,[68,69] cognition,[70–72] and the prevention or control of chronic disease[69] in older adulthood. For optimal health across the lifespan, the consistent consumption of a healthy diet that is high in fruits and vegetables, dietary fiber, and essential vitamins and minerals while low in saturated fats is strongly recommended according to the recently published *Dietary Guidelines for Americans, 2010*.[73] Adults over 50 years are also encouraged to consume foods fortified with vitamin B12.

Maintaining a healthy diet is also essential for weight reduction or maintenance. Research studies have shown that obese or overweight adults are at a higher risk for developing high blood pressure, diabetes, heart disease, arthritis, and certain forms of cancer.[74] Decreased mobility and daily function are also negative outcomes associated with being overweight or obese. Unfortunately, maintaining a proper diet is not always easy for many older adults as a result of physiological changes that result in compromised organ function, difficulties with chewing or swallowing, or diminished interest in food as a result of sensory changes affecting taste and smell.[74] Living alone has also been associated with an older adult's inability to meet his or her nutritional needs.[75]

In addition to the consumption of a well-balanced diet, findings from a small number of clinical and epidemiological trials have also demonstrated the benefits of calorie restriction (CR), reduced food intake, on multiple indices associated with SA. In addition to reducing the incidence of many age-related diseases,[76] other favorable findings include reductions in blood pressure, body mass index, triglyceride levels, and improved cholesterol profiles.[76–78] Improvements in memory have also been demonstrated after relatively short periods (3 months) of caloric restriction.[79]

More recently, an alternative strategy to CR has become the focus of growing attention by a number of research groups.[80] The development of CR Mimetics (i.e., compounds that target metabolic and stress response pathways and, thereby, mimic the effects of CR) is under way. These drugs (e.g., metformin, resveratrol) are intended to mimic the metabolic, hormonal, and physiological effects of CR without the need to actually restrict caloric intake. Although more longitudinal studies are needed to more fully evaluate the long-term influences of CR Mimetics on the aging process, preliminary findings are promising with respect to CRM's enhancing and neuroprotective effects.

Other nutrients that are essential to the physical health and cognitive function of older adults include calcium, which is critical for lowering the risk of bone loss and osteoporosis in both men and women,[81] folic acid, omega 3 fatty acids, and other antioxidant vitamins.[82] Some evidence also exists for the positive benefits of added vitamin D supplementation, particularly for older adults showing below-average baseline levels.[83] Inadequate vitamin D levels have been associated with increased risk for falls and related fractures that will significantly undermine the older adults' physical and emotional health.[84] Finally, some evidence suggests that dietary supplements in the form of enriched drinks can have positive benefits on selected measures of cognition.[85]

Social Engagement and Volunteerism

The importance of being socially engaged and having a strong social support network in older adulthood has been frequently cited as an important characteristic[4] or determinant of SA.[13] Recent intervention research, in particular, has focused on the benefits of involving older adults in a variety of different productive activities (e.g., working for a salary, caregiving), including volunteering.[86–91] One highly successful program that has been demonstrated to benefit both the older adult volunteers as well as those served is the Experience Corps (EC), a program that trains older adults to assist at-risk elementary school students learn math and other skills in a school setting.[86] In one of the first studies conducted to evaluate the program's efficacy, Fried et al. assigned 149 new older adult recruits to either an EC or control group. The older adult volunteers assigned to the EC group worked with elementary school students to improve their math and reading skills for a minimum of 15 h a week throughout the academic year. Outcomes at 1 year showed that the EC volunteers demonstrated significantly higher levels of physical activity, strength, cognition, and breadth of social support networks. What is perhaps most noteworthy about this program is that similar health benefits were derived by older adult volunteers categorized as being in only fair-to-good health.[87] Having older adults engage in productive activities has also been shown to be positively associated with physical and psychological health as well as survival rates of older adults.[89–91] Collectively, the results of these studies provide support for the value of older adults engaging in meaningful volunteer activities as a means of improving their level of physical, cognitive, and social health—all important determinants for SA.

IT'S NEVER TOO LATE: FACT OR FICTION?

While considerable research has demonstrated the negative effects of physical inactivity, obesity, smoking, excessive alcohol, and poor diet on morbidity and mortality,[92–94] there is evidence to suggest that much can be done to reverse many of the adverse effects associated with unhealthy lifestyle behaviors.[95] In fact, one of the many myths debunked as a result of the MacArthur Foundation studies was that it is too late for older adults to lower their risk for premature morbidity and mortality after decades of engaging in unhealthy (e.g., eating fatty foods, not exercising) or risky behaviors (e.g., smoking, excessive alcohol) once older adulthood is reached.[5] Research has also shown that most age-associated declines in physical performance can also be reversed with regular participation in even moderate levels of physical activity.[96,97] For example, the Lifestyle Interventions and Independence for Elders pilot

study, a multicenter, randomized clinical-controlled trial involving 424 sedentary persons aged between 70 and 89 years at risk for disability, has demonstrated both immediate[97] and longer-term improvements (2 year follow-up)[98] in physical performance and mobility disability following completion of a 12 month moderate-intensity physical activity intervention. As Rowe and Kahn[5] aptly state "Physical activity is at the crux of SA, regardless of other factors (p. 98)."

Research evidence also shows that smoking cessation, even in the case of previously heavy smokers, significantly lowers the risk for cardiovascular disease, lung cancer, and stroke.[99,100] According to the American Lung Association, within a year of quitting, former smokers reduce their risk of coronary heart disease by 50% with the risk further declining with each passing year.[99] The adverse effects of a poor diet can also be reversed through nutritional interventions that combine dietary screenings with individualized nutrition plans designed to address the specific needs of the older adult (e.g., malnourishment, obesity).[101,102] Bowen and Beresford,[103] following their review of 80 published dietary intervention studies, concluded that more intensive dietary interventions that set high goals for participants and recruited more selectively (i.e., more highly motivated participants) yielded the better outcomes.

ROLE OF HEALTH CARE PRACTITIONERS IN THE PROMOTION OF SUCCESSFUL AGING

Health care professionals can play an integral role in promoting SA among older adults. Health care providers are viewed by the majority of older adults as the primary source of health information and, therefore, have the credibility needed to be an influential force in getting older adults to embrace a healthier lifestyle. The very fact that adults in the United States visit a physician's office an average of three times per year provides the opportunity needed to implement successful health-promoting practices.[104] In spite of this knowledge, the percentage of older adults (65 years or older) who report receiving counseling about health-promoting behaviors such as regular physical activity are very low (approximately 31%).[105] In this final section of the chapter, I will briefly review the research evidence that supports a role for the health care provider and the types of intervention strategies that have yielded successful outcomes.

A number of research studies have explored the benefits of physician-based counseling of patients, particularly as it relates to physical activity,[106] smoking cessation,[107] alcohol consumption,[108] and nutrition.[109] Calfas et al.[110] demonstrated that previously sedentary patients provided with in-office structured counseling sessions as short as 3–5 min resulted in positive short-term changes in their patients' physical activity levels as well as their readiness to adopt physical activity. Other studies that have individually tailored the PA counseling by matching it to a patient's stage of motivational readiness for physical activity[111] (e.g., precontemplation, contemplation, preparation) have also proven effective, at least in the short term.[112,113] Patients enrolled in the Physically Active for Life project who received individually tailored PA counseling were more likely to be in more advanced stages of readiness for PA 6 weeks following their initial counseling appointment when compared with a group receiving standard care. Unfortunately, these gains were no longer evident after 8 months with no differences in physical activity levels evident between the two groups.[113]

In order to achieve more long-term behavior change among previously inactive older adult patients, Pinto et al.[114] supplemented a brief PA counseling session (approximately 3 min) delivered by the physician during the course of an office visit with regular telephone counseling by a health educator. Significantly higher levels of physical activity were reported for the group receiving the additional telephone counseling (additional hour/week) after 3 months when compared with a group receiving a single in-office counseling session (12.45 min/week). More importantly, the physical activity gains were sustained in the extended counseling group through 6 months of follow-up. In addition to counseling, providing older adult patients with a motivational tool in the form of a pedometer may also prove to be an effective intervention strategy. Findings from a study conducted by Bravata et al.[115] showed that pedometer use by adult outpatients resulted in higher physical activity levels and other health benefits (decreases in body mass index and blood pressure), at least in the short term. Given the knowledge that older adults can attenuate the progression of functional impairments by up to 55%, even by engaging in only moderate levels of physical activity,[116] providing physical activity counseling to all older adult patients, irrespective of health status, should be a high priority for the health care professional.

Physician-based counseling focused on alcohol consumption,[108] smoking cessation,[107,117] and improved nutritional practices[109] has also yielded successful outcomes. The efficacy of physicians providing two brief (10–15 min, 1 month apart) counseling sessions supplemented with follow-up phone calls from a nurse has been demonstrated to significantly lower alcohol use, episodes of binge drinking, and frequency of excessive drinking, in groups of at-risk patients reevaluated at 1 and 2 years after the first counseling session.[108] Similarly, physician counseling, often combined with nicotine replacement therapy or telephone quitlines, also constitute effective smoking cessation strategies.[107,117] Intervention strategies aimed at improving dietary behaviors have also yielded successful outcomes when delivered by health care providers in primary care settings. The most effective interventions appear to combine patient education, behavioral counseling, patient reinforcement, and follow-up. The interventions also tend to be more intensive, are conducted over a longer period of time, and are directed at patients at increased risk for chronic disease.[109]

Routine counseling of patients relative to the physical and cognitive benefits of social engagement as well as engaging in cognitively demanding activities should also be an integral component of the health care services provided to older adults. Encouraging older adults to add new cognitive, physical, and social activities into their daily routines and providing examples of appropriate types of activities

will be important. As indicated earlier in this chapter, certain types of computer-based cognitive training programs have been demonstrated to improve multiple domains of cognition (e.g., processing speed, memory, visuospatial orientation) in controlled trials conducted with older adults.[66] Although more controlled studies are needed, limited evidence also suggests that improvements in certain cognitive domains transfer to the performance of routine daily activities.[118] Indeed, many community-based centers and retirement communities have begun installing computer-based "brain fitness" training programs and other types of interactive video games (e.g., Nintendo Wii) aimed at improving the physical, cognitive, and social health of older adults.

Older adults who report unusual changes in their physical or cognitive health concerns to their health care provider should undergo further testing to distinguish between changes that are associated with age versus pathology. Because age-associated changes in muscle and bone predispose older adults to injury, additional care needs to be taken when prescribing physical activity for older adults and referring them to community-based classes. In the case of those older adults who are already experiencing significant changes in their functional abilities and are at heightened risk for falls, it will be especially important to have the appropriate health care professional conduct a thorough assessment of their physical abilities so that the exercise prescription can be appropriately matched to their ability level. While referrals to local community-based physical activity programs or directions on how to begin a self-directed walking program may be sufficient for more healthy patients, others will require more tailored and multifactorial interventions.[52] While some hospitals and outpatient centers currently offer on-site programs that include educational programs directed at improving chronic disease self-management skills as well as structured exercise programs focused on primary or secondary prevention of disease, many more are needed to address the growing needs of the middle-aged and older adult populations.

What are the core ingredients necessary for implementing interventions aimed at enhancing the health of older adults? Haber[119] recommends that in order to be successful, health promotion interventions aimed at older adults should include the following core elements: the development of short- and long-term health goals that are both modest and measurable, strategies for building and maintaining the patient or client's motivation, techniques for addressing barriers that have prevented success in the past and/or might become an issue in the future, fostering compliance so that the new behavior becomes a habit, and assisting the patient/client garner the social support needed to continue in the face of adversity. To accomplish these outcomes, an interdisciplinary team approach is going to be necessary.

SUMMARY

Despite the controversy that the term "successful aging" has sparked in the literature, both with respect to how it is defined and/or measured, research evidence strongly indicates that aging is not synonymous with an inevitable decline in one's physical and cognitive health. Modifiable lifestyle and behavioral factors clearly play a greater role in shaping the older adults' overall quality of life, both as it is perceived and actually experienced, than one's genetic inheritance. While making healthy lifestyle and behavior choices early in life are clearly important to optimizing health and well-being in later adulthood, the research shows that it's never too late for an older adult to alter the trajectory of his or her lifespan. The health care professional has the potential to serve as both an important catalyst for change as well as a mediator of that change. Regularly counseling older adult patients about the benefits of physical activity, eating a balanced diet, not smoking, and avoiding excessive alcohol intake can do much to improve their physical health. Similarly, encouraging older adults to engage in stimulating cognitive and social activities on a daily basis will also benefit them psychologically and emotionally.

The early identification of unusual physical and cognitive changes is an important first step in preventing or delaying the onset of more serious impairments that will threaten an older adult's ability to remain independent and socially engaged. This can be accomplished through regular screenings conducted by the appropriate health care provider and immediate referral for additional testing, if warranted, or to programs and/or services available in outpatient or community settings. In order to ensure long-term success, a systematic and collaborative team approach will be necessary because no single health care provider has the knowledge, skills, or resources available to address the many factors that contribute to whether an older adult does or does not age successfully. Building wellness teams that interface primary care physicians, physician assistants, physical and occupational therapists, and clinical nurse specialists, with health educators and other community- and home-based service providers will be needed if long-term behavior change can be expected. Added incentives in the form of allocating time for health care providers to receive the necessary training, providing additional resources and personnel to implement effective interventions, and providing financial reimbursement linked to outcomes may be necessary to help primary care providers, in particular, overcome many of the barriers that currently exist to the implementation of regular health-promoting practices with their older adult patients.

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105 Role of Physical Activity in Successful Aging

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CONTENTS

Introduction 1257
Benefits of Physical Activity for Older Adults 1258
Recommendations and Guidelines for Frequency, Intensity, Duration, and Type of Physical Activity 1260
Endurance Exercise for Older Adults 1260
Resistance Exercise for Older Adults 1260
Flexibility Exercise for Older Adults 1260
Balance Exercise for Frequent Fallers or Individuals with Mobility Problems 1260
Special Considerations for Prescribing Physical Activity for Older Adults 1260
Motivating Older Adults to Initiate and Maintain a Physically Active Lifestyle 1261
Social Support—Involving Friends and Family 1261
Self-Efficacy—You Can Do It! We Can Help! 1261
Active Choices—Finding the Program That Works For You 1261
Health Contracts—Making a Commitment 1261
Perceived Safety—It's Safe, It's Fun 1261
Regular Performance Feedback—How Are We Doing? 1261
Positive Reinforcement—Keep It Up, You're Doing Great! 1261
Communicating with Patients about Exercise and Physical Activity 1261
Step 1—Getting Started 1262
Step 2—Making Physical Activity Part of Your Life 1262
Step 3—Keeping It Up, Stepping It Up 1262
Step 4—Being Active for Life 1262
Answering Your Patient's Questions about Exercise and Physical Activity 1262
Patient Question: Why Should I Be Physically Active? 1263
Patient Question: How Much Physical Activity Do I Need? 1263
Patient Question: What Is the Best Exercise for Older Adults? 1263
Patient Question: How Many Times a Week Should I Exercise? 1263
Patient Question: I Have Not Exercised for Many Years, Where Should I Start? 1264
Patient Question: Will Physical Activity Help to Reduce My Risk for Specific Diseases and Conditions? 1264
Patient Question: Is Exercise Safe? 1264
Patient Question: Am I Too Old to Exercise? 1265
Patient Question: Do I Need Special Clothing and Equipment? 1265
Summary 1265
References 1266

INTRODUCTION

Is functional decline an inevitable and inescapable consequence of growing older? Or can we play an active role in determining the path that aging takes? There is a growing body of evidence to suggest that we may be able to postpone some of the negative consequences of growing older by maintaining a high level of physical activity. Avoiding a sedentary lifestyle and eating a healthy diet may be one of the most effective means of postponing the onset of functional decline, promoting independence, and maintaining high-quality of life in old age. During the past century, many developed countries have experienced an epidemiological transition in which the impact of infectious diseases has steadily declined and noncommunicable diseases (NCDs) have become the leading causes of disease, disability, and death [1]. Because chronic diseases and conditions typically take many years to develop, the increased levels of NCDs are disproportionately borne by older adults, many of whom have

increased risk of developing and dying from cardiovascular disease, type 2 diabetes, obesity, and certain cancers [1–5]. Many chronic conditions share common preventable causes that are both lifestyle related (unhealthy diets, physical inactivity, smoking, and alcohol abuse) and biological (hypertension, obesity, and dyslipidemia). In addition, there are also a number of social, economic, and environmental factors linked with chronic diseases, including education, availability, and affordability of healthy food, access to health services, and policies and infrastructures that support a healthy lifestyle.

Despite the complex relationships among the many determinants of chronic disease, the World Health Organization (WHO) has identified regular physical activity as an effective means by which an individual can reduce the risk of developing chronic diseases and conditions and, thereby, promote independence and age successfully [6]. Epidemiological research has consistently shown significant decreases in the relative risk of cardiovascular and all-cause mortality among persons who are classified as highly active compared with those in a similar age range who are classified as moderately active or less active [7].

In this chapter, we present an overview of current research and recommendations concerning the relationship between regular physical activity and successful aging. In "Benefits of physical activity for older adults" section, we briefly review some of the benefits that accrue to older individuals who adopt a physically active lifestyle. In "Recommendations and guidelines for frequency, intensity, duration, and type of physical activity" section, we summarize current U.S. government guidelines regarding the frequency, intensity, duration, and type of physical activity recommended for older adults. Next, in "Motivating older adults to initiate and maintain a physically active lifestyle" section, we focus on evidence-based strategies to help motivate older adults to initiate and maintain a physically active lifestyle. Finally, in "Communicating with patients about exercise and physical activity" section, we discuss how clinicians should talk to their patients about physical activity, focusing on the need to help patients to learn how to "be active their way." We conclude by providing answers to frequently asked patient questions about physical activity. Throughout the chapter, the Institute of Medicine definitions of physical activity and exercise and related concepts are adopted, where, physical activity refers to body movement that is produced by the contraction of skeletal muscles and that increases energy expenditure. Exercise refers to planned, structured, and repetitive movement to improve or maintain one or more components of physical fitness.

BENEFITS OF PHYSICAL ACTIVITY FOR OLDER ADULTS

Over the past 20–30 years, a very substantial number of studies have confirmed that there are many benefits for older adults who participate in regular physical activity. In 2008, the Department of Health and Human Services (DHHS) published, for the first time, official U.S. Government Physical Activity Guidelines (PAG) [8]. The DHHS PAG for Americans conclude that, compared with less active persons, more active men and women have lower rates of all-cause mortality, coronary heart disease, high blood pressure, stroke, type 2 diabetes, metabolic syndrome, colon cancer, breast cancer, and depression. In addition to these biomedical benefits, there are many other reasons older adults should be encouraged to find a way to build physical activity into their everyday lives. Regular physical activity can help to improve quality of life in old age. Physical activity can help older adults remain active and engaged within their families and communities.

A detailed review of the benefits of physical activity for older adults is beyond the scope of this chapter; however, several recent review articles are available, which provide excellent summaries of the existing evidence [9,10]. For example, the American College of Sports Medicine (ACSM) recently published a Position Stand on Exercise and Physical Activity for Older Adults [9], which summarizes the benefits of both long-term exercise and physical activity and shorter-duration exercise programs on the health and well-being of older adults. The ACSM Position Stand concludes that although no amount of physical activity can stop the biological aging process, there is evidence that regular physical activity can minimize the physiological effects of an otherwise sedentary lifestyle and increase healthy life expectancy by limiting the development and progression of chronic disease and disabling conditions. Importantly, physical activity not only benefits our physical health but there is also strong evidence that it can improve psychological health and well-being. Regular physical activity can favorably influence a broad range of physiological systems and may be a lifestyle factor that discriminates between those individuals who have and have not experienced successful aging.

In October 2007, the American Medical Association and the ACSM launched a major new initiative called Exercise is Medicine (EIM). The major goal of the EIM project is to make physical activity and exercise a standard part of a global disease prevention and treatment medical paradigm. The initiative recognizes that regular exercise can be an important element in the management of numerous medical conditions including coronary heart disease [11–13], hypertension [11,14,15], peripheral vascular disease [16], type 2 diabetes [17], obesity [18], elevated cholesterol [11,19], osteoporosis [20], osteoarthritis [21,22], claudication [23], and chronic obstructive pulmonary disease [24]. A joint statement from ACSM and the American Heart Association [10] concludes that physical activity is valuable in the treatment and management of depression and anxiety disorders [25], dementia [26], pain [27], congestive heart failure [28], syncope [29], stroke [30], back pain [31], and constipation [32]. In addition, there is some evidence that physical activity prevents or delays cognitive impairment [33] [34,35] and disability [36–38] and improves sleep [39,40].

TABLE 105.1
Individual Benefits of Physical Activity for Older Persons: Physiological Benefits

Immediate benefits
- *Glucose levels*: Physical activity helps regulate blood glucose levels
- *Catecholamine activity*: Both adrenalin and noradrenalin levels are stimulated by physical activity
- *Improved sleep*: Physical activity has been shown to enhance sleep quality and quantity in individuals of all ages

Long-term effects
- *Aerobic/cardiovascular endurance*: Substantial improvements in almost all aspects of cardiovascular functioning have been observed following appropriate physical training
- *Resistive training/muscle strengthening*: Individuals of all ages can benefit from muscle strengthening exercises. Resistance training can have a significant impact on the maintenance of independence in old age
- *Flexibility*: Exercise which stimulates movement throughout the range of motion assists in the preservation and restoration of flexibility
- *Balance/coordination*: Regular activity helps prevent and/or postpone the age-associated declines in balance and coordination that are a major risk factor for falls
- *Velocity of movement*: Behavioral slowing is a characteristic of advancing age. Individuals who are regularly active can often postpone these age-related declines

The WHO Guidelines have been placed in the public domain and can be freely copied and distributed (WHO, 1996).

TABLE 105.2
Individual Benefits of Physical Activity for Older Persons: Psychological Benefits

Immediate benefits
- *Relaxation*: Appropriate physical activity enhances relaxation
- *Reduces stress and anxiety*: There is evidence that regular physical activity can reduce stress and anxiety
- *Enhanced mood state*: Numerous people report elevations in mood state following appropriate physical activity

Long-term effects
- *General well-being*: Improvements in almost all aspects of psychological functioning have been observed following periods of extended physical activity
- *Improved mental health*: Regular exercise can make an important contribution in the treatment of several mental illnesses, including depression and anxiety neuroses
- *Cognitive improvements*: Regular physical activity may help postpone age-related declines in Central Nervous System processing speed and improve reaction time
- *Motor control and performance*: Regular activity helps prevent and/or postpone the age-associated declines in both fine and gross motor performance
- *Skill acquisition*: New skills can be learned and existing skills refined by all individuals regardless of age

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EIM strongly advocates that physical activity should be considered by all health care providers as a vital sign in every patient visit and that all patients are effectively counseled and referred with respect to their physical activity needs. The WHO suggests that the benefits of physical activity for older adults can be divided into two broad categories: (1) benefits of physical activity for the individual and (2) benefits of promoting physically active lifestyles among older persons for society [41]. Under the WHO schema, the individual benefits can be summarized into four general areas: physiological benefits (Table 105.1), psychological benefits (Table 105.2), social benefits (Table 105.3), and the benefits for society in an additional table (Table 105.4). As long ago as 1996, the WHO was recommending that virtually all older persons should participate in physical activity on a regular basis and that society has a responsibility to advocate for broad-based participation in physical activity whenever possible. The WHO Guidelines conclude that regular physical activity provides substantial health-related benefits. In addition, it is cheap, safe, and readily available.

TABLE 105.3
Individual Benefits of Physical Activity for Older Persons: Social Benefits

Immediate benefits
- *Empowering older individuals*: A large proportion of the older adult population voluntarily adopts a sedentary lifestyle, which eventually threatens to reduce independence and self-sufficiency. Participation in appropriate physical activity can help empower older individuals and assist them in playing a more active role in society
- *Enhanced social and cultural integration*: Physical activity programs, particularly when carried out in small groups and/or in social environments, enhance social and intercultural interactions for many older adults

Long-term effects
- *Enhanced integration*: Regularly active individuals are less likely to withdraw from society and more likely to actively contribute to the social milieu
- *Formation of new friendships*: Participation in physical activity, particularly in small groups and other social environments, stimulates new friendships and acquaintances
- *Widened social and cultural networks*: Physical activity frequently provides individuals with an opportunity to widen available social networks
- *Role maintenance and new role acquisition*: A physically active lifestyle helps foster the stimulating environments necessary for maintaining an active role in society, as well as for acquiring positive new roles
- *Enhanced intergenerational activity*: In many societies, physical activity is a shared activity, which provides opportunities for intergenerational contact thereby diminishing stereotypic perceptions about aging and the elderly

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TABLE 105.4
Societal Benefits of Promoting Physical Activity for Older Persons

- *Reduced health and social care costs*: Physical inactivity and sedentary living contributes to a decrease in independence and the onset of many chronic diseases. Physically active lifestyles can help postpone the onset of physical frailty and disease thereby significantly reducing health and social care costs
- *Enhancing the productivity of older adults*: Older individuals have much to contribute to society. Physically active lifestyles help older adults maintain functional independence and optimize the extent to which they are able to actively participate in society
- *Promoting a positive and active image of older persons*: A society which promotes a physically active lifestyle for older adults is more likely to reap the benefits of the wealth of experience and wisdom possessed by the older individuals in the community. A large proportion of the older adult population voluntarily adopts a sedentary lifestyle, which eventually threatens to reduce independence and self-sufficiency

The WHO Guidelines have been placed in the public domain and can be freely copied and distributed (WHO, 1996).

RECOMMENDATIONS AND GUIDELINES FOR FREQUENCY, INTENSITY, DURATION, AND TYPE OF PHYSICAL ACTIVITY

DHHS PAG for Americans recommendations for the frequency, intensity, and duration of exercise and physical activity for older adults are summarized in the subsequent sections. The PAG recommend 150 min/week of moderate-intensity aerobic activity for health benefits. However, the DHHS Guidelines note that additional benefits occur as the amount of physical activity increases through higher intensity, greater frequency, and/or longer duration. The DHHS PAG stress that if older adults cannot do 150 min of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow. The following recommendation for older adults describes the amounts and types of physical activity including endurance, resistance, and flexibility exercise.

Endurance Exercise for Older Adults

Frequency: For moderate-intensity activities, accumulate at least 30 or up to 60 min/day (for greater benefit) in bouts of at least 10 min each to total 150–300 min/week or at least 20–30 min/day or more of vigorous intensity activities to total 75–150 min/week or an equivalent combination of moderate and vigorous activity.

Intensity: On a scale of 0–10 for level of physical exertion, 5–6 for moderate intensity, and 7–8 for vigorous intensity.

Duration: For moderate-intensity activities, accumulate at least 30 min/day in bouts of at least 10 min each or at least 20 min/day of continuous activity for vigorous intensity activities.

Type: Any modality that does not impose excessive orthopedic stress, walking is the most common type of activity. Aquatic exercise and stationary cycle exercise may be advantageous for those with limited tolerance for weight-bearing activity.

Resistance Exercise for Older Adults

Frequency: At least 2 days/week.

Intensity: Between moderate (5–6) and vigorous (7–8) intensity on a scale of 0–10.

Type: Progressive weight training program or weight-bearing calisthenics (8–10 exercises involving the major muscle groups of 8–12 repetitions each), stair climbing, and other strengthening activities that use the major muscle groups.

Flexibility Exercise for Older Adults

Frequency: At least 2 days/week.

Intensity: Moderate (5–6) intensity on a scale of 0–10.

Type: Any activities that maintain or increase flexibility using sustained stretches for each major muscle group and static rather than ballistic movements.

Balance Exercise for Frequent Fallers or Individuals with Mobility Problems

Currently, balance exercise is recommended for individuals who are frequent fallers or for individuals with mobility problems. Unfortunately, due to a lack of adequate research evidence, there are currently no specific recommendations regarding the frequency, intensity, or type of balance exercises for older adults. However, the most balance and fall prevention programs include (1) progressively difficult postures that gradually reduce the base of support (e.g., two-legged stand, semi-tandem stand, tandem stand, one-legged stand), (2) dynamic movements that perturb the center of gravity (e.g., tandem walk and circle turns), (3) stressing postural muscle groups (e.g., heel stands and toe stands), or (4) Reducing sensory input (e.g., standing with eyes closed).

Special Considerations for Prescribing Physical Activity for Older Adults

If older adults have been sedentary for many years, it may be necessary to start out slow when beginning a new exercise program, particularly for older adults who are frail or who have chronic conditions that affect their ability to perform physical tasks. Increases in exercise intensity and duration should be gradual and tailored to tolerance and preference. Taking it easy and being patient are good strategies for deconditioned seniors. For some older adults, muscle strengthening activities and/or balance training may need to precede aerobic training activities. If chronic conditions prevent activity

at the recommended minimum amount, older adults should perform physical activities as tolerated so as to avoid being sedentary.

MOTIVATING OLDER ADULTS TO INITIATE AND MAINTAIN A PHYSICALLY ACTIVE LIFESTYLE

Developing the best, most well-rounded physical activity program is not going to be sufficient if we do not also pay attention to motivating older adults to participate in the program! In recent years, a great deal of attention has focused on the study of behavioral factors that increase the likelihood of an individual initiating and maintaining a regular program of exercise and/or physical activity. ACSM has summarized the Best Practices for Physical Activity Programs and Behavior Counseling In Older Adult Populations [42]. The ACSM Best Practice Statement suggests that incorporating a comprehensive behavioral management strategy in physical activity interventions can help maximize recruitment, increase motivation for exercise progression, and minimize attrition. The following behavioral strategies can increase the likelihood a person will sustain a new physical activity behavior.

Social Support—Involving Friends and Family

Social support from family and friends has been associated with long-term exercise adherence in older adults [43]. Examples of social support strategies include peer support (e.g., tell a friend and bring a friend, exercise buddy system) and professional health educator support (telephone counseling, mail follow-up).

Self-Efficacy—You Can Do It! We Can Help!

For many seniors, aging is associated with a loss of perceived control [44]. There is growing evidence that people are more likely to initiate and maintain physical activity if they feel confident about their ability to succeed and if they are afforded a variety of opportunities to actively participate in physical activity. Health contracts, practice/mastery experiences, modeling, and having choices enhance self-efficacy.

Active Choices—Finding the Program That Works For You

As part of a comprehensive behavioral strategy, tailoring the exercise program to the needs and interest of participants has successfully motivated older adults to initiate and maintain a routine of regular physical activity [45]. Therefore, physical activity leaders should work closely with individuals to design a physical activity regimen that reflects the person's preferences and capabilities. There is growing evidence that providing choices concerning exercise program characteristics (such as group-based vs. individual activity programs and choice of exercise location) contributes to greater adherence.

Health Contracts—Making a Commitment

A health contract is a written agreement negotiated between the participant and a health professional to accomplish a health goal [46]. The contract usually includes challenging but realistic goal setting and a measurable, specific, time-delimited plan or course of action for reaching the health goals. The use of a health calendar to record physical activity provides a means for the participant to monitor the targeted physical activity and to reinforce a commitment to the exercise routine. Self-monitoring is most effective when completed frequently (as it occurs or daily), focuses on the behavior (not absence of), and it is specifically defined.

Perceived Safety—It's Safe, It's Fun

Concerns for safety have been identified as a barrier to exercise by many older adults [47]. Physical activity programs can help alleviate inappropriate concerns about safety by educating participants about actual risks of physical activity and by helping individuals understand how to self-monitor their exercise intensity levels.

Regular Performance Feedback—How Are We Doing?

Providing regular and accurate performance feedback can assist older adults in developing realistic expectation of their own progress [48]. Performance feedback should be positive and meaningful to the individual. Observation of meaningful positive changes in performance and success in achieving expected outcomes are associated with exercise adherence in older adults.

Positive Reinforcement—Keep It Up, You're Doing Great!

Positive reinforcement is any procedure introduced in an intervention that increases the likelihood of maintenance of the activity [49]. Examples of effective reinforcement strategies in physical activity settings include recruitment incentives, rewards for reaching targeted goal, and public recognition for attendance and adherence. To maximize the effect of reinforcement, it should be valued by the individual being targeted.

COMMUNICATING WITH PATIENTS ABOUT EXERCISE AND PHYSICAL ACTIVITY*

It is important to help your patients understand that there are many different ways for older adults to be physically active. For some individuals, structured exercise programs led by certified exercise professionals will be the preferred option, whereas, others may wish to find other ways to build physical activity into their everyday lives. The notion that there is a single best way to exercise is no longer tenable, and it is increasingly clear that individuals will need to

* *Source*: DHHS, *Be Active Your Way*, 2008.

select the form of physical activity that works best for them. The DHHS "Be Active Your Way" guide that accompanies the 2008 PAG invites members of the public to select physical activities that meet their personal needs and preferences. The steps outlined in the "Be Active Your Way" guide provide an excellent framework for clinician patient discussions around exercise and physical activity.

Step 1—Getting Started

Before beginning an exercise or physical activity program, the "Be Active Your Way" guide recommends that older adults to first focus on identifying a personally meaningful motive for increasing their activity levels. You should discuss with your patients some physical activity goals that are personally meaningful to them. Among the possible reasons identified for increasing physical activity are the following:

- Be healthier
- Increase my chances of living longer
- Feel better about myself
- Have less chance of becoming depressed
- Sleep better at night
- Help me look good
- Be in shape
- Get around better
- Have stronger muscles and bones
- Help me stay at or get to a healthy weight
- Be with friends or meet new people
- Enjoy myself and have fun

Step 2—Making Physical Activity Part of Your Life

You should encourage patients who are considering a physical activity program to think about reasons why they have not been physically active in the past and to try to develop strategies for overcoming these barriers. The "Be Active Your Way" guide encourages people who have been sedentary for many years to choose something they already like to do and to try to build a physical activity component into the activity. For example, many people like to go shopping or to attend dances and other social events; by increasing the time they spend walking (or dancing), they can gradually combine their fun activity with a healthy dose of physical activity. Older adults should be encouraged to select an activity program that is personally meaningful. Among the strategies recommended are the following:

- Pick an activity you like and one that fits into your life.
- Find the time that works best for you.
- Be active with friends and family. Having a support network can help you keep up with your program.

Step 3—Keeping It Up, Stepping It Up

Once your patients have successfully integrated physical activity into their everyday lives, you should encourage them gradually increase the intensity and duration of physical activity until they are meeting the physical activity recommendations for older adults. This can be achieved in the following ways:

- By being active longer each time. Older adults already walking for 30 min, three times a week, could go longer—walking for 50 min, three times a week.
- By being active more often. If an older adult is biking lightly 3 days a week for 25 min each time, he or she could build up to riding 6 days a week for 25 min each time.

Step 4—Being Active for Life

Once older adults are successfully meeting the PAG, they should be encouraged to consider adding new elements to their physical activity regimen in order to keep physical activity interesting and fun. For example, once older adults are comfortable sustaining moderate-intensity activities on a regular basis, they could begin to add higher intensity activities. The "Be Active Your Way" Guide lists a number of moderate and vigorous physical activity options that are available to older adults.

"Be Active Your Way" moderate physical activity options:

- Biking slowly
- Canoeing
- Dancing
- General gardening (raking, trimming shrubs)
- Tennis (doubles)
- Using your manual wheelchair
- Using hand cyclers—also called arm ergometers
- Walking briskly
- Water aerobics

"Be Active Your Way" Vigorous Physical Activity Options:

- Aerobic dance
- Basketball
- Fast dancing
- Jumping rope
- Martial arts (such as karate)
- Race walking, jogging, or running
- Riding a bike on hills or riding faster
- Team sports
- Swimming fast or swimming laps
- Tennis (singles)

ANSWERING YOUR PATIENT'S QUESTIONS ABOUT EXERCISE AND PHYSICAL ACTIVITY

For those of us who make our living advocating for healthy and physically active lifestyles, it may come as a surprise to realize how little many older adults know about physical activity. However, many older adults were educated at a time

and in a culture in which little was known about the health benefits of physical activity and professionals and members of the public were skeptical about the need to remain physically active after retirement. In the final section of this chapter, we consider some frequently asked questions that older adults ask about exercise and physical activity with the goal of assisting you to provide succinct but accurate responses that will serve to motivate and inform your older clients.

Patient Question: Why Should I Be Physically Active?

Clinician response: There are many reasons you should build physical activity into your everyday life. Regular physical activity can help to improve quality of life in old age. Physical activity can help you stay active and engaged with your family and community. It can help you to manage or postpone some of the chronic diseases and conditions many of us have come to expect from old age. Aging does not have to be something that "happens to us"—on the contrary, being physically active can help us to play a more active role in our own aging. Physical activity can help us to live happier, healthier, and more productive lives.

Additional comment: For many years, exercise professionals have tended to focus on the health or medical benefits of exercise and physical activity when trying to motivate sedentary individuals to become more active. For some individuals, motives such as decreasing cholesterol levels, improving cardiac output, and increasing bone mineral density are effective motivators, but for many seniors, they are not. As a clinician, you should also stress that regular physical activity can be fun, can increase quality of life, and can help seniors continue to do the things that they like to do. It is doubtful that a single motivational strategy will work for all older adults. You should ensure that your clients are exposed to a variety of different motivational strategies in order to find the technique that works best for each of their clients.

Patient Question: How Much Physical Activity Do I Need?

Clinician response: Ideally, you should aim to do at least 150 min of moderate-intensity aerobic activity per week as well as 2 days/week of resistance exercises. However, start by doing what you can and gradually look for ways to do more. If you have not been active for a while, start out slowly. After several weeks or months, build up your activities—do them longer and more often.

Additional comment: The current PAG for Americans summarize the best available scientific recommendations, and a health professional should be prepared to summarize this information for their patients. However, it is important to understand that, for many older adults, 150 min of moderate-intensity aerobic activity per week can be an extremely intimidating target that may leave them discouraged or unwilling to even try to increase their physical activity. It is important that clinicians help patients understand that it is perfectly acceptable to gradually increase physical activity levels starting at easily achievable, nonthreatening levels, and slowly increasing as they become more comfortable with exercise and physical activity.

Patient Question: What Is the Best Exercise for Older Adults?

Clinician response: There is no single best exercise that works for all older persons. Depending on how you define it, "old age" can cover as much as a 50 year age span, ranging from 50 to 100 years of age and older. For this reason, it is impossible to recommend single set of activities that is best for all older persons. Some seniors can run marathons or compete in triathlons, whereas others may be more comfortable walking, gardening, or doing tai chi. Still others will get their exercise in a chair or in bed! The most important thing is to do regardless of your age is to avoid inactivity. The specific type of physical activity will always vary from person-to-person. A good idea is to select activities you enjoy. If possible, mixing up activities that promote stamina, strength, flexibility, and balance is a good idea.

Additional comment: The best exercise or physical activity program is the one that your patients are willing and able to do regularly, that they enjoy, and that adds to their quality of life. For some individuals, this will be a structured group exercise program at the local senior center or YMCA, but for others, it will be something much less structured, possibly involving activities such as healthy commuting, gardening, or walking the dog. Many health professionals grew up enjoying games and sports and are extremely comfortable "working out" in traditional exercise environments. It is important to remember that not all older adults have enjoyed similar positive experiences with traditional exercise programs. Work with your patients to understand their goals, aspirations, and personal preferences. For some individuals, identifying options for active living may be a much more successful strategy than simply referring an individual to an exercise program at a local fitness center or community agency.

Patient Question: How Many Times a Week Should I Exercise?

Clinician response: Generally, it is better to spread out physical activity throughout the week with a goal of being active on at least 3–5 days/week. By choosing activities that you enjoy, that are convenient and affordable, you may be able to find a way to be active on almost all days of the week. Try to mix up your physical activity program so you are not doing the same thing everyday. On some days, you might go for a walk in your neighborhood with a friend or family member, on other days, you might take advantage of a more structured exercise program at the senior center or church. Many people find that wearing a step counter can help them keep track of their activity levels. On days where you have not accumulated

many steps, an after-dinner walk can help you maintain your commitment to maintain an active lifestyle.

Additional comment: As a clinician, one of the most important things you can do for your clients is to empower them to be independently physically active and not to depend solely on you or other health professionals for advice about their physical activity. Clinicians should work with patients to help them develop activities that they can do on their own time and in their own space. By helping seniors understand that there are many different ways to be active, health professionals can help them develop a well-rounded, personalized activity program that selects from a menu of physical activity choices and helps them to be active on most if not all days of the week.

Patient Question: I Have Not Exercised for Many Years, Where Should I Start?

Clinician response: Forget the old saying "no pain, no gain"—it is simply not true! Too many of us learned in childhood that physical activity has to be painful or exhausting if it is going to do us any good. There are many excellent options for those of us who cannot or do not want to exercise vigorously. Walking is a wonderful way to increase your activity level. Stretching, tai chi, and water exercise are also good options. For example, the Arthritis Foundation offers excellent aqua exercise programs designed especially for those with arthritis and joint disorders. Gardening and working outdoors can also be a good form of physical activity. Remember—the most important thing is not what you do—rather—it is most important to avoid complete inactivity.

Additional comment: Prescribing exercise and physical activity is as much an art as it is a science. The most successful clinicians are those that have mastered both of these elements. Simply informing patients about the current scientific guidelines may not be sufficient to motivate them to change their behavior. Understanding some of the principles of behavioral change, discussed earlier in this article, can help you develop greater insight into how to identify the right place for an individual to start on their journey toward an active lifestyle.

Patient Question: Will Physical Activity Help to Reduce My Risk for Specific Diseases and Conditions?

Clinician response: Physical inactivity is a major risk factor for many physical and psychological conditions. Sedentary living is associated with heart disease, obesity, diabetes, and many other conditions. Inactivity is also linked to low self-esteem and psychological depression. Regular physical activity can positively influence all of the aforementioned conditions. Many studies have shown that activity can also help slow the loss of muscle and bone mass that often occurs with advancing age. In addition to these physical and psychological benefits, physical activity can often have significant social benefits. Many seniors enjoy group exercise programs where they have a chance to interact with fellow exercisers of all ages. Even for those individuals who prefer to be active alone or with a partner, physical activity can help them retain the strength and stamina necessary for playing an active role in everyday life.

Additional comment: One of the areas in which more scientific research is needed pertains to the specific mode, intensity, and duration of exercise and physical activity needed to bring about a particular clinical outcome. When approached by an older person with a specific disease or condition, it is especially important for a clinician to recommend an exercise or activity regimen that has been shown to be effective in the treatment and management of that particular condition. For example, when approached by an older woman with osteoporosis who was looking for an exercise program to increase her bone mineral density, it would probably not be optimal to recommend a low-intensity walking and calisthenics program conducted at the local senior center. Clinicians should familiarize themselves with the variety of exercise and physical activity options available in their community and be prepared to work together with their patients to help identify the most appropriate choice for each individual. The online Exercise Assessment and Screening for You (EASY) screening tool, http://www.easyforyou.info/, is an excellent resource for clinicians wishing to tailor physical activity to the needs of a particular client.

Patient Question: Is Exercise Safe?

Clinician response: Yes! Almost everyone can find a safe and effective exercise program tailored toward his or her health status, physical activity goals, and personal preferences. It is far more risky to your health to be sedentary than it is to begin a program of light-to-moderate-intensity physical activity. The greatest risk is that your muscles will be sore in the first few weeks of an exercise program. There are some things that you can do to reduce these risks. Learn to read your body's signals. On days that your body feels tired or weary—take it easy. On good days, take advantage of your body and enjoy yourself! Once we learn how to read our body's signals and respect its needs, we get a better sense for how to adjust our activity programs as we grow older. Very few individual will be able to (or would want to) run or dance as energetically in their seventies as they could in their twenties. Many believe that the secret of successful aging is learning how to adjust to changing needs and circumstances while remaining an active and vibrant member of society.

Additional comment: While there are some risks associated with participation in regular physical activity, the risks of being sedentary are much greater! Physical activity risks are related to level of intensity, with lower-intensity physical activity being associated with the lowest risk. Low-intensity physical activity reduces the risks of injury and muscle soreness and may be perceived as less threatening than moderate-to-high intensity routines. While lower risk is associated with lower-intensity exercise, the consensus is that moderate

physical activity has a better risk/benefit ratio, and moderate-intensity physical activity should be the goal for older adults. Although speaking with a health care provider is always a good idea, the involvement of a primary care provider prior to beginning a program of physical activity may not always be necessary and depends on a person's health condition and the level of intensity and mode of physical activity they plan to pursue. The ACSM Best Practice Statement recommends that before starting or increasing their level of physical activity, older adults should have a strategy for risk management and prevention of activity-related injuries.

Recently, an online website has been developed to help older adults identify the physical activity program most suited for their personal needs, preferences, and health condition [50]. The EASY (http://www.easyforyou.info) is a tool developed to help older individuals, their health care providers, and/or exercise professionals identify different types of exercise/physical activity regimens that can be tailored to meet the existing health conditions, illnesses, or disabilities of older adults. The EASY tool includes six screening questions that were developed based on an expert roundtable and follow-up panel activities. The philosophy behind the EASY is that screening should be a dynamic process in which participants learn to appreciate the importance of engaging in regular exercise, attending to health changes, recognizing a full range of signs and symptoms that might indicate potentially harmful events, and becoming familiar with simple safety tips for initiating and progressively increasing physical activity patterns [51]. The EASY screening philosophy represents a paradigm shift from traditional screening, which excludes individuals from participating in exercise in favor of a more inclusive approach that tailors physical activity to meet the needs of virtually all older adults.

Patient Question: Am I Too Old to Exercise?

Clinician response: No! You are never too old to exercise! Physical activity has been shown to be of benefit for individuals of all ages including persons as old as 90 and 100 years. Many people just like you are active on a daily basis. You can find a physical activity program that you will enjoy, that will make you feel better, and that will increase your quality of life. Think about what you most like to do in life and what you hope to gain from being active. An exercise professional can help you to develop a physical activity program that will help you to achieve these goals.

Additional comment: It is increasingly clear that beneficial effects of regular physically activity can be observed at all stages of the life course ranging from the very young to the oldest-old. In recent years, many excellent and well-publicized studies have focused our attention on the benefits of regular physical activity in those cohorts of seniors who were previously thought to be "too old" or "too frail" to partake in physical activity. There are a number of reasons why the frail and the oldest-old tend to be the most sedentary members of society. First, many of the oldest-old do not think of themselves as candidates for physical activity. They are unaware of the many benefits that can accrue to them if they increase their physical activity levels, and they do not realize that many people just like them enjoy activity on a regular basis. Second, for many years, exercise and physical activity professionals were reluctant to expose the oldest-old to the rigors of even the most modest physical activity regimens. It is only recently that professional organizations and Institutional Review Boards have begun to recognize that the benefits of physical activity are much greater than the very small risks they pose. Third, many of the exercise and physical activity programs traditionally employed with the middle-aged and young-old are poorly suited for use with the frail and the oldest-old. However, there are now an ample number of effective evidence-based programs that have been proven to work in frail and older adult populations.

Patient Question: Do I Need Special Clothing and Equipment?

Clinician response: No! Special clothing and equipment are seldom needed. Safe and effective physical activity can be performed wearing comfortable street shoes and loose fitting everyday clothes. Effective strength training can be achieved with inexpensive equipment such as elastic bands and water-filled jugs.

Additional comment: Many older adults have significant discretionary income and are ready and willing to spend it on club memberships, exercise equipment, and clothing; however, many others are in less fortunate financial circumstances and do not have a lot of money to invest in physical activity. Clinicians should be sensitive to the resources available to their patients and tailor their advice and recommendations accordingly. In my own clinical experience, probably the most important equipment needed to maintain an active life style is a well-fitting pair of shoes, which are both comfortable and provide adequate cushioning to minimize the risk of muscle and joint injuries.

SUMMARY

Although no amount of physical activity can stop the aging process, there is strong evidence that regular physical activity can minimize the physiological effects of aging and increase active life expectancy by limiting the development and progression of non-communicative diseases and promote independency and quality of life in older age. A combination of aerobic and resistance training activities appear to be more effective than either form of training alone in counteracting the detrimental effects of a sedentary lifestyle on the health and functioning of the cardiovascular system and skeletal muscles. While there are clear fitness, metabolic, and performance benefits associated with higher intensity exercise training programs in healthy older adults, it is now evident that such programs do not need to be of high intensity to reduce the risks of developing chronic cardiovascular and

metabolic disease. Social support, self-efficacy, perceived safety, and regular feedback are important behavioral factors that can help increase the likelihood of an individual initiating and maintaining a regular program of physical activity. Physical activity risks are often related to level of intensity, but the risks associated with a sedentary lifestyle far exceed them.

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Part XIX

Epidemiology of Lifestyle-Related Diseases

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106 Epidemiology of Child and Adolescent Obesity

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CONTENTS

Defining Overweight and Obesity among Children and Young People 1271
Prevalence of Child and Adolescent Obesity 1271
Recent Trends in Child and Adolescent Obesity 1272
Population-Level Variations in the Prevalence of Obesity 1272
Age 1272
Ethnicity 1273
Socioeconomic Position 1273
Environmental Determinants of Child Obesity 1273
Implications for Health and Other Outcomes 1275
Cardiovascular Risk Factors 1275
Type 2 Diabetes 1275
Sleep Apnea and Asthma 1275
Nonalcoholic Fatty Liver Disease 1275
Life Expectancy 1276
Psychosocial Issues 1276
Economic Costs of Child Obesity 1276
Conclusions 1277
References 1277

In 2010, the International Obesity Taskforce (IOTF) estimated that approximately 1 billion adults worldwide were overweight, with an addition 475 million obese. Among school-aged children, overweight and obesity are estimated to affect approximately 200 million children. This chapter will review the rapidly changing prevalence of child overweight and obesity, variations in the prevalence of child obesity, key environmental determinants affecting youth eating and activity behaviors, and the health, social, and economic impact of the burden of obesity in young people.

DEFINING OVERWEIGHT AND OBESITY AMONG CHILDREN AND YOUNG PEOPLE

Body mass index (BMI) is a well-accepted measure of adiposity for children and young people [1] and is used extensively internationally. Several approaches of categorizing BMI to define overweight and obesity among children and young people have been developed and are important to acknowledge, particularly when comparing prevalence statistics across populations. The Centers for Disease Control and Prevention (CDC) [2], the IOTF, and the World Health Organization (WHO) [3] have all developed BMI-based definitions of overweight and obesity for child and adolescent populations, and these definitions have been used throughout the academic literature to describe the prevalence of overweight and obesity among populations.

Comparisons of the prevalence of overweight and obesity given by these measures suggest that the definitions give similar but variable results. Compared with the CDC definitions of overweight, the IOTF definitions give lower prevalence statistics of overweight for younger children and higher estimates for older children [4]. The WHO definitions for overweight and obesity give higher rates of overweight and obesity than the CDC and the IOTF definitions [5]. For example, the prevalence of obesity among New Zealand adolescents is 10% when defined by IOTF criteria and 14% when defined by WHO criteria [6]. Given these variable results, acknowledging how overweight and obesity are measured among children and young people is important when comparing population-level estimates.

PREVALENCE OF CHILD AND ADOLESCENT OBESITY

In 2004, it was estimated that the prevalence of overweight and obesity among school-aged children and adolescents was 10% globally [1]. Available data suggest that the prevalence of overweight and obesity is highly variable by country and region of the world with the highest prevalence observed in

the United States (>30% of children), followed by Europe (20%), and lowest in sub-Saharan Africa (<0.5%) [1]. The burden of childhood overweight and obesity has developed rapidly. Between the early 1970s and 2003, the prevalence of overweight (BMI for age ≥95th percentile) for 12- to 19-year-old adolescents in the United States increased threefold, from 6% to 18% [7,8]. Over the past 20 years, the prevalence of child obesity has increased 0.5% per annum in the United States and Brazil and nearly 1% per annum in Canada, Australia, and the United Kingdom [1]. Trends in childhood obesity follow closely with adult obesity. Between 1980 and 2008, the average BMI among adults increased markedly (approximately 0.5 kg/m^2 per decade), with the highest rates of adult obesity now in the United States and many countries in Oceania [9].

Data from the 2003–2004 National Health and Nutrition Examination Survey (NHANES) survey estimated the prevalence of overweight and obesity among American young people at >35% (IOTF) [10]. A national health survey of Mexican young people (10–17 years old) reported that approximately one-quarter of children were overweight or obese (IOTF), but children living close to the U.S. border had a much higher prevalence [11].

National survey data for the United Kingdom in 1997 reported 19% of young people (age 4–18 years) were overweight or obese (IOTF) [12]. A more recent survey in Ireland (2002) found that approximately one in four children (4–16 years) were overweight or obese (IOTF) [13]. Prevalence estimates in Europe are similar but variable with Northern European countries tending to have lower prevalence levels of overweight and obesity than Southern European countries [14].

Data collected in Australia in 1995 estimated the prevalence of overweight and obesity (IOTF) to be 20% for children aged 2–18 [15]. In New Zealand, the prevalence of overweight and obesity (IOTF) among children (ages 2–14 years) in 2007 was 29% [16] and for adolescents was 34% [6]. Smaller studies conducted in the Pacific have estimated the prevalence of overweight and obesity to be approximately 40% among Tongan adolescents and 30% among Indigenous Fijians [17].

RECENT TRENDS IN CHILD AND ADOLESCENT OBESITY

Several countries around the world have begun to report that the prevalence of child obesity has begun to stabilize. In the United States, there were no appreciable increases in the prevalence of overweight and obesity among children and young people between 2003 and 2006 [18]. Likewise, reports from Australia [19] and France [20] have reported minimal or no increases in the prevalence of child overweight/obesity in the early 2000s. Moreover, a decline in the prevalence of overweight among children in Switzerland was observed between 2002 and 2007 [21].

While these recent reports look promising for public health, it remains unclear as to why a leveling of childhood obesity may be occurring. Many countries have implemented numerous nutrition and activity interventions and policies to address the issue of childhood obesity and it may be that these are having an effect. Overall, however, it is probably too soon to assume that childhood obesity has reached a plateau and will not worsen.

There are numerous factors that affect population variations in the prevalence of obesity (see subsequent sections). While national averages in the prevalence of child obesity may not change year to year, these averages may not capture fluctuations among subpopulations who bear the greatest burden of obesity. In New Zealand, data from nationally representative samples showed that there were no changes in the prevalence of child overweight/obesity between 2002 and 2007 [16]. However, a smaller study of adolescents attending high schools in high deprivation areas of New Zealand experienced a significant increase in obesity alone, from 19% in 1997 to 31% in 2005 (average annual increase of 7%) [22]. In the United Kingdom, the overall prevalence of overweight and obesity was steady from 2002/2003 to 2006/2007, but the socioeconomic gradient in obesity widened [23]. Thus, relying on reports of national averages may result in a worsening of the problem for segments of the population at greatest risk.

Population-Level Variations in the Prevalence of Obesity

The extent of the obesity epidemic is more prevalent among certain population groups. Demographic characteristics and socioeconomic factors associated with the prevalence of child and adolescent obesity are described in the subsequent sections.

Age

Isolating the developmental stages or periods in which children and adolescents are likely to become overweight/obese has important public health implications for targeting prevention efforts, but reviews of the evidence suggest this is difficult to achieve [24]. Large epidemiologic studies generally suggest that the prevalence of overweight/obesity increases throughout childhood and adolescence, but these findings are not consistent. For example, among the young people (4–18 years) participating in the 1997 National Diet and Nutrition Survey (United Kingdom), the prevalence of overweight/obesity significantly increased with age among boys, but not girls [12]. Pooled data from the 2003–2006 NHANES surveys reported that 24% of 2- to 5-year-olds had BMI values indicating overweight/obesity compared with 33% among 6- to 11-year-olds and 34% among 12- to 19-year-olds [25]. Of more interest, a 5 year longitudinal study of overweight/obesity during adolescence in the United Kingdom found that, among their sample of nearly 6000 students (11–12 years at baseline), few new cases of overweight or obesity emerged during adolescence, suggesting that persistent obesity may develop prior to adolescence [26].

Ethnicity

Ethnic and racial disparities in child and adolescent obesity have been documented in most Western countries. In the United States, the prevalence of overweight (CDC) based on the most recent NHANES survey data is significantly higher among African American (21%) and Mexican American (21%) children compared with white children (15%) [25]. The prevalence of overweight has increased significantly among these two population groups of children in the United States between NHANES III (1988–1994) and NHANES 1999–2000, while no significant increases were observed among white children [8]. Studies involving Pima Indians (United States) show that the median BMI of Pima Indian children compares with the 90th–97th percentiles of the CDC reference values for the general population of American children [27]. In the United Kingdom, the prevalence of overweight and obesity is considerably higher among Indian (38%) and Pakistani (35%) boys and Afro-Caribbean (46%) and Pakistani (34%) girls than children in the general population (27% for boys and 28% for girls; IOTF) [28]. In New Zealand, the prevalence of overweight/obesity is highest among children of Maori and Pacific Island ethnicities, with >40% of Maori children and young people and >60% of Pacific children and young people meeting the definition of overweight and obesity (IOTF), compared with approximately 25% of those of European ethnicity [6,29].

One of the most discussed evolutionary theories explaining the ethnic disparities in obesity and type 2 diabetes is the thrifty gene hypothesis. The theory was first introduced by James Neel in 1962 [30] and poses that, over time, populations who were exposed to periods of famine experienced genetic changes to maximize their ability to store energy. When food is abundant, these populations would then store more energy, which would result in higher rates of obesity in the modern context. The theory continues to attract academic support and further research in some quarters, but there are several problems with this theory from biological and ethical perspectives. First, current evidence suggests that genetic variation among humans is homogenous [31]. While genetic variation is geographically structured, and certain ethnic population groups have long been geographically isolated, substantial overlap has occurred between populations meaning that ethnic populations do not have discrete genetic types [31]. Second, the obesity epidemic has occurred too rapidly for changes in the genetic makeup of a population to be a sole factor [32]. The obesity epidemic has become most evident over the past 30–40 years; complex genetic adaptations do not happen that quickly. Third, it has been argued that any contributions that genes make to the obesity epidemic did not adapt in response to periods of famine since severe famines have actually been very rare and mortality due to starvation has been very low [32].

Several criticisms of the thrifty gene hypothesis from an ethical perspective have been made and are important and relevant to public health [33]. First, reliance on hypotheses like the thrifty gene hypothesis to explain ethnic disparities in disease assumes that ethnicity is a proxy measure for genetics, and as a result, ethnicity becomes an unmodifiable risk factor for obesity. Second, the thrifty gene hypothesis also perpetuates attributions to ethnicity that may be explained by other overlooked social factors, such as socioeconomic factors. Last, discussion of the thrifty gene hypothesis precludes any prevention efforts that may be culturally appropriate or beneficial to susceptible populations. It is reasonable to conclude then that the thrifty gene hypothesis is contentious and has the potential to further widen ethnic disparities in health.

Socioeconomic Position

In economically developed countries, childhood obesity is inversely associated with socioeconomic status, while in less economically developed countries, the burden of obesity has affected young people in urban areas and more affluent families [1,14]. Findings from the 1997 National Diet and Nutrition Survey (United Kingdom) demonstrated that young people from poorer social classes were significantly more likely to be obese than those from the wealthier social classes [12]. Likewise, studies of household income [34] and parental education [35] also show inverse relationships between socioeconomic indicators and child obesity. Research is now emerging to document the effects of neighborhood deprivation on child obesity [6,29,36,37]. These studies demonstrate that children living in poorer neighborhoods are significantly more likely to be overweight, even when controlling for individual measures of socioeconomic position and other demographic characteristics.

ENVIRONMENTAL DETERMINANTS OF CHILD OBESITY

Unhealthy weight gain is simply understood as the consequence of an energy imbalance where people consume more energy than they expend. What is less simple to explain are the underlying causes of this energy imbalance. That is, why is the greater population suddenly (within the past few decades) eating more and exercising less? Given the short time period over which population body weights have increased, particularly for children, great academic interest has been devoted to understanding the environmental factors underlying the behaviors promoting increased body weights. Specifically, the focus has highlighted the changes in the availability, affordability, and marketing of unhealthy foods (e.g., fast food, soft drinks, snack foods, and sweets) and increasing opportunities for sedentary activities.

At the core of the major changes to population eating behaviors is the shift to the modern food system. A food system is the entire set of components that link agriculture to human consumption, including food production, processing/packaging, distribution/transport, and consumption. The modern food system is characterized by large-scale, industrialized production methods that emphasize high yields and

low price, globalized distribution networks, high processing and packaging, minimal cooking, and excessive waste [38]. This is in comparison with traditional food systems, which emphasize small-scale, limited, and seasonal production, local distribution networks, and home cooking with limited waste [38].

Food systems exert an enormous influence over how and what populations eat. The modern food system encourages the consumption of highly processed, convenience foods as these foods have a long shelf life and are more profitable than fresh foods [39]. Furthermore, multinational food companies invest heavily in food marketing; a large body of evidence demonstrates that marketing routinely promotes unhealthy foods and is extremely effective in changing human behavior [40].

This transition to our modern food system is recent. While the industrialization of the food system globally has occurred throughout the twentieth century, the most dramatic changes have occurred over the past few decades. Between 1950 and 2000, the number of farms in the United States decreased by >60%, while the average size of farms increased by more than half [41]. The vertical integration of farming was accompanied by an emphasis on producing corn and soy resulting in a massive loss of diversity of crops [41]. Corn and soy became cheap ingredients for animal feed and processed foods, and their abundant supply created a global market for highly processed, convenience foods and mass-produced low-priced meat [42]. Advances in intensive agricultural methods, biotechnology, and national and international policies also facilitated this transition.

Evidence of the impact of the modern food supply on the American diet is notable. Between 1970 and 1990, the consumption of foods and ingredients most commercialized (snack foods, fats, and sugars) increased in the United States, while consumption of fresh foods decreased (eggs and dairy) [43]. Approximately one-third of the total food budget for married couples in the United States is spent on commercially prepared foods outside the home [44], and fewer than half of all main dishes served during the main meals are "fresh" or "homemade" [45]. The impact of the industrialization of the food supply on population body weights is evident through studies of the nutrition transition in developing countries [46] and the effects of migration or urbanization in Western countries [47–50]. These studies consistently demonstrate that as the food supply becomes Westernized, population diets change dramatically and risks of obesity increase markedly.

Within Western countries, however, research of the impact of the immense changes to the food supply on child eating behaviors and obesity has largely been focused on behavioral aspects of nutrition and physical activity. Soft drinks and snack foods have received substantial attention with regard to child obesity given their ubiquity in the diets of young people. Findings from analyses of the U.S. Nationwide Food Consumption Surveys between 1977 and 1996 reveal that the total amount of energy consumed as part of meals decreased, while the energy consumed as snacks increased by >70% [51]. Furthermore, the proportion of energy that children consumed as fast food, soft drinks, candies and desserts, and modern snacks increased during this time span, while the proportion of energy consumed as fruits and vegetables; meat, fish, or poultry; and milk products all remained constant or decreased [51].

Research examining the role of soft drink consumption on child overweight and obesity is convincing. Soft drinks are thought to have a unique contribution to child and adolescent obesity given their high energy content, low satiability, pervasiveness in the environments of children and young people, heavy investment in marketing to this age group, and low cost. A meta-analysis by Vartanian et al. [52] found that soft drink consumption among young people was associated with increased energy intakes, increased body weights, and increased risk of other poor health outcomes (e.g., diabetes).

Snacks contribute approximately 20%–25% of energy to the total diet [51,53,54]. Analyzing data of 10-year-old children from the Bogalusa Heart Study, Nicklas et al. [55] found that consuming snacks and consuming low-quality foods were both positively associated with overweight status. The research on snacking, snack foods, and child obesity is suggestive but inconclusive in the contribution of snack foods to weight gain [56]. Overall, it is likely that the state of the science on the relationship between food intakes and child obesity is limited by inconsistent and weak dietary measures, a rapidly changing food environment (especially in the highly processed food categories), and the relatively narrow line of scientific inquiry, which attempts to attribute significant weight gain to single foods.

Like energy intake, energy expenditure is a key component of weight control. With regard to energy expenditure and child and adolescent obesity, the key limitation in the research is a lack of valid measures of energy expenditure that are feasible for population-level studies and that have been consistently used for monitoring purposes over an extended period of time. Factors like reductions in active transport and reductions in overall physical activity patterns have been suggested as having an important contribution to child obesity, but the overall effect is likely to be small [1].

The environmental changes encouraging sedentary behaviors among children and young people, particularly television viewing, appear to play a far more convincing role in child obesity. American children, on average, consume 3 h of television each day [57]. Television use is thought to promote unhealthy weight gain in numerous ways, e.g., by displacing time spent being active, affecting metabolic rate, increasing snacking behaviors while viewing, or increasing exposure to advertising for unhealthy foods. It has been estimated that up to one in three cases of child obesity is attributable to the effects of television advertising [58]. Numerous studies have reported a positive relationship between television use and child obesity [59,60]. At least one intervention study has demonstrated that reducing television use among young, overweight children results in healthier body weights [61].

IMPLICATIONS FOR HEALTH AND OTHER OUTCOMES

Obesity during childhood results in a wide range of poor outcomes for children and young people, some of which have long-term consequences. Obesity during childhood affects a young person's psychological well-being, physical health, and has long-term social and economic implications for the wider community [1,62,63]. Health implications of unhealthy weight gain during childhood affect most systems of the body, with reasonable evidence suggesting child obesity adversely affects the cardiovascular, metabolic, pulmonary, gastrointestinal, skeletal, and hormonal systems [63].

The poor outcomes for young people resultant from unhealthy weight gain are compounded by the persistent nature of obesity. That is, young people who become overweight are much more likely to remain overweight into adulthood [62]. Several longitudinal studies have shown that overweight occurring as early as 6 years of age is predictive of overweight well into adulthood [64–68]. In a cohort study of American young people, >80% of those who were obese at 10–14 years were obese as adults [68]. Similarly, 83% of Canadian young people who were obese during childhood (7–18 years) remained obese as adults, 22 years later [67].

Cardiovascular Risk Factors

Reviews of the health impacts of obesity consistently conclude that child obesity negatively affects the cardiovascular system [1,62]. A large study of 5- to 17-year-old children found that overweight was associated with poorer indicators of higher total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, and triglycerides, even among the younger children [69]. Additionally, there have been numerous studies that have suggested that childhood obesity predicts cardiovascular disorders later in life [70,71]. Findings from the Bogalusa Heart Study showed that overweight during adolescence persists into young adulthood and increases the risk of multiple cardiovascular risk factors [71]. Overweight adolescents were significantly more likely to have hypertension, high total serum cholesterol, high LDL serum cholesterol values, and low HDL serum cholesterol values at ages 27–31 years than their lean counterparts. It has been suggested, however, that child obesity does not independently predict adult cardiovascular events, rather it is dependent on the persistence of obesity into adulthood [72]. Given that such a high proportion of obese young people become obese adults, these distinctions may be less relevant for public health.

Type 2 Diabetes

Until recently, onset of type 2 diabetes among children and adolescents was extremely rare but has become more common in the wake of the obesity epidemic. Complications of type 2 diabetes include accelerated development of cardiovascular disease, renal disease, vision impairment, circulatory problems, and premature death [73,74]. Limited data that document trends in the incidence and prevalence of type 2 diabetes among children and adolescents suggest this is a rapidly growing problem affecting countries worldwide. For example, one study of a regional pediatric diabetes referral centre in Ohio found that the incidence of type 2 diabetes increased 10-fold between 1982 and 1994 [75]. A similar study in Arkansas also found a dramatic increase in the number of new cases of type 2 diabetes among youth between 1988 and 1995 [76]. This study also showed that youth with type 2 diabetes were significantly more likely to be overweight/obese compared with those with type 1 diabetes. Annual studies of hundreds of thousands Japanese school children have also documented increases in the incidence of type 2 diabetes that mirror the prevalence of obesity [77]. In 1975, there were between one and two new cases of type 2 diabetes per 100,000 per year, increasing to more than seven new cases per 100,000 per year in 1995. During this time span, the prevalence of obesity among the population also increased from <5% to >8%.

Sleep Apnea and Asthma

Sleep-disordered breathing is a well-accepted, but underacknowledged, complication of obesity in both children and adults. Several studies have documented that children and young people who are obese are at increased risk for sleep-disordered breathing and snoring [78–80]. The relationship between child obesity and asthma has also been documented [81–84], but the underlying mechanisms are less clear. This is an important point as much of the research on the relationship between obesity and asthma is based on cross-sectional research and it may be that children with asthma may do less physical activity or take medication that may affect weight gain. That said, at least one longitudinal study has found that the incidence of newly diagnosed asthma among school-aged children was significantly higher in those who were overweight compared with those who were not [83] indicating that the overweight precedes the onset of asthma.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is a largely asymptomatic condition in which fat is deposited into the liver, which is not attributable to alcohol use. NAFLD is one of the most common liver conditions affecting children [85] and is considerable more problematic among obese young people. It has been estimated that NAFLD affects approximately 10% of children and adolescents; among obese young people, up to 80% are affected [86]. The most effective therapeutic strategies for NAFLD are lifestyle modification, similar to what is indicated for weight loss. Exercise and dietary changes, which result in weight loss can result in significant improvements in the progress of NAFLD [1,86].

Life Expectancy

The increasing prevalence of obesity and its health-related complications pose a serious threat to life expectancy. It has been projected that obesity could stop or decrease the mean life expectancy in the United States that has been on a slow, steady increase for a thousand years [87]. In a cohort of American Indian children without diabetes, rates of death (from endogenous causes) among the heaviest children were more than double that of the leanest children over time [74]. This has serious implications for the current generation of children and adolescents as they may, on an average, live shorter lives than their parents. Among adults, the risk of death from all causes increases with BMI throughout the overweight classifications [88], but this area of research is the topic of ongoing debate. A systematic review of cohort studies found better health outcomes among adults in the overweight and mildly obese groups [89], though the authors suggest that this was likely due to the limitations of the BMI as a specific measure of adiposity rather than a reduced risk attributable to adiposity. Another study of a nationally representative sample of adults in the United States found that the association between BMI and mortality varies by cause of death [90]. For example, being overweight was associated with a decreased risk from all-cause mortality, but an increased risk of death from diabetes and kidney disease combined.

Psychosocial Issues

Obesity during childhood and adolescence can result in numerous psychological and social issues that present an immediate and ongoing concern for young people. Depression is common among adolescents and can persist into adulthood. Given that adolescence is a critical period for the development of both depression and obesity, research has been unclear as to whether depression is a risk factor for later depression or vice versa. A recent meta-analyses of 16 studies found that depression during adolescence was a significant predictor of adult obesity, particularly among females [91]. Conversely, a longitudinal study of adolescents found that obesity was predictive of depressive symptoms (but not clinical depression) in the following year [92]. Thus, identifying the direction of the relationship between depression and obesity is difficult, but available evidence suggests that adolescent obesity is a risk factor for depressive symptoms among young people.

Children and young people who are overweight experience numerous difficulties with peer relationships and social stigmatization. As early as the 1960s, research revealed that young children viewed overweight body shapes negatively (e.g., lazy, naughty, mean, and dirty) [93]. A nationally representative survey of Canadian young people found that overweight young people were more likely to be the victims of bullying, teasing, and violent behaviors than their healthy weight peers [94]. Furthermore, overweight young people who experience weight-based teasing and bullying are at greater risk for disordered eating behaviors, depressive symptoms, anxiety, and low self-esteem than those who are not teased [95].

Recently, several population-based studies have documented that overweight young people are significantly more likely to engage in weight-control behaviors, especially unhealthy weight-control behaviors, than healthy weight or underweight young people [96–98]. Weight-control behaviors are pervasive among adolescents and include a wide spectrum of behaviors from eating more fruits and vegetables to purging or starvation [99,100]. Adolescent dieting results in psychological, physical, and nutritional disturbances with limited sustained benefits to body weight. Adolescents who employ extreme dieting behaviors have high levels of depression and anxiety [101] and are more likely to develop suicidal behavior into young adulthood [102]. Likewise, adolescents adopting unhealthy weight-control behaviors have poorer nutrient intakes [103] and poorer eating behaviors [104]. Adolescents who diet are more likely to develop binge eating behaviors [105] and gain more weight [106] over time. Approximately 20%–25% of unhealthy dieters develop partial or full syndrome eating disorders [107].

Health-related quality of life is a multidimensional concept, which captures a person's subjective view of their physical, emotional, and social well-being. Children and young people who are obese report markedly lower ratings for all dimensions of quality of life [108–111]; one study found that obese children reported the same level of quality of life to children with cancer [109]. The dimensions of life that appear to be most affected by obesity are physical competencies, appearances, and social functioning [108]. The long-term impact of obesity during childhood on health-related quality of life is largely unknown, yet emerging studies suggest that treatment of obesity results in better quality of life for young people. A 4 week weight loss program for adolescents demonstrated that weight loss is associated with improvements to quality of life [112]. Moreover, a study of the effectiveness of laparoscopic adjustable gastric banding of severely obese young people resulted in significant weight loss as well as significant improvements on indicators of quality of life [113].

Economic Costs of Child Obesity

The most recent estimates suggest that the medical costs of obesity in the United States are close to $150 billion [114]. Direct costs of adult obesity account for 2%–7% of total health care costs in developed countries [115]. Identifying the economic burden of child and adolescent obesity alone is difficult to do given the few medical treatments provided for child obesity, the inconsistent recording of body weights during clinical assessment, and the undiagnosed related disorders [1]. Between 1979 and 1999, hospital discharge records documented drastic increases in obesity-related diseases among children adolescents [116]. Available research has confirmed that obese children and young people have higher health care costs than normal-weight young people, including greater expenditures on prescription drugs and emergency room visits [117].

Indirect costs of obesity—those related to reductions in economic opportunity—are also difficult to quantify for children and young people because the contribution that children and young people make to an economy is variable. It has been suggested that child obesity may have high indirect costs through time off of school for illness or costs to schools and the education system for special resources [1,63]. Indirect costs of child obesity may also be quantified through parental time off work to care for a sick child or costs of premature death due to early onset obesity.

Child obesity may also result in high intangible costs which, again, are difficult to quantify. As mentioned earlier, losses in quality of life and psychosocial stresses may result in an economic burden resultant from childhood obesity. Furthermore, several studies have demonstrated that obesity during adolescence is also associated with less educational achievement [118–120] and lower earning potential as adults [119,120].

CONCLUSIONS

Given the poor outcomes for children and young people who are overweight, the persistent nature of childhood obesity and the costs of the burden to the wider population, strategies to prevent or treat obesity early on are warranted. Though there has been some suggestion that the prevalence of child obesity may be stabilizing, it would be prudent to ensure disparities in obesity-related behaviors and health disorders were not worsening. Targeting the excessive consumption of highly processed and unhealthy foods, promoting physical activity, and reducing the excessive use of sedentary behaviors (e.g., television) appear to be the most relevant behaviors for maintaining healthy body weights. Early treatment of obesity could have wide-ranging and long-term benefits as many of the adverse effects of childhood obesity could be ameliorated if the obesity were resolved prior to adolescence [110]. Child and adolescent obesity is one of the most urgent and important health issues facing the current generation of young people and, if unabated, will continue to bear a great cost to the health and well-being of young people, their families, and the wider community.

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107 Epidemiology and Prevention of Type 2 Diabetes

Edward W. Gregg, PhD

CONTENTS

Introduction 1281
Diabetes Definitions, Etiology, and Burden 1281
Explaining Recent Trends in Diabetes 1283
Evidence for Prevention 1284
Translation of Intervention Evidence: A Pyramid for Prevention of Diabetes and Its Complications 1285
References 1286

INTRODUCTION

Diabetes has emerged as one of the most important global health threats due to its increasing prevalence and the excess disease and economic burden that its comorbid complications carry with it. The current type 2 diabetes problem is a prototypical chronic disease epidemic in that its rise appears to be linked to cultural change, and its public health response will have to be multifactorial. New surveillance reports indicate that at least 11% of American adults (or 25.6 million) now have diabetes and prevalence approaches 20% among minority ethnic groups [1–2]. The rate of new cases continues to increase substantially (Figure 107.1). This, when combined with continued decreases in mortality rates [4], has led to projections that the proportion of adult Americans with diabetes will exceed 20% of the adult population by the year 2030 [5]. The implications of this increased diabetes on morbidity of the population is extensive due to the well-documented risks of coronary heart disease, stroke, vision loss, amputation, end-stage renal disease, and mortality, as well as nontraditional outcomes ranging from dementia to certain cancers [6,7]. Although type 2 diabetes appears to develop through multiple physiological mechanisms and numerous risk factors, increases in obesity, aging, and detection are the predominant factors in the ongoing increases in type 2 diabetes incidence observed both in the United States and worldwide [5,8]. Fortunately, strong evidence exists for the role of lifestyle interventions, when applied to high-risk adults, to reduce type 2 diabetes incidence by 50% or more [9–11]. In this chapter, we review the primary modifiable risk factors for type 2 diabetes, the factors explaining the current trends in the disease, and the health system and policy-based interventions most likely to impact trajectories in the current epidemic.

DIABETES DEFINITIONS, ETIOLOGY, AND BURDEN

Diabetes is a metabolic condition characterized by high levels of blood glucose due to impaired insulin production or action, or both [12]. More than 90% of diabetes cases are type 2, which is typically preceded by insulin resistance, wherein the body's cells don't use insulin properly. Although type 2 diabetes has received the most attention for its increasing incidence, type 1 diabetes, characterized by a virtual lack of insulin production, and gestational diabetes (GDM), defined as glucose intolerance only occurring during pregnancy, have both increased in frequency in the United States and many regions of the world [13,14]. Diabetes is diagnosed when one has an elevated fasting plasma glucose (FPG; ≥126 mg/dL), a postchallenge or random blood glucose >200 mg/dL, or an elevated hemoglobin A1c (≥6.5%) on two separate occasions. Prediabetes, a condition referring to elevated glucose levels below the diabetic threshold, associated with subsequent diabetes and macrovascular morbidity, is defined as FPG 100–125 or an A1c of 5.7%–6.4% or a 2 h plasma glucose in a 75 g oral glucose tolerance test (OGTT) 140–199 mg/dL.

The pathogenesis of type 2 diabetes is complex, involving at least 20 genes, diverse pathophysiological processes, and multiple environmental exposures [15,16]. However, for the vast majority of cases of type 2 diabetes, excess adiposity plays a central role, leading to excess nonesterified fatty acids, release of proinflammatory cytokines, which affects insulin action on cells, and ultimately affecting beta cell function. Excess glucose ultimately results from a failure of insulin secretion to adequately compensate for declining insulin sensitivity [15,16].

Consistent with its role in the pathogenesis of type 2 diabetes, obesity is the strongest modifiable risk factor for type 2 diabetes. Each standard deviation of body mass

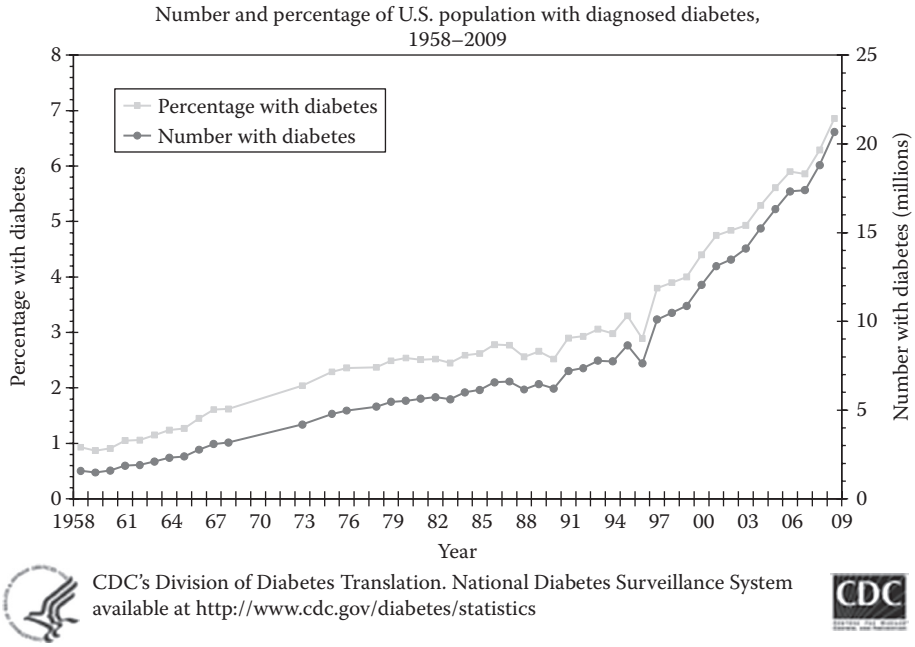


FIGURE 107.1 Number and percentage of U.S. population with diagnosed diabetes, 1958–2009.

index (BMI) (about 3–5 kg/m^2 in most populations) or waist circumference (about 10 cm) is associated with an approximate 80%–90% increased risk of type 2 diabetes [17,18]. In the United States, diagnosed diabetes incidence ranges from about 0.2% per year among normal weight adults to about 0.5% (2.2 times as high) among overweight adults to about 1.7% per year among obese adults (i.e., eight times as high) [4]. Increasing age also carries a large magnitude of diabetes incidence, since incidence increases from 0.3% per year among adults aged 18–44 years to 1.1% (i.e., three times as high) per year among those aged 45–64 years, to 1.3% (i.e., four times as high) among those aged 65 years [4]. As a result, compared with young adults, the prevalence is about three times as high among middle-aged adults (13.7%) and seven times as high among older adults.

After obesity and age, physical inactivity, poor diet, hypertension, and non-white race/ethnicity are the next set of common risk factors that carry a high magnitude of risk. Increasing physical activity levels [19] has been consistently associated with a reduced incidence of type 2 diabetes. Although part of this relationship is explained by obesity, moderate intensity physical activity is associated with reduced risk even after adjusting for BMI [19]. The relationship appears to follow a dose-response relationship with energy expenditure and total duration of physical activity. People who engage in more vigorous physical activity appear to have a particularly reduced incidence, but whether that reduction in risk is truly independent of energy expenditure has not been confirmed. In other words, people who engage in more vigorous physical activity may have a greater reduction in risk because they also spend more time in physical activity.

Having a family history, known hypertension, low birth weight, being a smoker [20], having depressive symptoms [21], dysfunctional sleep [22], and exposure to environmental pollutants have each been associated with elevated type 2 diabetes risk [23], while coffee intake and moderate alcohol consumption have each been associated with decreased risk [24]. However, there have not been intervention studies to determine whether acting upon any of these risk factors with specific interventions is effective or practical. Modification of smoking risk, for example, may actually lead to some weight gain and thus counteract the benefit of removing smoking as a diabetes risk factor [20]. Similarly, there is no evidence that treating hypertension, depressive symptoms, or poor sleep influences disease risk although each is plausible.

Several nutritional factors may influence insulin resistance or type 2 diabetes risk above and beyond their effects on obesity [25]. Some of the most consistent findings exist for whole grains and cereal fibers, as consuming at least 8.8 g/day (the highest quintile) has been associated with a 37% lower diabetes risk than those who consume fewer than 3.8 gm/day (i.e., the lowest quintile) adjusting for other nutritional and body composition factors [26,27]. The quality of fats in the diet also appears important; consumption of polyunsaturated and monounsaturated fats may reduce risk, whereas saturated fats and total intake have been associated with increased risk [25].

Consumption of sugar-sweetened beverages (SSBs), including soft drinks, sweetened carbonated beverages, and fruit drinks, have more than doubled in the U.S. population over the past two decades and have been implicated as important risk factors for obesity, insulin resistance, and type 2 diabetes [28,29]. Several mechanisms have been proposed for linking SSBs and type 2 diabetes, including inadequate satiation of SSBs leading to greater compensatory and overall caloric consumption, along with hypotheses that SSBs have direct effects on insulin resistance through their glycemic properties. Longitudinal evidence is, however, spotty.

Data from the Nurses' Health Study found that women reporting more than seven servings per week of SSB had an 80% greater diabetes risk than those reporting <1 serving/week [30]. However, other cohort studies found only modest or nonexistent associations with diabetes risk. There is also insufficient evidence from randomized control trials that replacing SSBs or supporting policies of SSB reduction will result in appreciable reductions in type 2 diabetes incidence [28,29].

Type 2 diabetes is strongly associated with family history and genetics. Numerous common genetic markers have been identified, many of which have significant but modest associations with type 2 diabetes incidence [31]. In a study of 18 single-nucleotide polymorphisms among adults in the Framingham Heart Study, a genotype score was developed and shown to be highly predictive of subsequent diabetes, such that persons within the top decile of a continuous genotype score had about two and half times the incidence of adults in the bottom quarter of the genotype score. However, the ability of the genotype score to discriminate between cases and non-cases was only slightly more predictive than a conventional risk score composed of self-reported risk factors along with glucose and triglyceride levels. Genotype-based scores may still become an important part of risk prediction in the future, but this is likely to depend upon a better understanding of how genes interact with lifestyle and environmental factors.

Estimation of county-level diabetes prevalence indicates that diabetes in the United States appears to cluster within specific regions and belts (Figure 107.2). Counties with a high diabetes prevalence (defined by diagnosed diabetes prevalence >10.6%) were clustered in a belt extending from the Mississippi river valley in the South to the coastal Carolinas and the Appalachian Mountain region. Almost three-fourths of counties in Alabama, Georgia, Louisiana, Mississippi, and South Carolina had high diabetes prevalence, while almost two-thirds of counties in West Virginia and Tennessee had high prevalence. In addition, counties in the Western and Plains states with large populations of Native Americans also have high prevalence. This clustering of counties with high diabetes prevalence is largely a function of the classic factors described earlier. However, high levels of poverty both at the individual and community level appear to play a particularly important role in increasing the amount of clustering of diabetes risk [32,33].

In addition to the multitude of risk factors for type 2 diabetes described earlier. Presence of elevated FPG (100–125 mg/dL), impaired glucose tolerance (IGT) or A1c are associated with yearly diabetes incidence of 2.5%–3%, compared with about 1% per year in the overall population and <0.5% per year in people with normal glucose tolerance [34]. As will be described in more detail in the subsequent sections ("Translation of Intervention Evidence" section), measures of glycemia and GDM are increasingly recommended as efficient ways to risk stratify the population for intervention referral.

EXPLAINING RECENT TRENDS IN DIABETES

Despite the large number of risk factors explaining variation in type 2 diabetes risk for individuals, the principal factors underlying increases in type 2 diabetes in the population as a whole are not necessarily the same factors that explain risk in individuals. For example, exposure to several of the risk factors for type 2 diabetes, such as smoking levels, saturated fat intake, or organic pollutants, are unlikely to explain the recent increases in incidence in the population because exposure to those factors have been declining steadily for several

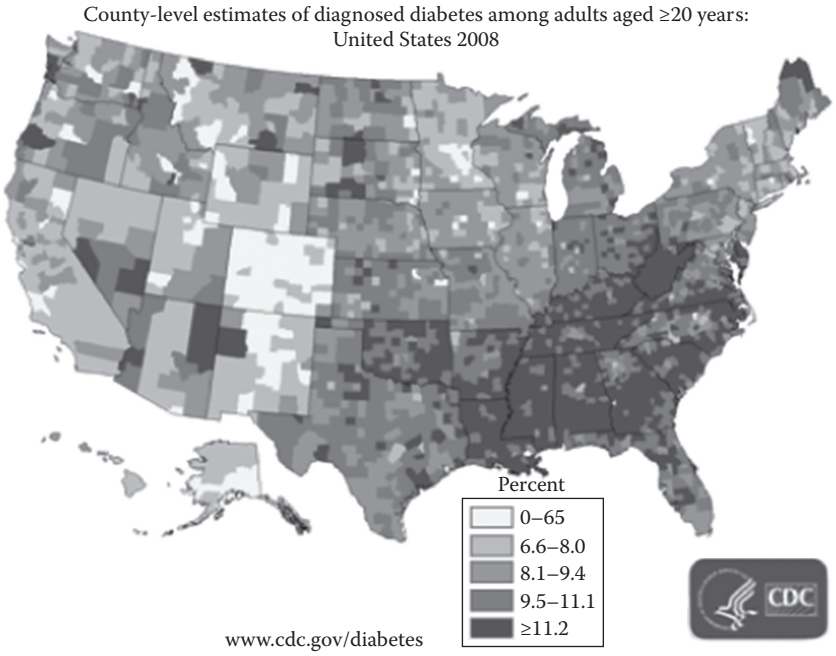


FIGURE 107.2 County-level estimates of diagnosed diabetes among adults aged ≥20 years: United States 2008.

decades. Even the contribution of physical activity levels to the changes in type 2 diabetes prevalence is unclear. However, it appears that the increase in obesity occurring in virtually all segments of the population has explained the majority of prevalent and incident cases. When diabetes prevalent cases are partitioned into BMI categories, it is apparent that 25% of new cases relative to the previous decade came from the overweight segment of the population, 75% came from the obese population, and none of the increase came from the lean population [35]. This is consistent with a similar analysis showing that, within BMI strata, there has been no increase in diabetes risk; instead, there are simply many more people with moderate and severe obesity [36].

Several secular trends and cultural factors have been proposed as possible explanations for the change in obesity of the population, including increased portion sizes [37–39], refined carbohydrates and corn syrups, and increased SSBs. Sleep duration has decreased, and treatment for depression using s*elective serotonin reuptake inhibitors* have increased dramatically, but whether and how much these have affected obesity or diabetes trends is not known.

In addition to the behavioral and social factors affecting diabetes incidence rates through their impact on obesity, the increases in diabetes prevalence in the adult population may have also been fueled by increases in the detection rate of undiagnosed diabetes, declining mortality of the diabetic and nondiabetic populations, and possibly increases in the immigration patterns, increasing the proportion of higher-risk ethnic groups in the United States [40].

EVIDENCE FOR PREVENTION

The observational evidence associating lifestyle factors with type 2 diabetes risk led to a series of large randomized controlled trials beginning in the late 1990s [9,41]. To ensure adequate number of events (i.e., incident diabetes cases) in these trials, virtually all were conducted among high-risk populations, defined as presence of IGT and/or elevated FPG. To maximize intervention effectiveness, most studies tested multifactorial interventions, combining reduced caloric intake, increased physical activity, increased fiber and whole grain intake, etc. [9–11,41].

The first randomized trial of lifestyle intervention screened the entire adult population of Da Qing, an oil city in Northeastern China, to find adults with IGT [42]. Thirty-three clinics were then randomized to four conditions: control, diet, exercise, and diet plus exercise. The dietary intervention involved counseling to reduce fat, simple sugars, and alcohol intake, while the exercise condition involved counseling to increase moderate and vigorous leisure-time exercise and sports activities. The study found significant 31%, 46%, and 42% reductions in type 2 diabetes incidence in the diet, exercise, and diet plus exercise conditions, respectively. The study was also notable, however, in that it was conducted among a fairly young population and, more importantly, had its effects with essentially no weight loss achieved over 6 years by the intervention conditions [42].

Four and five years later, findings from the Finnish Diabetes Prevention Study (DPS) and the U.S. Diabetes Prevention Program (DPP) were published [10,11]. Each study randomized adults with IGT to intensive group and individual-based lifestyle interventions, defined by reduced total and saturated fat intake and increased leisure-time physical activity and behavioral support. The Finnish study was also notable in that it employed a high fiber diet. Both studies achieved 58% reductions in diabetes incidence. The benefits of lifestyle interventions were observed across diverse age, sex, and race-ethnic groups. Follow-up studies reported by both studies [43,44] highlighted the importance of modest weight loss (7 and 4.2 kg at year 1 in the DPP and DPS, respectively) as a central factor along with the importance of the multifaceted aspects of the interventions. In the DPS, for example, the number of goals achieved was strongly inversely associated with the incidence of diabetes, such that incidence was about 8% per year for those meeting zero goals, about 5% per year for those meeting two goals, and about 2% per year for those meeting four or more goals [45,46].

In subsequent years, similar studies were published from Japan [47], India [48], Iran, and Italy [49,50]. These studies further expanded the geographic scope of evidence of these trials, indicating that structured, lifestyle interventions can be effective in diverse settings and populations. Formal quantitative meta-analyses have estimated that lifestyle interventions result in a 49% reduced incidence of diabetes, a magnitude of risk reduction that is significantly stronger than the effect observed with pharmacologic interventions [9,41]. Further, of all the putative benefits of a healthy lifestyle, the magnitude of effect from these studies is arguably the strongest effect of lifestyle interventions observed for any chronic condition. Common characteristics of these interventions included an intensive, multi-visit educational curriculum covering 6–12 months and an extended period of counseling support for 2 years of more. Perhaps, most importantly, the successful programs employed a comprehensive set of behavioral strategies, including staging of information over multiple sessions, tailoring of lifestyle change to the individual, observational learning for dietary change, and self-monitoring of key behaviors and goals.

Three of the lifestyle intervention trials have examined the extended impact, or the "legacy effect," of lifestyle interventions several years beyond the completion of the primary intervention [43,44,51]. The Finnish DPS found that 4 years following the completion of the trial (7 years from baseline), adults randomized to the intervention condition still had a significant 43% reduction in diabetes incidence [43]. The Da Qing DPS found that 14 years following the intervention (20 years after baseline), intervention was still associated with a 43% reduction [51]. Most recently, the DPP reported a 24% reduced incidence 8 years following the completion of the trial (10 years after baseline). Only one of these trials has reported effects on long-term complications of diabetes. Gong et al. reported a significant reduction in incidence of severe retinopathy associated

with the intervention, a nonsignificant reduction in cardiovascular disease (CVD) mortality but no association with CVD incidence [52].

At the same time, the limitations of these studies limit the implications and raise other questions. First, all studies were limited to the selected adult population with IGT and, in some cases, people with impaired fasting glucose and IGT. Thus, it is unknown whether structured lifestyle interventions also reduce incidence of prediabetes or progression in people below the prediabetes threshold, leading to debate about who should be identified for interventions. Second, the degree to which implementation of the isolated subcomponents of the diabetes interventions can also be expected to affect risk is not known. Although post hoc analyses indicated that meeting individual goals reduces risk, it should not be interpreted as an indication that implementation of single component interventions will be similarly effective. This has led to debate about whether dietary or exercise interventions in the absence of multidisciplinary behavioral support are likely to be effective uses of resources. One randomized controlled trial of high-risk adults randomized to Mediterranean diets had 52% reductions in diabetes incidence. These data, combined with findings from the Da Qing Prevention Study, suggest that dietary interventions can be effective without an aggressive weight loss component [53].

The evidence for type 2 diabetes prevention has led to considerable debate about how best to identify people for public health interventions. Although most of the prevention trials used OGTTs to identify people with IGT, many consider OGTTs to be impractical and IGT unnecessarily exclusive for practical real-world interventions. Fasting blood glucose and A1c are commonly accepted alternatives as are multicomponent risk scores that use demographic, behavioral, health status, and glycemic data to separate screened populations into those at low and high risk of subsequent diabetes. Others have begun to explore multicomponent assays that incorporate several metabolic markers, including inflammatory factors, insulin, and glucose into prediction scores.

TRANSLATION OF INTERVENTION EVIDENCE: A PYRAMID FOR PREVENTION OF DIABETES AND ITS COMPLICATIONS

Changing the course of the diabetes epidemic will ultimately require a multi-tiered strategy in which evidence-based interventions are tailored to the level of risk and morbidity (Figure 107.3). The principal objective among the 19 million adults who already have diagnosed diabetes is to reduce the incidence of diabetes complications and related morbidity by improving diabetes management and achieving optimal levels of glycemic, blood pressure, and lipid control and performing regular screening for early foot, kidney, and eye disease. The second tier involves efficient early identification of adults with undiagnosed diabetes so that the evidence-based therapies can be initiated to reduce the incidence of complications.

The remainder of the prevention pyramid (Figure 107.3) involves several tiers designed to reduce the incidence of type 2 diabetes. The first step involves efficiently identifying adults who are at high risk for the development of type 2 diabetes. While population-wide haphazard screening is not recommended, diagnostic testing of adults with risk factors (family history, overweight or obese, age >45 years, hypertension, non-white race/ethnicity, or history of GDM) is recommended to identify people with prediabetes or undiagnosed diabetes. Those with prediabetes or a history of GDM (primary prevention tiers 1 and 2) should ideally be referred to community-based structured prevention programs to reduce their risk.

The Centers for Disease Control and Prevention has recently developed a recognition program to promote and certify evidence-based prevention programs for community settings. As a prototype for such an approach, it has

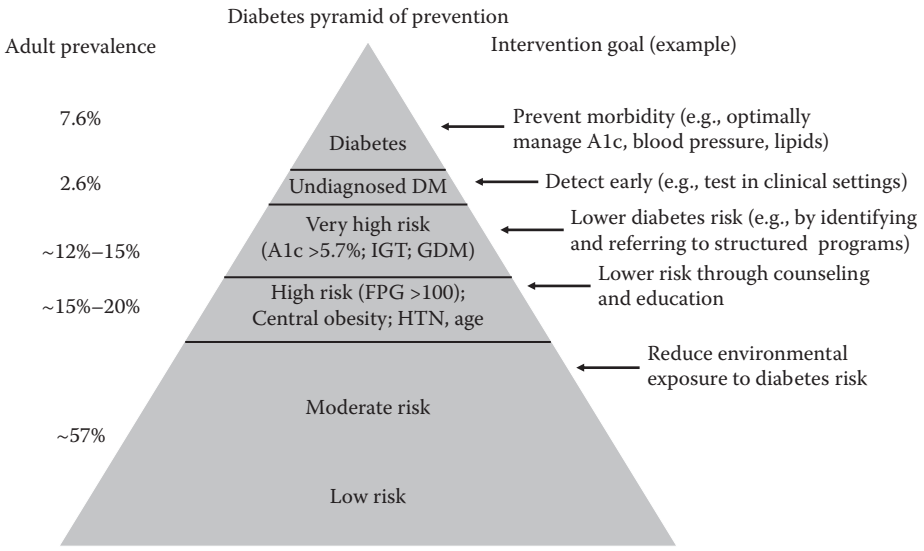


FIGURE 107.3 Diabetes pyramid of prevention.

also partnered with the national Y (formerly YMCAs) and United Health Care to provide reimbursement and a centrally recognized training and recognition program of prevention programs. The *National Diabetes Prevention Program* is based on observations that structured lifestyle programs in community settings such as Ys YMCAs and churches have achieved 1 year weight loss ranging from 2% to 7% among adults at high risk for diabetes [54–56], levels of weight loss that have been consistently associated with reduced diabetes incidence. Since access to effective community programs for diabetes is lacking in many parts of the United States and reimbursement remains spotty, it is important for primary care settings to enhance efforts at awareness, counseling, and referral to program with trained staff to stimulate and support changes in lifestyle to achieve a healthier diet, weight, and pattern of regular physical activity.

Since the majority of the population and roughly half of eventual diabetes cases over a 10 year period will come from the population without established prediabetes or GDM, additional population-wide strategies will be necessary to change incidence trends. At least three general targets of population-wide policy targets exist: the food environment, the physical environment, and the social environment. Plausible interventions for the food environment include food and menu labeling, crop subsidy and pricing strategies to encourage whole grain content of foods and healthy portion sizes and discourage refined carbohydrates, sugared sodas, and saturated fats. Incentives for communities to support diverse healthy foods and farmers markets have also been proposed. Policies recommended to improve the food environment included increasing availability and affordability of healthy foods in public areas, improving geographic availability and giving incentives for supermarkets and healthy foods in underserved and poor areas, instituting smaller portion sizes in public settings, limiting advertisements of unhealthy foods and beverages, and discouraging consumption of sugared beverages. Changes to the food environment may ultimately require direct engagement with private industry to change the content of available foods in grocery stores. Recommended strategies to improve the physical activity environment include requiring school physical education and increasing the amount of physical activity in school physical education, increasing opportunities for extracurricular physical activity and access to recreational facilities, reducing screen time in public settings, improving access to public transportation, promoting access to mixed use development, and enhancing personal and traffic safety in public areas [57].

Unfortunately, rigorous research that would support the prioritization of the multitude of policy-level interventions that have been proposed is lacking. Although numerous innovative policies are regularly developed by health systems, communities, business organizations, and legislatures, rigorous empirical examinations of such initiatives are scarce. As a result, there are few clear evidence-based policies for preventing or controlling the progression of diabetes that can be targeted at large segments of the population [58–61]. This has led to calls for new research platforms, including natural experiments and comparative effectiveness research for health services interventions to improve the science base for health system and policy-level interventions. Ultimately, changing the course of the current diabetes trends will require improvements in both the evidence base as well as the delivery of established interventions across individual, health system, and societal levels.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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108 Physical Activity and Aging

Caroline A. Macera, PhD

CONTENTS

Introduction 1289
Who Is an Older Adult? 1289
Concept of Health as Applied to Aging 1290
  Quantity versus Quality of Life 1290
  Disability 1290
Chronic Diseases and Physical Activity 1291
  High Blood Pressure 1291
  Arthritis 1291
  Coronary Heart Disease 1291
  Cancer 1291
  Diabetes 1291
  Metabolic Syndrome 1292
  Osteoporosis 1292
  Depression 1292
How Much Physical Activity? 1292
Surveillance Data 1292
Measuring Physical Activity 1293
Barriers to Being Physically Active 1293
  Injury 1294
  Environmental 1294
  Urinary Incontinence 1295
  Arthritis/Osteoarthritis 1295
  Medication 1295
  Chronic Conditions 1295
  Surgery 1295
  Cancer Treatments 1295
  Obesity 1295
Summary 1296
References 1296

INTRODUCTION

The purpose of this chapter is to synthesize the existing literature on physical activity as it applies to older adults. In the process of doing this, there are several concepts that need to be explored. First of all, the term "older" adult will be discussed and the question of how to apply a standard definition when the field and the participants are so diverse. Next, the concept of health as applied to aging will be discussed, and the focus will be on measurements issues. Paramount among these ideas will be the concept of length of life versus quality of life and the important role of physical activity at every stage. To explore this, the type and form of physical activity that can accommodate aging-related physical changes and comorbidities will be shown for the most common chronic conditions. Surveillance data will be used to identify declines in physical activity typically associated with aging, and when available, for adults with particular chronic conditions. The final section includes a discussion of the barriers to being physically active that are most relevant for older adults along with specific suggestions for dealing with these barriers and increasing physical activity.

WHO IS AN OLDER ADULT?

One of the challenges in working with the aging population is how to characterize these adults. While "years of age" is an easy marker, the differences that exist among individuals as they age preclude using chronological age as an optimal method to classify older adults. A more practical way would be to classify adults according to functional markers, which is possible to do for an individual but difficult to do on a population level. While age has many dimensions, surveillance

reports, such as those documenting physical activity, are limited to categorizing individuals by chronological ages or by presence of chronic conditions. The usual classification defines an older adult as age 65 years and older, although the exact cut point can vary.

The growth in the number and proportion of older adults is unprecedented in the history of the United States. Two factors—longer life spans and aging baby boomers—will combine to double the population of Americans aged 65 years and older during the next 25 years. Estimates suggest that by 2030, there will be 71 million American older adults (larger than the current combined population of the entire states of California, Texas, and New Jersey), and these older adults will comprise about 20% of the U.S. population [1]. Recognizing these trends, several public health initiatives (such as those designed to increase physical activity) are focused on keeping older adults healthy and active.

CONCEPT OF HEALTH AS APPLIED TO AGING

The diversity of older adults leads to another important issue: health. There are several ways to conceptualize health including absence of disease, absence of activity limitations, or physical and mental well-being, with each concept providing important information on some aspect of health. Whatever way health is conceptualized, measuring this construct is the challenge. For older adults, the assessment tool should take into account aging-related declines that may not be diseases but may contribute to a poor quality of life. Examples of contributors to poor health that are common among older adults are joint pain, visual problems, and hearing problems. Over one half of adults over age 65 years reported joint pain in 2009 [2]. In addition, 13% of U.S. adults over age 65 years reported visual problems and 7% reported having hearing problems or being deaf [2].

Because of this, assessing health status involves more than just documenting the presence of particular diseases but should include quality of life issues as well. Among the tools that have been used to measure overall health status is a survey item that asks adults to rate their health on a 5-point scale ranging from poor to excellent. This question can also be asked as "rate your overall health status for your age" or "rate your overall health status compared to others your age." The question without mention of age or comparison with others has been shown in numerous countries and populations to have an association with mortality such that those who rate their health as fair or poor have a higher mortality rate than those who rate their health as good, very good, or excellent [3,4]. Unfortunately, data from the United States in 2009 found that 24% of adults aged 65 years and older rated their health as fair or poor [2]. Among adults of any age, those who report a disability (defined as being limited in any activities because of a physical, mental, or emotional problem or a health problem that requires use of special equipment such as a cane, a wheelchair, a special bed, or a special telephone) are more likely to report fair or poor health than those without such a disability [1]. Adults aged 65 years and older reported an average of 5.5 physically unhealthy days in the past month according to 2004 Behavioral Risk Factor Surveillance System (BRFSS) data [1].

Quantity versus Quality of Life

Life expectancy in the United States has increased from 47 years for Americans born in 1900 to 78 years for those born in 2007. For adults who were already aged 65 years in 2007, the additional life expectancy was 19 years and for those already aged 75 years in 2007, the additional life expectancy was 12 years [2]. While all adults would like to extend their life spans, the goal should be not to live longer but to live healthier. This is where physical activity can be an important component of aging. It is known that several diseases develop or become worse due to physical inactivity. While these diseases (an example is arthritis) may not directly cause mortality, they play a huge role in quality of life. Data from 2008 to 2009 found that among community-living adults aged 80 years and older, 15% of women and 10% of men needed health with personal care activities (eating, bathing, dressing, getting in or out of bed or chairs, using the toilet, or getting around inside the home). The most common need for personal care activities was with bathing or showering or dressing [5].

Disability

One of the best measures of quality of life is the ability to live independently and perform necessary activities of daily living. However, over time, many adults develop functional problems that limit their ability to live independently. Because this process occurs in stages, it is useful to use a standard nomenclature to assess disability [6]. One system commonly used is the Nagi [7] classification of disability, which describes four stages beginning with pathology and ending with disability. These stages are shown in Table 108.1 using knee osteoarthritis as an example. While every person may incur some degree of impairment

TABLE 108.1
Stages of Disability and Example of Each Using Knee Osteoarthritis

Label	Description	Consequence
Pathology	Underlying changes have occurred with or without clinical symptoms	Joint changes in knee
Impairment	Dysfunction in specific body systems	Pain when bending knee
Functional limitation	Restrictions in physical/mental function	Unable to walk long distances
Disability	Unable to conduct activities of daily living without assistance	Unable to walk; may not be able to continue working

or functional limitation over time, the goal is to keep complications at a minimum to prevent or delay disability. Physical activity can play a major role in preventing disability, but among adults aged 65 years and older, only 26% are physically active compared with 42% of adults without disabilities [1].

CHRONIC DISEASES AND PHYSICAL ACTIVITY

Lifelong physical activity is important in maintaining functional health and independence. However, over time, the type and form of physical activity may change to accommodate related physical changes and comorbidities as well as age-related changes. About 80% of older Americans (aged 65 years and older) are living with at least one chronic condition [1], meaning that the type and intensity of physical activity must be modified to reflect presence of these conditions. The leading cause of death among adults aged 65 years and older is heart disease, followed by cancer, and stroke, while the most common chronic conditions are high blood pressure, affecting just over half of older adults, followed by arthritis, affecting about half of older adults. At lower prevalence, the rest of the top six chronic conditions include coronary heart disease and stroke, cancer, diabetes, metabolic syndrome, osteoporosis, and depression. Some of these conditions for which physical activity has been shown to be beneficial are described in this section.

High Blood Pressure

Also known as the silent killer, elevated levels of blood pressure are usually asymptomatic while causing major damage to many organs. High blood pressure is a major risk factor for stroke as well as coronary heart disease [8]. Data from 2005 to 2008 identified 70% of adults aged 65 years or older with elevated blood pressure. Although there is treatment to lower blood pressure, only 79% of those with elevated blood pressure were being treated. However, 46% of those with treated elevated blood pressure did not have it under control. In addition to medication, increasing physical activity is often recommended as a way to control blood pressure.

Arthritis

Although the term arthritis includes over 100 separate diagnoses characterized by joint degeneration, over 95% of all arthritis is osteoarthritis. Based on U.S. data from 2007 to 2009, about 50% of adults aged 65 years and older have arthritis and almost half of them (46%) have some arthritis-attributable activity limitation. Because there is evidence that sports injuries eventually lead to the development of arthritis at the site of the injury, many individuals assume that physical activity is not recommended. Just the opposite is true. Participation in physical activity keeps joints moving and flexible, bringing much needed blood circulation to the affected joint(s).

Coronary Heart Disease

Most of the early work on physical activity began with its role in preventing the leading cause of mortality, heart disease. Although the mortality rates have consistently decreased since the 1980s, coronary heart disease is still the leading cause of death among adults over age 65 years and continues to be a problem for older adults. The lifetime prevalence of coronary heart disease in 2009 for men was 31.2% among those aged 65–74 years and increased to 45.8% among those aged 75 years and older compared with 14.5% for those aged 54–64 years. The lifetime prevalence of coronary heart disease in 2009 for women was 21.1% for those aged 65–74 years, 30.7% for those aged 75 years and older, compared with 11.7% for those aged 45–64 [2]. Even at older ages and after the disease has developed, participation in physical activity reduces the risk of additional complications.

Cancer

Although there are many types of cancer, each with its own set of risk factors, physical activity has a documented effect on the development of cancer of the colon and the breast. There is a strong possibility that physical activity can reduce the risk of endometrial, lung, and prostate cancers. Cancer is one of the leading causes of death among older adults, and the number of people living with cancer increases with age. A lifetime prevalence of cancer among men in 2009 was found to be 4.8% among adults aged 45–64 years and increased to 18.9% among adults aged 65–74 years and to 22.7% among adults aged 75 years and older. Among women, the lifetime prevalence of cancer was found to be 15.3% for those aged 65–74 years, 16.9% for those aged 75 years and older compared to 8.7% compared to those aged 45–64 years [2]. These numbers reflect persons who were alive in 2009 and who had been diagnosed with cancer.

Diabetes

Diabetes prevalence increases with age. In 2005–2008, 4% of adults aged 20–44 years, 14% of those aged 45–64 years, and 27% of those 65 years of age and over had diabetes. From 1988–1994 to 2005–2008, diabetes prevalence increased among adults who were 65 years of age but not among adults 45–64 years of age [2]. Diet, weight loss, and medication have been used individually or together to control diabetes. For many years, it was assumed that physical activity had no direct effect on diabetes, but an indirect effect mediated by weight loss. However, meta-analyses and systematic reviews of the literature provide evidence that physical activity can have a beneficial effect on the control of diabetes and subsequent complications, even in the absence of weight loss [9]. In spite of these findings, a recent study found that older adults with diabetes were less physically active than similarly aged adults without diabetes and that the prevalence of physical activity among them decreased within each age group (65–70 years; 71–74 years; and 75 years and older) [10].

Metabolic Syndrome

The metabolic syndrome is usually defined as the presence of at least three of the following symptoms: fasting glucose at or above 110 mg/dL; blood pressure at or above 130/85 mm Hg; high density lipoprotein below 40 mg/dL for men and below 50 mg/dL for women; triglycerides at or above 150 mg/dL; or waist circumference more than 102 cm for men or more than 88 cm for women. People with this syndrome have an increased risk of developing and dying from chronic diseases, most notably, diabetes and cardiovascular disease. Data from the National Health and Nutrition Examination Survey III, 1988–1994, found that the prevalence of metabolic syndrome among adults aged 60 years and older was over 40% [11]. A physically active lifestyle can positively improve the symptoms associated with the metabolic syndrome.

Osteoporosis

Osteoporosis is a common problem among older adults that causes bones to become abnormally thin, weakened, and easily broken (fractured). Women are at a higher risk for osteoporosis after menopause due to lower levels of estrogen, a female hormone that helps to maintain bone mass. Estimates from the staff at the National Osteoporosis Foundation suggest that by 2010, about 12 million people over the age of 50 years are expected to have osteoporosis and another 40 million to have low bone mass. By 2020, the numbers are expected to increase to 14 million cases of osteoporosis and over 47 million cases of low bone mass. Hip fractures are one of the major problems associated with low bone density. Weight-bearing exercise, especially resistance exercise, can help to maintain bone mineral density among older adults.

Depression

A common mental health problem, depression, occurs in the United States and worldwide and often accompanies other chronic diseases. Although the prevalence of major depressive disorder is lower among older adults than younger adults (5% for adults aged 50 years and older compared with about 8% for adults aged 18–49 years), in 2009, 10% of men and 17% of women over age 65 years reported a prescription for antidepressant drugs [2]. Physical activity has been shown in numerous studies to be useful in preventing and managing depression and also to protect against development of subsequent depression [12].

HOW MUCH PHYSICAL ACTIVITY?

One question that is often asked pertains to how much physical activity is necessary for health benefits. While the exact amount and type of physical activity varies depending on a person's functional age, there are additional differences related to physical abilities and comorbid conditions. For healthy older adults with no limitations, a good approach is to follow the guidelines for adults as presented in the 2008 Physical Activity Guidelines project [13] and summarized in Table 108.2.

TABLE 108.2
Key Physical Activity Guidelines for Adults

General statement: All adults should avoid inactivity. Some physical activity is better than none, and adults who participate in any amount of physical activity gain some health benefits

- For substantial health benefits, adults should do at least 150 min (2 h and 30 min) a week of moderate-intensity or 75 min (1 h and 15 min) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity Aerobic activity should be performed in episodes of at least 10 min, and preferably, it should be spread throughout the week
- Adults should also do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on 2 or more days a week, as these activities provide additional health benefits
- For additional and more extensive health benefits, adults should increase their aerobic physical activity to 300 min (5 h) a week of moderate-intensity, or 150 min a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond this amount

The Key Guidelines for Adults also apply to older adults. In addition, the following guidelines are specific for older adults:

- When older adults cannot do 150 min of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow
- Older adults should do exercises that maintain or improve balance if they are at risk of falling
- Older adults should determine their level of effort for physical activity relative to their level of fitness
- Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely

The guidelines go on to say that adults (of any chronological age) with chronic conditions need to participate in regular physical activity, according to their abilities and ensuring that the physical activity is safe. These activities should be selected with help from their health care provider. However, for general situations, Table 108.3 provides guidance or a starting point for several common conditions. Note that for all conditions, overweight or obesity adds more stress to the body and physical activity can help maintain weight.

SURVEILLANCE DATA

Surveillance of physical activity behavior among U.S. adults is conducted through a number of national surveys. The National Health Interview Survey (NHIS) is an annual "in-person" interview with a representative sample of U.S. noninstitutional adults. Questions on the type, frequency, and duration of various physical activities are obtained, and these prevalence data are statistically weighted to represent the U.S. population. The BRFSS is a state-based

TABLE 108.3
Commonly Recommended Physical Activities for Selected Chronic Conditions

Condition	Why Physical Activity Is Important	Type of Activity
Arthritis and osteoarthritis	Improves blood flow through joints and keeps them lubricated. Improves flexibility and range of motion	Aquatic or land-based programs Low-impact aerobic and/or resistance training
Osteoporosis	Weight-bearing activities promote bone health and help maintain bone density	Climbing stairs, walking, Tai Chi, dancing, hiking, aerobics and step classes, jogging, racquet sports skipping rope, lifting weights
Cancer	Helps build endurance to combat fatigue	Activities suited to individual; start slowly with both aerobic and resistance activities
Diabetes	Improves insulin resistance	Walking and resistance training
Cardiovascular disease	Helps reduce risk factors of hypertension, high cholesterol	Walking and other aerobic activities
Depression	Help stabilize mood	Aerobic and resistance activities

survey using standard measures so that state-specific data as well as national estimates can be calculated. The BRFSS is conducted annually and is telephone-based. Questions on physical activity range from doing "any" leisure-time physical activity for at least 10 min at a time to more detailed questions assessing the frequency and duration of physical activity. This is one of the few surveillance systems that assesses occupational activity through one question regarding the amount of time during work spent sitting, walking, or doing heavy labor. The NHIS and the BRFSS are the two major sources of national data on the prevalence of physical activity.

Recognizing that individual differences apply, it is generally known that physical activity decreases with age. Recent data from the NHIS survey found that 12% of men and 9% of women over age 65 years meet the 2008 federal guidelines for all aerobic and muscle-strengthening activities [2]. Using BRFSS data and looking only at aerobic activities, about half of adults over age 65 years meet the 2008 federal guidelines [14]. Data published prior to 2008 may use previous guidelines, but regardless of the system used, older adults are less active than younger adults. Using data from the 2004 BRFSS, 28% of adults aged 65–74 years and 36% of adults aged 75 years and older report no physical activity in their leisure time in contrast to only 19% of those aged 18–29 years who report no physical activity [1].

Note that the statistics reported here are based on physical activity performed outside of an occupational setting. As more adults reaching the "magic" age of 65 years continue to work, the contribution of occupational physical activity should not be ignored. Recent data from the state-based BRFSS suggest that including occupational physical activity increases overall prevalence of meeting the physical activity guidelines among adults aged 65 years and older by a modest 1.8% among men and 1.1% among women compared with about 10% for men and 6% for women aged 18–54 years [15].

MEASURING PHYSICAL ACTIVITY

The best way to collect information on physical activity is to use simple questions that can be compared with published national data. Although objective methods of measuring physical activity are thought to obtain more accurate measures than pencil and paper tests, there are major limitations to using these methods. Accelerometers measure heart rate and activity in multiple planes but cannot be worn when doing water activities. In addition, they must be worn correctly, cost several hundred dollars, and the data collected by the device must be downloaded and analyzed for interpretation. These problems make accelerometers more appropriate for research studies than for measuring physical activity in a community or clinical setting. Pedometers are a much cheaper alternative that counts steps while being worn around the waist. While they also cannot be used around water, they are much cheaper (can be found for less than $20) and give instant feedback to the user. Because of these issues, the best use of a pedometer is as a motivation tool to encourage individuals to be more active (increase daily step counts to reach a goal). For a quick assessment and subsequent recommendation, simple questions about the time spent doing aerobic activities are efficient ways to determine adequate physical activity. Questions should include some measure of intensity (e.g., type of activity such as walking or running), time spent doing activity, and how often the activity is done. These questions do not need to be too detailed in order to get a rough idea if the person meets the guidelines for physical activity.

BARRIERS TO BEING PHYSICALLY ACTIVE

Although most adults are well aware of the need to participate in physical activity, about half do not, and this proportion is even higher among older adults. Physical activity can prevent or delay the occurrence of many chronic diseases, including arthritis, hypertension, diabetes, heart disease, for example, which become more common as individuals age. Even when chronic diseases are present, participation in physical activity can prevent worsening of the condition or developing new conditions related to physical inactivity. However, surveillance data consistently report that participation in physical activity decreases as people age. Reasons

for this decrease are varied but some are particularly relevant for older adults, such as functional problems limiting mobility, lack of safe venues for activity, and lack of knowledge about appropriate activities. For all adults, the most common barrier to being physically active is lack of time. However, for older adults, the barriers to being physically active include such things as chronic illnesses, injury, and lack of skill [16]. For example, those with chronic back pain reduce activity levels out of fear of worsening the pain, even though physical activity has been shown to improve the condition [17]. In addition, motives for exercising differ among older adults. A study of community-dwelling older adults in Finland found that those with mobility limitations exercise for disease management, while those without mobility limitations exercise for health promotion and positive experiences [18]. For older adults, the barriers become much more complex and are summarized in Table 108.4 along with some strategies that may facilitate physical activity.

Injury

While injuries occur with many sports, they are often minor and do not represent a major shift in the direction of an active lifestyle. However, for older adults, even minor injuries may involve a prolonged period of recovery. During this recovery period, significant deconditioning may occur, leading to difficulty in resuming physical activities. In addition, the type of injury could be devastating and may discourage future activity. For some older adults, the fear of injury, rather than an actual injury is a major barrier.

Environmental

The newest area of research on physical activity prevalence has to do with the role of the environment. Several features of the environmental design can promote physical activity, especially among older adults. Access to safe walking areas, free from crime and traffic, is important for all adults but essential

TABLE 108.4
Common Barriers to Physical Activity for Older Adults

Type of Barrier	Major Concern	Strategies
Injury	Slow recovery time	Encourage cross-training to let injured body part heal
		Promote low-impact activities
	Deconditioning	Restart minimal activity after injury and increase slowly to pre-injury levels
	Falls	Develop and use safety checklist
		Use proper footwear
	Fear of injury	Educate on safe exercise practices
Environmental	Crime	Identify safe areas for walking or other activities
	Traffic	Ensure that crossing lights allow enough time for older adults to cross
	Falls	Ensure sidewalks are available and in repair
	Fatigue	Identify areas with benches or resting places
	Extreme heat or cold	Identify climate-controlled areas for walking (e.g., malls)
Urinary incontinence	Lack of facilities	Identify areas with appropriate facilities
Arthritis pain	Fear of increasing pain	Educate on benefits of physical activity for arthritis
	Unable to perform usual activity	Identify alternative activities
Medications	May cause dizziness and balance problems	Identify walking or exercise partners, identify safe exercise venues that are well lit with solid pathways
Chronic conditions (ear or hearing problems)	May cause balance problems	Identify walking or exercise partners
Surgery	Limited mobility and fatigue during recovery	Educate on alternative physical activities, start minimally and increase activity slowly
Cancer treatments	May cause dizziness, fatigue	Identify walking or exercise partners, start activity program slowly
Obesity	Inability to participate in many types of physical activity	Start with conditioning, work up to aerobic activities, such as walking
	Embarrassment	Find clothes that fit, join groups with same problem

for older adults who may not be able to travel to other areas just to be active. The nature of physical activity changes as a person ages and opportunities to walk for transportation (errands) or gardening (own or community gardens) become more important. To encourage walking, street connectivity, stores in proximity to housing and public transportation, and places to sit along the way are characteristics that promote activity.

Urinary Incontinence

While many older adults, women in particular, have some form of urinary incontinence, it is difficult to obtain exact prevalence data. Although about 25% of older adults report problems with urinary incontinence, it is estimated that less than half of women with urinary incontinence mention it to their provider. This has a particular impact on physical activity. Although urinary incontinence is a barrier for participating in physical activity, there is evidence that suggests physical activity actually reduces the risk of urinary incontinence among older women.

Arthritis/Osteoarthritis

Arthritis is a disabling disease that results in joint pain as the cartilage degenerates. Although pain may limit some activities, it is important for adults to know that physical activity is important in maintaining joint function. Adults with arthritis should also know how to provide alternative exercises so that painful joints are not unduly stressed. Because there is no known cure for orthrictis research focuses on prevention and symptomatic treatment of the disorder. In this regard, a beneficial effect has been shown for aerobic and strengthening exercises on pain relief and joint function [19].

Medication

Overall, about 80% of adults have at least one chronic condition [1]. A recent study of adults aged 57–85 years found that 75% of them had one or more comorbid conditions (including high blood pressure, stroke, myocardial infarction, heart failure, diabetes, thyroid problems, Alzheimer disease or dementia, cancer, and any type of arthritis) [20]. The same study found that among adults aged 65–85 years, 80% took at least one medication per day, while 29% used five prescription medications per day. Over-the-counter drugs were also common with almost half of those aged 65–85 years using a combination of at least one prescribed medication along with an over-the-counter drug or supplement. Surveillance data for the United States in 2005–2008 found that 65% of adults 65 years and older used three or more prescription drugs in the past month [2]. In addition to the known side effects for a particular drug, there is the possibility for unforeseen problems due to interactions among multiple medications, including over-the-counter drugs or supplements. The most common side effects include sleepiness, dizziness, or visual problems, all of which could lead to falling. Persons taking a number of medications should still exercise, but the form may be dependent on personal cognitive and functional conditions. There are several preventive techniques that can be applied in this situation. Physical activities should be low impact and done with a partner who can watch for any problems. The venue should be safe with good lighting.

Chronic Conditions

A number of chronic conditions, in and of themselves, can affect physical activity directly or indirectly. For example, ear problems may affect balance and preclude activities where there is a risk of falling. Persons with visual problems, such as macular degeneration, may have to give up their usual forms of activity and may need assistance in developing alternative exercises. Muscle problems such as Parkinson's disease and muscular dystrophy may limit the types of activity that can be done. There are numerous resources for promoting appropriate physical activities for people with chronic conditions.

Surgery

Often the fatigue associated with recovery from surgery may limit the type and volume of physical activity. To avoid the deconditioning process, mild activities, such as standing and taking a few steps, should be started soon after surgery as feasible. Then increasing the duration and intensity of the activity should occur slowly over the next few weeks, as healing allows. There is evidence to suggest that physical activity actually promotes healing and should be an integral part of recovery.

Cancer Treatments

Cancer treatments including chemotherapy and radiation take a toll on the body. While exercise may not be high on a patient's priority list, a slow return to physical activity may help combat the effects of treatment. The most common activity that cancer patients do is walking. Because of the safety of walking and the ability to adjust walking speed from a low to a high intensity, this is a very reasonable type of activity to begin a program of physical rehabilitation after cancer treatment. Strength training is an often overlooked activity that will help build endurance.

Obesity

Becoming involved in any type of physical activity and increasing endurance over time is an important adjunct to diet when trying to lose weight or to prevent weight gain. However, to start, an extremely overweight individual may have particular issues including finding clothes that fit and dealing with the embarrassment about exercising in public, even in pools. Once these issues are successfully overcome, perhaps by connecting overweight individuals with others in the same situation, a physical activity program that starts off slowly and builds endurance can have important implications for self-esteem and health benefits over and above any weight loss that might occur.

SUMMARY

While much is known about the general decline in physical activity associated with age and the related adverse health events that can accompany this inactivity, there needs to be more emphasis on the variety of activities that are appropriate for adults of any age. The Physical Activity Guidelines specify that older adults need aerobic as well as strengthening and flexibility activities to prevent or delay aging-related physical decline. The strategies to achieve these guidelines will vary depending on the functional status and comorbidities present among older adults. The key point is that physical activity is essential at any age and maintaining functional health and independence is the major goal. Several themes emerged regarding the particular issues older adults face with regard to keeping physically active. These themes include special attention to safety issues around the home and outside the home where physical activity is usually performed. With the projected increase in the proportion of the U.S. population over the age of 65 years, low participation in physical activity among older adults becomes an important public health problem that will need to be addressed.

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109 Sex Differences in the Prevention and Treatment of Hypertension

The Physiological Responses to Exercise

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CONTENTS

Introduction 1297
Epidemiology of the Disease 1297
Sex Differences 1297
Hypertension 1298
Sex Differences in Hypertension 1298
Exercise 1298
Conclusion 1299
References 1300

INTRODUCTION

There is an increasing body of literature detailing sex differences in the development, prevention, and treatment of cardiomyopathies throughout the human lifespan. This indicates that more research is being undertaken in single cohort studies in both the clinical science and pharmacologic fields. The results of these comparative studies can now be used to provide the most beneficial course of sex-specific clinical treatment. This chapter will present some of the recent data detailing sex differences in response to acute and chronic resistance and cardiovascular exercise. Since cardiovascular disease (CVD) is associated with the greatest morbidity and mortality worldwide and there are sex differences with the treatment of the disease, this chapter will also delve into the effects of exercise on resting hemodynamics and vascular responsiveness in a hypertensive cohort.

EPIDEMIOLOGY OF THE DISEASE

CVD is the largest single cause of mortality among women, accounting for 38% of all deaths among females. For example, in the United States, 42.1 million (36.6%) women live with CVD, and the population at risk is even larger. While CVD is a large public health issue in women, it is not solely related to mortality due to the recent advances made in sex-specific research allowing women to have greater chances to survive CVD. Hypertension is a large contributor to CVD and is defined as a systolic blood pressure (BP) greater than 140 and/or a diastolic BP greater than 90 mmHg (respectively). Hypertension has been diagnosed in 76.4 million U.S. adults, and as our population ages, this figure will increase since hypertension prevalence increases with age [1]. A nonclinical diagnosis of prehypertension may be considered when your systolic pressure is between 120 and 139 mmHg and/or your diastolic BP is between 80 and 89 mmHg most of the time [2]. If you have prehypertension, it has been shown you are more likely to develop hypertension.

SEX DIFFERENCES

Sex differences are detected during puberty as differential effects of sex steroids give rise to the differences of primary and secondary sex characteristics. While previously unthought of, the development of these sex differences may start the inflection point for increases in the incidence of CVD increasing the need for more cardiovascular studies in adolescents. It has been shown that in females, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) cause estrogen production from the ovaries, which instigates pelvis broadening, increased bone growth, targeted fat depot sites, and breast development. However, puberty in males is a result of FSH and LH causing testosterone production from the testes, which upregulates bone formation and muscle mass as well as increased erythropoietin production from the kidneys. This hormone shift leads to physiologically divergent responses in both the cardiovascular and skeletal muscle systems within the human body. Perhaps the greatest impact of sex differences are shown in a population of chronic diseased individuals (i.e., hypertension) where men progress from normotensive to prehypertensive to hypertensive from their thirties when few women present with this disease; however, women catch and surpass men in the incidence of hypertension by their sixth decade of life [1]. This is disturbing information since

women do not respond to many of the antihypertensive medications in the same fashion. Women reported twice as many adverse effects than men during the Treatment of Mild Hypertension Study, prompting sex-specific adverse effects profiles for many antihypertensive medications. Common medications such as angiotensin-converting enzyme inhibitors (ACEi) and AT_1-receptor blockers (sartans) have shown fetal development complications making these drugs contraindicated for women who are or wish to become pregnant. Further, ACEi treatment results in twice as many coughs reported in women than men. Diuretics, commonly a drug of choice in elderly women due their propensity to decrease hip fractures, have shown a greater incidence for women to develop diuretic-induced hyponatremia and hypokalemia. Lastly, women have reported more cases of peripheral edema while taking a calcium channel blocker as an antihypertensive.

HYPERTENSION

Aside from what can be explained with kidney disease, the etiology of hypertension is mostly unknown, yet there are several contributors to the disease that research has elucidated within the last several years. Some of these risk factors point to microvascular dysregulation due to several functional and structural adaptations. Increased sympathetic outflow, pulse pressure, and endothelial dysfunction are mechanisms leading to hypertrophic remodeling. When normalized, the internal diameter of the artery shows a decreased lumen diameter, increased reactivity, increased arterial stiffness, and an increased wall to lumen ratio. All of these negative remodeling factors brought about by uncontrolled hypertension lead to functional changes within the arterial matrix giving rise to deleterious consequences. Further, vascular smooth muscle cells may be separated from endothelial cells leading to decreased vasodilatation and a microvessel loss (microcirculatory rarefaction). Also, endothelial cells are attenuated and there is some evidence that they may become separated from their basement membrane. Therefore, understanding endothelial-dependent vasoactivity and oxidative stress are important to furthering our knowledge of possible contributors to hypertension. The increased vascular resistance caused by the narrowing of the arterial lumen results in a baroreceptor resetting to the higher pressures, making the baroreceptor less sensitive, further increasing BP variability.

SEX DIFFERENCES IN HYPERTENSION

Dr. Kathryn Sandberg's laboratory recently has shown that the sex chromosome complements are factors in sex differences in hypertension regardless of gonadal sex, meaning the X chromosome may have a greater role in BP control throughout adult life [3]. Documented studies of individuals with X chromosome inactivation have shown cardiovascular complications ranging from vessel complications to hypertension [4,5]. Little is known regarding the sexual dimorphism of CVD; however, some recent animal studies by Sandberg et al. have shown tissue-specific enzyme expression that may contribute to the differences in the evolution of hypertension. Sandberg and colleagues have shown that renal angiotensin-converting enzyme 2 (ACE 2), which synthesizes the vasoconstrictor angiotensin 2, exhibits higher activity in the male kidney under basal conditions [6]. This is an important finding as it demonstrates that ACE 2 is lower in the kidney of the female counterpart due to ovarian effects, which may start to explain the sex differences in the etiology of CVDs such as hypertension. With this new knowledge, therapeutic prescriptions that target sex-specific hormone milieu may be more beneficial for the prevention or treatment of CVD. Women show a slightly greater percentage of awareness and ability to control their disease as shown in the NHANES III data from 1991. However, there is an alarming disparity in the rates of awareness as only about 60% of the hypertensive population is aware they have the disease and only about 20%–30% of those aware have their BP under control [7]. Men and women alike are at risk for developing CVD, underscoring the importance of a heart-healthy lifestyle to prevent or treat CVD. Included in lifestyle changes are weight loss, improved eating habits including a substantial decrease of sodium and alcohol in the diet, and increased amount of physical activity. Since the microcirculation is involved in the genesis and sustainability of hypertension, more research in this area needs to be completed to better elucidate the functional changes that may be prevented with lifestyle changes such as weight loss and exercise.

EXERCISE

It has been shown that exercise confers its benefits on the vessel wall through sheer stress, which increases the bioavailability of endothelial nitric oxide, in turn increasing vasodilatation [8]. Therefore, exercise may be as or more beneficial to a particular sex than the current potpourri of pharmacological interventions. In relation to acute exercise, males and females exhibit similar mechanisms of motor control and similar muscle quality and show no difference in lower-body muscle strength when it is expressed relative to body weight [9]. However, women have been shown to posses less upper body strength than their male counterparts [10]. Yet, women show greater resistance to fatiguing contractions, which may, in part, be the result of increased muscle blood flow during contraction and the differential responses in muscle metabolism between males and females [11]. Since women have less muscle mass, the muscle contraction may not occlude blood flow, thus enabling the muscle to maintain the exercise longer than males [11]. Another potential mechanism may be a difference in motor unit discharge rate as women show greater recruitment synergism

and relative muscle activation of the muscle compartment than age-matched men and a lower rating of perceived exertion during the task [12]. In relation to muscle mass, older women may show a blunted response to hypertrophic resistance training that may be related to an attenuation of protein synthesis [13]. Further data to support this evidence suggest that women have decreased muscle protein synthesis following the ingestion of a meal [14]. However, even though women have less muscle mass on average, they still show considerable strength gains following a progressive resistance training regimen [15]. Taken together, women show greater fatigue resistance to acute exercise; however, they exhibit a resistance to skeletal muscle hypertrophy via an attenuation of protein synthesis with resistance training compared with men.

Women are consistently improving their world record times in events that are related to cardiovascular fitness (i.e., track and field and marathoning) at a faster rate than their male counterparts. The cardiovascular responses to acute exercise show dissimilarities that are mostly reflective of stature and mass differences between the sexes. Women show higher heart rates yet similar cardiac output responses at relative and absolute submaximal loads, respectively. Women show no difference in maximal heart rates; however, they have a lower stroke volume due to sheer size of the internal ventricular volume. On average, women have lower hemoglobin content and less potential for increasing the arterial to venous oxygen difference [16]. These factors along with the fact that women have more sex-specific body fat storage translate into a VO_{2max} that is 70%–75% of their age-matched male counterpart.

With cardiovascular training, both men and women increase their fat-free mass and decrease their relative fat mass leading to decreases in total body mass. However, the magnitude of changes in body composition (fat mass to fat-free mass) is correlated to the amount of energy expended over time than to the individuals' sex. With cardiovascular training, both sexes show increases in stroke volume due to increased heart contractility and blood volume. The increases in VO_{2max} has been shown to result from increases in maximal cardiac output accompanied by small increases in arterial to venous oxygen differences. Ventilation differences are more of a result of differences in size, not necessarily sex; however, maximal ventilation can be increased with either sex following cardiovascular training. These data show that most cardiovascular and respiratory changes following training do not exhibit sex specificity.

Perhaps the greatest sex differences lie in the amount of studies completed in men than their female counterparts. With the recent creation of the Organization for the Study of Sex Differences and more attention given to women's health initiatives, increased knowledge of the physiological and mechanistic differences between males and females will be elucidated, lending to better prevention and treatment of disease by sex specificity. As with the progression of most diseases, the cornerstone of treatment is lifestyle intervention, which usually starts with an increase of physical activity. CVD is the leading cause of mortality worldwide [17], and while the trend of reported CVD for men has recently leveled off, it continues to climb for women. Further, women experience longer hospital stays and greater disability and show less successful response to antihypertensive medications than men [18,19]. Aerobic exercise has been shown to reduce cardiovascular events by 30%, which is equivalent to the reduction in cardiovascular risk following antihypertensive and lipid lowering therapy [20]. In addition to lowering cardiovascular risk, aerobic exercise lowers BP and improves vascular reactivity, thought by primarily increasing the bioavailability of nitric oxide [21]. Resistance exercise has also been shown to reduce BP to the same extent as moderate intensity aerobic exercise; however, weight training has been shown to increase arterial stiffness in young healthy and hypertensive populations [21,22]. Recently, sex differences in vascular parameters have been shown following the inclusion of weight training in a fitness regimen [23,24]. Females have not shown significant increases in arterial stiffness following resistance training when compared with their male counterparts. These protective benefits are still seen in women following menopause when estrogens can no longer provide active cardioprotective benefits. Therefore, females reap the benefits of resistance training without any significant increases in arterial stiffness, which is important in an aging hypertensive population. Women can include resistance training, which will also help prevent and treat osteopenic and osteoporotic conditions, without any further increases in arterial resistance.

Subtle sex differences exist following acute and chronic exercise training. While most of these differences can be explained by stature and mass, the mechanisms that underlie arterial changes following resistance exercise may provide windows into how we can make our arterial tree more resilient as we age.

CONCLUSION

Lifestyle changes are the cornerstone for the prevention and treatment of hypertension. Aerobic exercise has been shown to reduce BP by employing its effects on the endothelial wall via increases in sheer stress making it as effective as antihypertensive medications with few side effects. Increasing the amount of moderate intensity exercise to at least 120 min per week has shown to be effective at decreasing ambulatory BP. Considerations should be given when prescribing exercise so women can derive more cardiovascular and skeletal muscle benefit such as the addition of a progressive, weight-bearing resistance training regimen. However, aerobic exercise should be prescribed by physicians and backed by incentives from insurance companies as a way to decrease the incidence of hypertension and decrease out-of-pocket insurance costs to companies that provide wellness initiatives for their employees.

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Part XX

Health Promotion

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110 Health Promotion in the Workplace

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CONTENTS

Introduction: The Imperative to Achieve Healthier People and Healthier Economics in Health Care 1303
Rationale for Corporate and Workplace Health Promotion Programs 1303
Health Promotion Programs Provide Value for Employers 1304
Case Study: The Dow Model 1304
Dow's Business Case for Health 1304
The Dow Health Strategy 1304
Preventive Health Promotion Program: A Fundamental Choice 1305
People Resources: A Global Health Promotion Team 1305
A Key Focus: Shared Responsibility 1305
Reducing Tobacco Use 1306
Increasing Physical Activity 1306
Impacting Overweight and Obesity Issues 1306
Improving Dow Family Health 1307
Measuring Success 1307
Dow's Results 1307
Community Impact 1308
Lessons Learned 1308
References 1309

INTRODUCTION: THE IMPERATIVE TO ACHIEVE HEALTHIER PEOPLE AND HEALTHIER ECONOMICS IN HEALTH CARE

From obesity and tobacco use to diabetes and cardiovascular disease—the current overall health situation in the United States is not a positive story. Rising costs are not sustainable, and the health implications are staggering.

Health promotion in the workplace is a critical tool, both in terms of enhancing employee health and company economics. Successful programs can advance business goals and corporate social responsibility commitments while delivering highly valued services to employees. By implementing dynamic, effective health programs in the workplace, we can help our people and our companies become healthier.

This chapter focuses on workplace health promotion programs, the rationale for their adoption, as well as a case study on The Dow Chemical Company's (Dow) positive experience with them.

RATIONALE FOR CORPORATE AND WORKPLACE HEALTH PROMOTION PROGRAMS

As a vital component of a true health system, companies can make a positive difference in the health of their people, and they can have a peripheral impact in the communities where they operate. Well-conceived workplace health promotion programs can improve health and quality of life for employees, reduce their risks for disease, control unnecessary health care utilization, limit illness-related absenteeism, and decrease health-related productivity losses.

The worksite is the right place to tackle many of our health problems because adults spend so much of their active waking hours at work. As Dr. Ron Goetzel—a nationally recognized expert in health and productivity management, return on investment (ROI), program education, and outcomes research—points out, health promotion programs at work make sense because of the following:

- They can reach large segments of the population not exposed to and engaged in organized health improvement efforts.
- Workplaces contain a concentrated group of people who share a common purpose and culture.
- Communication with workers is straightforward.
- Social and organizational supports are available.
- Certain policies, procedures, and practices can be introduced, and organizational norms can be established.
- Financial or other types of incentives can be offered to gain participation in programs.[1]

Further, there is a direct, logical basis for workplace health prevention:

- Many of the diseases and disorders are preventable.
- Many of these diseases and disorders are triggered by modifiable health risks.
- Many modifiable health risks are associated with increased health care costs and decreased worker productivity.
- Modifiable health risks can be improved through health promotion and disease prevention programs.
- Improvements in the health risk profile of a population can lead to reductions in health care costs and absenteeism, and heightened productivity.
- Well-designed and well-implemented worksite health promotion and disease prevention programs can save money and produce a positive ROI.[2]

Health Promotion Programs Provide Value for Employers

Investing in workplace health promotion programs provides value to organizations through a number of dimensions. Financial estimates indicate that a company can save $350 annually when a low-risk employee remains low risk and $153 annually when a high-risk employee's health risks are reduced.[3] One meta-review of 56 published studies of workplace health promotion programs shows the following benefits[4]:

- Average 27% reduction in sick leave absenteeism
- Average 26% reduction in health care costs
- Average 32% reduction in workers' compensation and disability management claims costs
- Average $5.81-to-$1 savings-to-cost ratio

After closely examining their organizations' data, many large U.S. companies have also concluded poor health increases employees' utilization of health care services and diminishes employee performance, safety, and morale—thus incurring higher costs to their employer. For a business, workers in poor health—as well as those with behavioral risk factors—mean greater medical expenditures, more frequent absenteeism, increased disability, more accidents, and suboptimal productivity.[5–13]

In terms of the bottom-line value, for a Fortune 50 company, simply keeping U.S. direct dollars in the lower end of projected inflation for health care costs can save hundreds of millions of dollars over a 10 year period.

CASE STUDY: THE DOW MODEL

The Dow Chemical Company has offered an employee occupational health program for 90 years and has had a focused health promotion program for more than 20 years. This outcomes-focused, data-based program aims to enhance the health of the Dow population, including the prevention of injury and illness, through education and support for healthy lifestyle change. It addresses the health issues that Dow people face, on and off the job.

Dow's long-term vision for its health promotion program is to improve health, reduce health risks, positively impact health-related costs of Dow people, improve employee performance, and achieve a high level of satisfaction—with improved health being the highest priority. This will be achieved through a strategy that ensures that "Total Health"-related programs and services are established, prioritized, leveraged, and implemented on a global basis, in the most cost-effective and efficient way. These objectives are consistent globally—at all of Dow's 214 work locations located in 37 countries. They are supported by regional targets and plans that provide local prioritization and focus to the objectives.

Dow's Business Case for Health

In 2004, at the request of Dow's CEO and executive team, Dow Health Services and Healthcare Benefits groups developed a business case analysis of the situation related to the health of Dow people. Here is a simplified summary of the business case:

- Dow has a very large economic impact associated with the health of its people, and the inflation on this large base typically increases at a rate greater than general inflation or economic growth.
- Translating this economic impact into cents/share demonstrates it as a significant priority.
- There is strong evidence that Dow has an opportunity to change the situation through improved quality, through addressing waste and ineffectiveness in the system, and through prevention.
- Health advocacy is a priority as reform agendas are vital to the future.

This business case drove development of a simple yet powerful corporate-level health strategy.

The Dow Health Strategy

It is imperative to have a long-term view for and commitment to health. Company leadership at Dow approved a corporate Health Strategy in 2004, which confirmed health as a corporate priority. Dow's Health Strategy is built on four pillars:

1. Prevention
2. Quality and effectiveness
3. Health system management
4. Advocacy

The strategy includes all aspects of the impact of health for "Dow family" members (including employees, dependents, and retirees). It is reflective of Dow's belief in the alignment between the health of its people and the success of the

company and the view that health spending is an investment. Based on a long-term commitment, Dow Health Services and Benefits have set multiyear goals as well as annual objectives for each pillar of the strategy.

Preventive Health Promotion Program: A Fundamental Choice

Focusing on the prevention aspect of the health strategy, Dow's comprehensive health promotion program incorporates best practice design and implementation characteristics: awareness, motivation strategies to engage employees, skill-building programs, and supportive environments. It includes a variety of health-related company policies and initiatives: periodic health examinations, Dow-directed testing, consultation, referral and follow-up, health education through intranet and Internet channels, small group programs, health/disease risk topic-focused campaigns, on-site wellness centers, self-care and consumer education, and tools such as an electronic personal health record.

In addition, Dow offers strong prevention coverage in its health benefit plans as well as initiatives—such as the Healthy Workplace Index (HWI)—to create a supportive environment.

Dow launched the HWI in 2007 at its domestic and global worksites to reinforce the connection between workforce culture, environment, and health. The HWI measures the health parameters of a worksite, such as access to healthy food, access to exercise, participation in programs, and a tobacco-free campus. A site's status on all of the parameters is ranked by its level of achievement and assigned points accordingly. The cumulative index score of all individual elements is used to classify worksites as achieving bronze, silver, gold, or platinum levels.

The global strategy features a blend of corporate efforts and local plans to ensure Dow meets the needs of its diverse workforce, and it emphasizes shared responsibility between the company, local leadership, and employees for improved health.

People Resources: A Global Health Promotion Team

In alignment with Dow's Health Strategy and overall health services package, an updated Global Health Promotion team was chartered in late 2009 to provide strategic leadership to the program. The team is lead by the global health promotion leader and includes regional health promotion coordinators from five different regions, plus subject matter experts for the priority health targets of weight management, tobacco, resiliency, and physical activity.

It is important to note that health promotion occurs throughout all service lines within Dow's Health Services organization, such as Clinical Care and Health Assessment. The intent is that achievement of prevention and health promotion is accomplished across all service lines.

Formal subject matter experts and/or teams are in place for a wide variety of health topics and technologies (e.g., counseling, measurement/evaluation). These contacts monitor internal and external practices, research, and trends to help drive best practices in the program. They also take ownership in developing and updating communications and programs on their topics—to help ensure consistency of message and integration of best practices.

Regional health directors, regional health promotion coordinators, and other Health Services staff prioritize and customize base and local programming to meet regional needs with available resources.

Only one-quarter of Dow work locations have an on-site Health Services staff member. Reaching the entire workforce thus requires the active involvement of employees across the company. This includes Dow's global network of site and workgroup health contacts. The primary purpose of this network is distribution of programming and information. These contacts provide feedback and customize the program to ensure that central or regionally developed strategies are implemented.

In addition, a small core group of staff provides support with language translations, data management, and communication.

A Key Focus: Shared Responsibility

One of the premises of Dow's health promotion program is that individual health is most effectively achieved when there is a shared responsibility between employees, company leaders, and the company. While individual behavior is inevitably essential, a healthy culture and environment established through policies, benefits, and leadership behaviors is also essential. This results in shared benefits for both the company and the employee: improved health, personal performance, and lower costs:

- Employees need to be educated medical consumers, make decisions and take actions to improve their personal health, and utilize the tools and resources provided by the company.
- Company leaders need to proactively facilitate a supportive environment, such as supporting access to healthy foods and physical activity.

Health Services communicates regularly and consistently to both leaders and employees across Dow, constantly striving to build a health-centered culture and promote various programs. It is widely recognized that leaders are essential to creating a culture that encourages employees to live healthy lifestyles. Communications methods thus target both leaders and employees.

Health Services uses various tools to reach these two audiences. Broad communications include internal news resources; reports with important findings, updates, and successes; and newsletters and web casts/videos. A health intranet site has a vast amount of information and resources for employees. Dow's external website contains additional health resources that are available to employees

and their dependents, retirees, and community members. Communications delivered on-site include messages on TV monitors, posters, presentations, safety meetings, discussion panels, and awards. Health Services also communicates more personally to the individual through home mailings and e-mails.

Communications are consistent across the globe, with the flexibility to adjust for cultural differences and program plans. This allows for customization of messages as appropriate, whether that means releasing a communication in the local language and/or communicating about local events and promotions. Most of Dow's global programs and communications are translated into 13 languages. Dow is fortunate to have a corporate translation department to manage initial translations and use local contacts for review and adjustment of content, examples, and measures.

The following are some examples of programs Dow has implemented globally, often with local customization, to enable employees to take a more active role in their health.

Reducing Tobacco Use

The Dow Corporate Smoking Policy was first enacted in the United States in 1993. It has been updated, and since January 1, 2003, all Dow property and meetings in the United States have been smoke-free. Outside the United States, all Dow buildings and meetings have been smoke-free since January 1, 2004. The difference in the two policies represents the necessity for utilizing a multicultural approach. The global policy was written as a minimum standard with room for flexibility in implementing at a local level.

One example is Dow's annual No Tobacco Day, which urges tobacco users to make a commitment to quit using tobacco for at least 1 day. Communicated in 15 languages across all Dow sites globally, tobacco users are asked to commit online. Participants then receive motivational messages and the chance to win gift card prizes. In the inaugural year of 2007, 6% of tobacco users (representing 27 different countries) committed to quit and 56% of those met the 24 h challenge. At 6 months, 11% of participating employees remained tobacco-free. Site leaders from 30 sites also committed to making their work environment more supportive and sponsored activities like tobacco cessation workshops, tobacco-free worksites, free "cold turkey" lunches, educational sessions for employees' families, and free massages. In 2010, 7% of tobacco users (representing 28 sites and 18 different countries) committed to quit using tobacco and 34% met the 24 h challenge. This event, combined with internal health counseling efforts and improved medical benefit plan design, has resulted in a 3% point reduction in prevalence of tobacco users since its inaugural year (2007).

Eliminating the negative impacts of tobacco use requires more than a policy and program. As part of Dow's comprehensive approach, the company has strengthened internal health counseling efforts and improved its U.S. medical benefit plan to cover tobacco cessation consultation and pharmacotherapy at 100%, using evidence-based, best practice recommendations from the National Business Group on Health and U.S. Preventive Services Task Force.

Increasing Physical Activity

Dow implemented a global year-long physical activity challenge, MOVE for Good Health, to increase emphasis on regular physical activity at both an individual and organizational level. Nearly 5000 people from 53 countries registered for MOVE and made sustained changes in their physical activity level:

- 89% of previously sedentary participants became active (i.e., were sedentary at baseline and now exercise at least once per week).
- 47% of high- to moderate-risk participants moved into low risk during the program (i.e., started at high or moderate risk and now exercise three or more times per week).
- MOVE contributed to a 2008 Dow global population improvement in physical activity level—a 1% point reduction in high risk (from 26% to 25%) and 1% point increase in low risk (from 39% to 40%).

Since 2005, efforts to improve access to physical activity at Dow worksites, global physical activity challenges, and partnerships with groups like the U.S. President's Council on Physical Fitness and Sports have helped support a 12% point increase in Dow's low-risk population and a 6% point reduction in high risk for physical activity in the United States alone. Globally, the improvements were 7% points and 7% points, respectively.

Impacting Overweight and Obesity Issues

Dow participated in National Heart, Lung, and Blood Institute-funded research to examine the health and economic benefits of worksite and environmental interventions on overweight and obesity. The environmental interventions, called LightenUP, aimed to decrease unhealthy eating and increase physical activity among workers. Interventions included the following:

- Moderate-level treatments that introduced relatively inexpensive environmental changes to the physical environment, such as walking paths, healthy food choices, nutritional information in vending machines and cafeterias, and employee recognition
- More intensive-level treatments that encouraged an organizational culture of healthy behaviors through leadership training, top management involvement, integration of behavior change programs into the company's established business practices, and leadership accountability
- Control sites continued to receive the core health promotion programs, including individual-based programming (e.g., counseling), but did not receive the environmental interventions

After 1 year of the study, researchers found employees who participated in the LightenUP interventions reduced their blood pressure risk and maintained a steady weight when compared with employees at control sites who received only individual-focused interventions. After 2 years, Dow saw an increase in physical activity, better nutrition habits, reduction in tobacco use, increase in leadership support, and increase in employee awareness. These results suggest even moderate changes to the work environment can have a positive impact on employees by reducing at least one health risk and helping the well stay well.

Analysis of Dow's year 3 data indicates statistically significant results. Average weight loss at the intervention sites was significantly greater than at control sites, as were the reductions in mean blood pressure and cholesterol levels. Intervention sites also achieved significantly greater improvements in diet and exercise. These results indicate that adding environmental interventions to individual-level programs improves biometric and behavioral risk factors.

Improving Dow Family Health

In addition to addressing modifiable risk factors, Dow health promotion efforts engage employees, retirees, and family members as active participants in their health care. Dow provides health resources and information on the company's external website that are available to employees and their dependents, retirees, and community members. It includes benefits information, engaging programs, and more.

Dow's Positive Action health care consumerism program increased awareness of the consumer's role, helped participants become more comfortable with the U.S. health care system, and taught valuable skills such as self-care and adequately preparing for a doctor's visit. In the 9 months following the program pilot, participants experienced fewer health care claims than nonparticipants, which equated to a half million dollars in savings to employees and approximately $300,000 in savings to Dow within the first year after the program.

Since Dow still bears partial responsibility of health care costs for early retirees in the United States and Dow retirees help to shape the health culture in communities where Dow operates, a focused Retiree Health Empowerment Program is also implemented in the United States. Health promotion deliverables are extended to retirees in other geographies, as appropriate.

Measuring Success

The success of The Dow Chemical Company in establishing and maintaining a global culture of health can be seen as a systematic process. The support of leadership is unquestionably ingrained, and the health of employees is directly linked to business goals and objectives. This approach and strong focus on prevention translates to comprehensive worksite health promotion that is uniquely tailored to Dow employees.

Dow has a standard process and definitions for capturing, recording, and reporting participation. Hard copy forms and/or a web-based registration portal are used for global and local programs. Each country and/or region maintains a database for coding participation in health promotion as well as other employee health services. Rates are calculated and reported annually. Participation can be assessed by location, participant, topic, type of intervention, and actual intervention name.

Dow also identified the health risks with the greatest potential to impact its health strategy objectives. Ten-year targets were established to support the business case. These targets are tracked globally and regionally each year. Progress is also reported to the company executive leadership and the Board of Directors. As such, the targets are a significant driver for the program. They also serve as a unifying force across regions. While each region may have a slightly different prioritization, all regions share this common set of targets.

Dow tracks satisfaction, awareness of services, costs of services, participation, percentage of population reached, and progress in the HWI. The HWI quantifies site adherence to best practice recommendations for establishing a supportive work environment that contributes to the reduction of health risk, health-related injury/illness risk, and employee productivity. A formal customer satisfaction survey is conducted for each service component every 3 years to a random sample of the employee population.

Dow's Results

Driven by the 2004 strategy, many of Dow Health Services' recent program dimensions are still young, but indicators are already demonstrating the positive health impact. Here are a few, as of year-end 2010:

- The company has seen increases in the percent of Dow people who believe Dow sincerely cares about their health and well-being. Using global assessments, Dow saw an improvement of 11% points in 2010 versus 2005 in employee perceptions.
- Approximately 89% of global employees and 82% of U.S. employees voluntarily participate in health assessments. According to satisfaction surveys, 93% value this option—which is why Dow is able to attain such high participation rates without direct financial incentives to participate.
- Eighty-one percent of Dow's people globally and 79% in the United States participate in one or more internal Dow health services each year.
- Ninety percent of Dow's sites with >200 employees are engaged in the HWI. This represents approximately 57% of the Dow global employee population. Sites report total scores and are recognized for various achievement levels—bronze, silver, gold, and platinum. Through 2010, 61% of these sites reached the bronze level or above, which equates to

a 152% improvement since the 2008 baseline. Five sites were recognized by senior EH&S and Health Services leaders for achieving the silver level, and one was recognized for reaching the gold level.

- Dow tracks 11 key health risk indicators, which are measured from information obtained in periodic health assessment exams: blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, fasting glucose, body mass index (BMI), physical activity level, tobacco use, stress, depression, nutrition (fat consumption), and nutrition (fruit and vegetable consumption). Using an established baseline of global employees from 2004, Dow has seen a decrease in the high-risk level for 6 of the 11 health risk factors (total cholesterol, BMI, tobacco use, physical activity, depression, and nutrition [fruit and vegetable consumption]). Over this same period, Dow has increased the number of employees in the low-risk category in 8 of the 11 measures (total cholesterol, HDL cholesterol, BMI, tobacco use, physical activity, depression, nutrition [fat consumption], and nutrition [fruits and vegetables consumption]).
- In 2010, Dow continued its trend of reducing health risks in the employee population for the company's top three risk targets of tobacco use, physical activity, and obesity. Between 2004 and September 2010, there was a 25% reduction in high-risk people and a 19% increase in low-risk people in these three categories.
- Using U.S. data, Dow can illustrate the impact of one of its key services, health advocacy case management, in total economic benefit. In 2010, Health Services reported 14,533 absenteeism days saved resulting in $18 million in direct and indirect savings.

These results affirm the value of Dow's specific efforts and of corporate health programs generally. With a sustained focus, Dow will continue to have an impact on the health of its people because corporate health strategies offer one of the best opportunities to effectively engage adults to maintain and improve health.

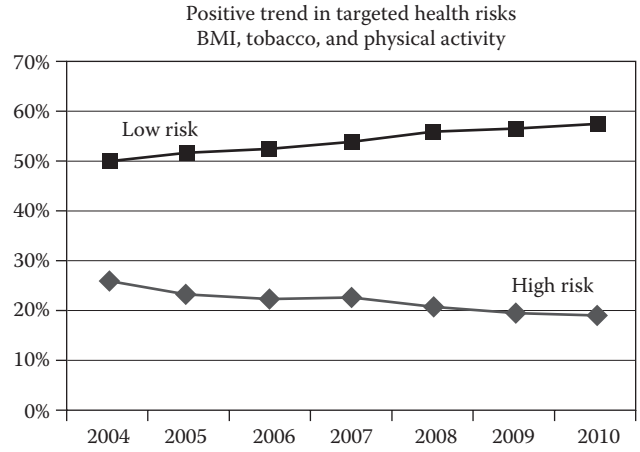


FIGURE 110.1

Community Impact

Beyond Dow employees and their families, the company has a long-standing commitment to the health of the communities in which Dow operates, tracing back to founder Herbert H. Dow. Over the years, Dow has worked hard to establish

- Employee health programs that are recognized for their excellence
- Community advisory panels at all major production locations
- Direct financial contributions to health needs in communities as an integral part of corporate giving
- Medical departments at major sites that work closely with local community health services
- Public health value, because Dow performs and publishes important health research

One example of community partnership is Dow's investment to help establish the Michigan Health Information Alliance (MiHIA), a multistakeholder collaborative covering 14 counties in central Michigan that is dedicated to improving the health of the people in the region through the innovative use of health information. MiHIA is also a Chartered Value Exchange as designated by the Department of Health and Human Services through the Agency for Healthcare Research and Quality. Aligned with the mission is a commitment to advance the cornerstones of value-driven health care through the development and implementation of interoperable health information technology and the dissemination of price and quality information.

LESSONS LEARNED

Worksite health programs, such as those implemented by Dow around the world, are key components of empowering people to take control of their health. The reality is that it is not any single resource, policy, or initiative that works—it is the combination of efforts and a long-term, strategic, and well-integrated program that adds the greatest value. The following aspects are key lessons that have contributed to Dow's success in implementing and maintaining an effective health promotion program:

- *Corporate requirement and strategy*—helps insure that the program is available to all employees and sites and implemented consistently worldwide
- *Strong, detailed business case*—essential to secure management commitment
- *Economic impact*—determine the total economic impact of all health-related costs, both direct and indirect
- *Extensive metrics and evaluation*—complement these by a focus on outcomes and reporting on progress and value delivered
- *Multi-year targets*—metrics and required multi-year strategic plans drive program growth and encourage regions and sites to tailor the program to their critical targets

- *Truly comprehensive program*—prioritize and adjust through regular review of data and best practices, maintain integrity, and focus on serving the health of individuals
- *Organizational integration*—organize into core of the company (leader development, site goals, safety, HR, integrated medical model)
- *Engage stakeholders*—includes local health contacts, internal partnerships, labor organizations, as well as internal company stakeholders
- *Shared responsibility and healthy culture norms*—develop and nurture at individual, workgroup, and leader levels
- *Standard cycle of programming*—a set of global interventions initiate behavior change, develop lifestyles, and create a supportive environment for the priority health targets, focus on continual improvement, and implementation excellence
- *Balance of central and local influence*—a global base of deliverables, which can be easily customized, provides consistency, and allows for local application; this also helps maintain cultural sensitivity
- *HWI*—this supports the creation of a supportive environment that allows individuals to practice and maintain their healthy habits
- *Subject matter experts*—experts for each key risk factor can monitor performance, evidence, and best practices and consult on program improvement
- *Confidentiality*—ensure absolute privacy and confidentiality of all personal health data

Every company has its own unique objectives and challenges. A company-wide health promotion program that addresses these strategic needs while balancing standardization with local customization can lead to healthier people and a healthier company.

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111 Health Promotion in Health Systems

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CONTENTS

Introduction....1311
Purpose....1312
Population Health Promotion in Health Systems....1312
Economic Rationale....1312
Framework for Multistakeholder Alignment....1313
Organizing around the Triple Aim....1313
Four Key Stakeholders....1314
Community Context....1317
Approach to Healthy Lifestyle Integration....1318
Awareness....1318
Engagement....1318
Behavior Change....1318
Supportive Environments....1319
Strategies and Tactics....1319
Framework for Action....1319
Program Mix....1319
Evidence-Based Approaches....1320
Program Topics....1320
Patient Protection and Affordable Care Act....1321
Summary....1321
References....1321

INTRODUCTION

The relative importance of a healthy lifestyle on the protection of health and prevention of illness cannot be overstated. On the one hand, chronic diseases are recognized as a major global burden to public health. On the other hand, most of the chronic diseases are preventable in nature as one of the main underlying causes of this premature mortality is modifiable lifestyle behavior. Chronic diseases, such as heart disease, stroke, cancer, chronic respiratory diseases, and diabetes, are by far the leading cause of mortality in the world, representing 60% of all deaths. Out of the 35 million people who died from chronic disease in 2005, half were younger than 70 years and half were women [1]. In the year 2000, the top 10 leading causes of death accounted for more than 1.9 million of the 2.4 million deaths in the United States [2]. Among these leading causes, heart disease (29.6%) and cancer (23%) top the list of reasons for premature mortality.

The notion that modifiable lifestyle behavior represents a causal factor for premature death has been well documented by the Centers for Disease Control and Prevention in the United States [2,3]. Smoking, physical inactivity, poor diet, and alcohol consumption combined account for approximately 40% of all preventable deaths. Research has demonstrated that nearly 90% of the impact from perfect care for heart disease would accrue from interventions before and between acute events—with most impact coming from primary prevention. Risk-factor interventions before or between acute heart disease events is amplified by the fact that these interventions also reduce the risk of death from other chronic diseases [4,5]. Obviously, it is important to ensure the best quality of care for people with diagnosed conditions. However, preventing or delaying the onset of chronic disease would protect at-risk individuals from increased illness burden; reduced physical, emotional, and psychological functioning; increased health care expenditures; as well as lower quality of life. In fact, not only would individuals benefit, others, including children, spouses, and families, employers, health plans, and the community at large, would reap rewards as well.

From a population health perspective, health plans across the United States are in a unique position to reach a vast majority of Americans with health promotion messages. For example, America's Health Insurance Plans (AHIP) is the national association representing nearly 1300 member companies providing health insurance coverage that reaches at least 200 million, or about 65%, of all Americans through its member organizations [6]. Health plans have the opportunity

and capability to influence individuals, groups, decision-makers, policy-makers, and other community stakeholders to direct more attention to the integration of lifestyle behaviors into strategies that address awareness of the importance of healthy living, engagement into actions and programs, behavior change toward healthier activities, and the creation of supportive environments that lead to sustainable solutions [7]. Health plans tend to play an active role in their communities and have obvious relationships with purchasers of health care (government, employers), care delivery organizations (care systems, clinics, physicians, and others), and their members. In this context, health plans have large potential to influence the health care system as a whole toward enhanced focus on the important role of modifiable health behaviors.

Purpose

It is the purpose of this chapter to consider and discuss the opportunity that resides within health systems to integrate modifiable lifestyle behaviors into their products and services, their relationships with other stakeholders, and the potential benefits that may be gained by doing so.

POPULATION HEALTH PROMOTION IN HEALTH SYSTEMS

Promotion of population health makes good sense for health plans. Health in itself may be regarded as a central objective since lack of health is associated with increased health care expenditures. Health plans first and foremost represent an insurance function. As such, health plans are interested in optimizing the management of the financial risk associated with their covered population.

Economic Rationale

In law and economics, insurance is a form of risk management primarily used to evade the risk of a potential loss. Insurance is defined as the equitable transfer of the risk of a loss, from one entity to another, in exchange for payment. Insurance involves pooling funds from many insured entities (known as exposures) to pay for the losses that some may incur. The insured entities are therefore protected from risk for a fee, with the fee being dependent upon the frequency and severity of the event occurring [8].

Specific to health care, health insurance policies will cover the cost of medical services and treatments. If financial risk exposure is lowered, better managed, or more predictable as a result of health promotion efforts, the promotion of better health of the population becomes a business opportunity for health plans.

A treatment-only strategy is not sufficient—strategies that protect and promote health need to be implemented alongside each other in a complementary and integrated manner. Primordial prevention efforts are needed to reduce the likelihood that risk factors for disease occur in the population; primary prevention efforts are needed to reduce incidence of new disease and diagnosis and reduce mortality; and secondary and tertiary prevention efforts are needed to find and treat disease early, prevent exacerbations of existing disease, and reduce mortality [9]. However, disease prevention and health promotion strategies that improve health, reduce the need for health care services, and increase the affordability of health care lie with services that focus on the preservation of health rather than those that disrupt disease progression [10].

As efforts move from primordial to tertiary prevention, per person medical care costs increase. Furthermore, individuals at lower risk tend to have lower overall health care costs for the population (as they are below average), whereas those with health risks or diagnosed disease experience higher health care costs due to their need, demand, and consumption of medical care resources [11]. Those at higher risk tend to incur more costs. Moreover, more than 50% of the highest cost group in a given year is replaced in the following year by people at lower cost in the current year. This concept is depicted in Figure 111.1. Hence, a treatment-only strategy without a comprehensive prevention strategy is not sustainable from a cost perspective and does not shut down the pipeline of disease. Today, the United States spends more than 95% of its health care expenditures on treatment of those with health risks and disease—less than 5% is spent on prevention [12]. The approach of waiting for people to get sick and then treating the ailments is a very expensive one. As Americans see health care expenditures continue to increase, it is important to focus on strategies that reduce the incidence, prevalence, and cost of preventable diseases. Health plans interact with multiple audiences (members, employers, payers, providers, etc.) in a variety of settings (community, workplace, clinic, home, etc.) over an extended period of time and are well positioned to make a meaningful impact on the health of the population. They also have the technical capability to reach their enrollees with health promotion and disease prevention technology [7].

Whereas the discussion so far has centered on health care costs, other economic reasons to worry about ill-health exist as well. Cost drivers besides medical, hospital, and pharmacy costs include disability, workers' compensation, absenteeism, presenteeism (reduced on-the-job effectiveness due to ill-health), recruitment, retention, morale, safety, emergency preparedness, and national security [13–15]. Evidence of effectiveness for many approaches to address these issues exists in the literature today. For example, the Task Force on Community Preventive Services has published recommendations related to worksite health promotion efforts based on strong evidence of effectiveness that shows such programs improve health [16]. This evidence of effectiveness is supported with an economic rationale that indicates a positive return on investment for employers. Several reviews and meta-analyses point to a return on investment for health care costs of approximately 3.25:1 [17,18], absenteeism-related savings of approximately 2.75:1 [18], and intangible, but not less important, returns on higher morale and the organization's culture [19].

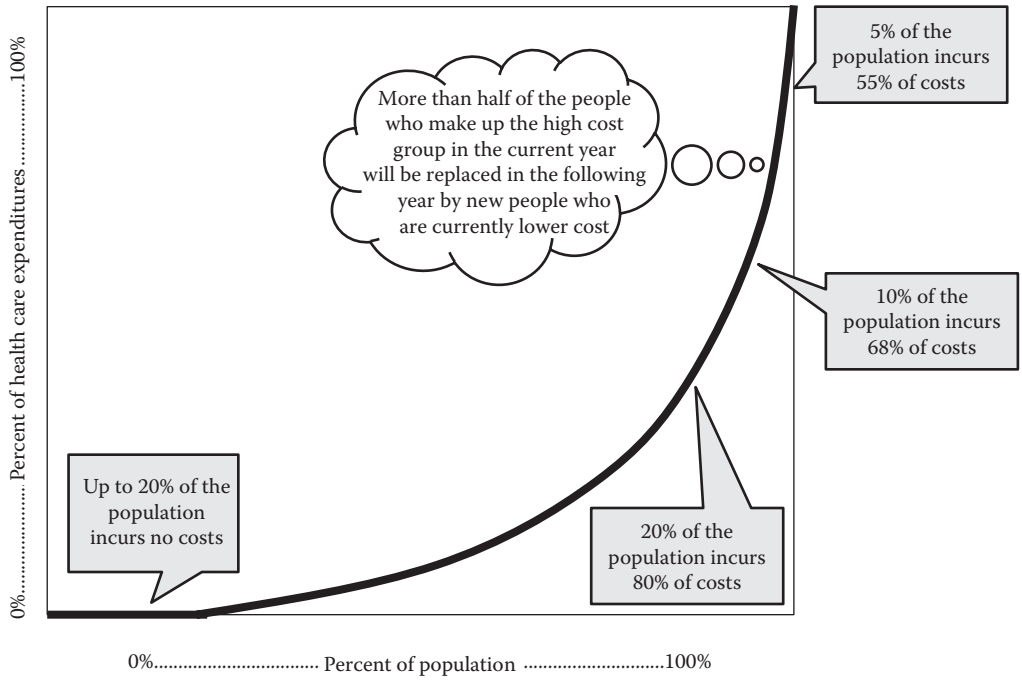


FIGURE 111.1 Health care expenditures by population percentile.

From a societal perspective, cost-effectiveness analysis of community-based physical activity interventions ranged between $14,000 and $69,000 per quality-adjusted life year (QALY) gained, relative to no intervention [20]. In this analysis, interventions exemplifying each of four strategies strongly recommended by the Task Force on Community Preventive Services were evaluated: community-wide campaigns, individually adapted health behavior change, community social-support interventions, and the creation of or enhanced access to physical activity information and opportunities. Each intervention was compared to a no-intervention alternative. All of the evaluated physical activity interventions appeared to reduce disease incidence, to be cost-effective, and based on comparative effectiveness, to offer good value for money. Maciosek et al. [21] carefully considered the cost effectiveness of clinical preventive services in the United States that are likely to be delivered by health plans. In this study, the few services that actually appear to be cost saving included daily aspirin use for men (age 40 years and older) and women (age 50 years and older), childhood immunizations, and advice and support to help adults quit smoking. Considering these results, many stakeholders may benefit greatly from a strategic focus on health promotion as implemented through health care systems. Such a strategic approach would benefit from a framework designed to align the interests of key stakeholders.

Framework for Multistakeholder Alignment

Arguably, for an organization to invest resources into any strategy, the strategy has to generate positive net value. Ideally, this value proposition extends to all of the stakeholders involved—the organization itself as well as its customers. In the context of health systems, four key stakeholders are identified: (1) the individual *person* who receives insurance coverage (and their dependents when applicable), (2) the health *plan*, (3) the *providers* of health care services and treatments (physicians, nurses, care systems, clinics, etc.), and (4) the *payers* of health care (employers, government, individuals). These stakeholders all come together in the context of a larger community, which is influenced by factors such as local or national policies, legislation, and social norms. To make the argument related to the integration of health promotion and disease prevention efforts into a health care system's products and services, a clearly defined set of outcomes is needed that resonate with the value proposition of the entire effort. Here, we argue that those outcomes need to include several domains that come together in a synergistic manner, namely, the simultaneous improvement of population health, per capita costs of care (health care affordability), and individual experience of care and service. This set of outcomes has been introduced in the health care context by the Institute of Healthcare Improvement (IHI) and is aptly named the "Triple Aim" [22]. A framework that is centered on the needs and experiences of the user, generates improvements in health, reduces health care costs, aligns the interests of key stakeholders, and is implemented with explicit goals to connect to the larger community is arguably a strong model for multistakeholder and multisectoral collaboration. Figure 111.2 depicts the framework.

Organizing around the Triple Aim

In 2008, leaders at the IHI introduced an important new and elegant strategy for improving health care [22]. In order to

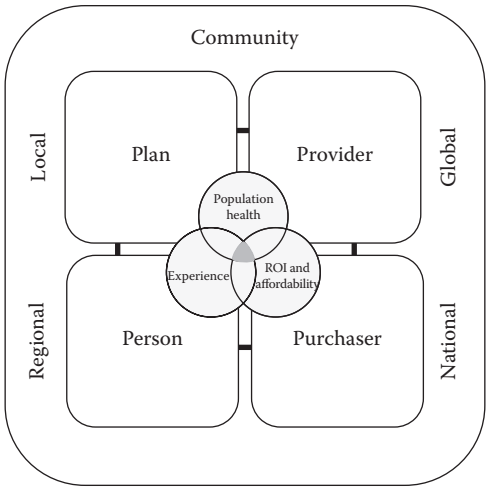


FIGURE 111.2 Alignment of stakeholder and outcomes for health promotion in health care systems.

achieve high-value health care, the IHI proposed the pursuit of a system of linked goals called the "Triple Aim." The IHI Triple Aim defined this set of interdependent health care delivery goals as follows: the simultaneous improvement of population health, per capita costs of care, and individual experience of care. This pursuit of high-value health care as the central objective of the IHI Triple Aim may in itself be seen as a major innovation in stimulating improvements in health care delivery. Since population health is prominently featured as one of the three aims, the IHI Triple Aim provides a significant opportunity for clinical care delivery to move beyond the clinic walls and reach deeper into the community. Such action would represent a departure from traditional care delivery roles, which are largely limited to clinic-based care.

Extending deeper into the community will provide significant potential to pursue and incorporate novel approaches that affect nonmedical determinants of health. Given that estimates of the impact of health care on the health of populations range between 10% and 20% [23,24], it seems reasonable to suggest that the IHI Triple Aim would benefit greatly from a nonmedical determinants of health agenda to increase the likelihood of achieving breakthrough success in population health improvement. Furthermore, in order to achieve significant and sustainable reductions in per capita cost of care following initial elimination of unnecessary care costs, population health improvement is a prerequisite since changes in health care expenditures represent a lagging indicator that *follows* changes in health status of the population [25,26]. Finally, any programs that are implemented in a manner that generates an exceptional experience for users are likely to be rewarded with high participation rates, high satisfaction ratings, and many people willing to refer others into the programs.

One might wonder whether it is possible to actually achieve this notion of the Triple Aim, i.e., simultaneous achievement of population health, exceptional experience, and reduced cost. One successful example comes from the worksite health promotion literature and is the result of a health system collaborating with an employer [27]. In this case study, a successful multiyear employer–health plan partnership generated measurable improvements in population health, high levels of program participation and satisfaction, and an overall return on investment of approximately 3:1. Expressed in medical cost savings, the 3 year program impact accumulated to almost U.S.$1 million, or 3.3% of overall expected medical care costs. In addition, the program savings related to reductions in excess health-related productivity losses were estimated to be in excess of U.S.$1 million.

Another successful example of progress toward the achievement of the IHI Triple Aim includes the experience from the HealthPartners Medical Group related to population-based care for diabetes. Since 2004, HealthPartners has reduced its total cost index from slightly above the Minnesota statewide average to nearly 10% points below the statewide average [28]; HealthPartners Medical Group has increased optimal diabetes care (defined as achieving goal for hemoglobin A1c, blood pressure and cholesterol, the patient is taking aspirin daily, and the patient is not using tobacco) for its diabetes population from 9% to more than 42% of all patients being at goal, and the proportion of patients who would recommend HealthPartners clinics is consistently greater than 95%. This experience is depicted in Figure 111.3.

Four Key Stakeholders

The four key stakeholders identified in the framework are the person, the plan, the provider, and the purchaser—in short, the "4 Ps." Collaboration among the 4 Ps may be facilitated by approaches designed to meet the interests of all—interests represented by the Triple Aim.

The Person

From an individual perspective, health in and of itself is clearly an important goal. Health of all family members is also important. Health insurance is one of the best known and most common means used to obtain access to health care. Increasingly, the evidence points to the negative health and economic consequences related to being uninsured [29]. The integration of additional health promotion services into health insurance products would provide additional value.

Second, when health promotion and disease prevention programs reduce the need and demand for more expensive and invasive clinical care delivery services, the individual will enjoy cost savings as a result of fewer co-payments, avoidance of deductibles, and reduced use of pharmaceuticals. In addition, healthier people tend to miss less work, are less likely to be disabled long term, and return to work faster after injury or illness [25]. Higher physical and psychological functioning brings rewards to the workplace in terms of performance [13] that may benefit the employee beyond wages and employment, per sé.

Furthermore, when the program experience is rewarding, engagement with the program components, participation

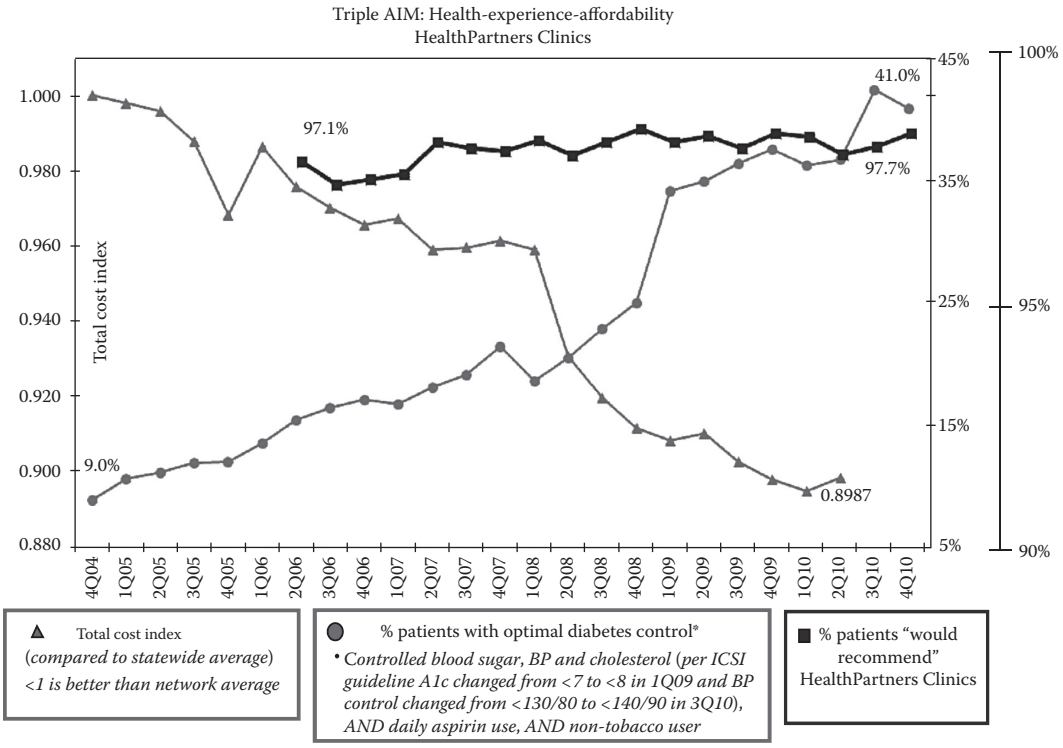


FIGURE 111.3 TRIPLE AIM: Health-experience-affordability. HealthPartners Clinics.

intensity, and adoption of new behaviors is more likely to occur. This is especially important as adoption and maintenance of new behaviors is challenging, but critical, to achievement of long-term health outcomes. A good experience should be associated with ongoing access to health promotion services instead of only linked to short-term, campaign-like experiences. Rather than a focus on programs that last 6–8 weeks and calling out short-term impact on behaviors, ongoing programming should promote long-term participation in healthy behaviors that builds intrinsic motivation for continued engagement. Obviously, a positive experience is a key driver for both short-term and longer-term health outcomes. As the value proposition also attempts to generate cost savings, ongoing engagement and participation in health promotion programs and healthy behaviors will eventually allow for a quantification of a positive return on investment [25,27]. A decision to "do nothing" has been shown to generate significant health care expenditures even in the short-term [25,30].

The Plan

The decision for a health plan or health care system to integrate health promotion into its products and services would first and foremost be related to the potential for reductions in health care costs. The notion that healthy people cost less in terms of health care has been clearly described [11,25,30]. Less agreement exists around the idea that less healthy people can improve their health through adoption and maintenance of healthy lifestyles and thereby lower overall costs. Despite increasingly convincing scientific evidence that has emerged over the past decade indicating that health promotion can improve population health and reduce per capita health care costs, health care systems and health plans have been relatively slow to adopt such strategies. However, as many plans include evidence-based approaches to resource allocation, the fairly recent emergence of evidence of effectiveness based on systematic reviews of health promotion programs will allow barriers to be reduced and innovations in health improvement solutions to occur [31].

The integration of health promotion into health plan services also supports health care delivery services. For example, an overweight, sedentary smoker who, following treatment for cardiovascular disease, attempts to quit using tobacco may find excellent resources in the form of health coaching, access to covered quit aids, weight management programs, or financial incentives to join a local fitness center that are supported by the health plan [32,33]. Providing such services supports clinical care delivery, prevents repeat medical events (such as a repeat myocardial infarction), and avoids repeat hospitalizations among those at high risk and, as a result, saves money.

The Provider

Health promotion services can directly support the efforts of care delivery. In essence, when care teams attempt to optimally manage the health of their patients, consideration needs to be given to the relative role of healthy behaviors, including lifestyle behaviors such as healthy diet, physical activity, no tobacco use, rethinking drinking,

and regular sleep, as well as behaviors more directly related to the care process such as medication adherence and regular preventive maintenance through primary care. In fact, many clinical care guidelines include advice and referral to health promotion services and in many cases consider these services to be first line of intervention [34]. Unfortunately, healthy lifestyle interventions are difficult to deliver in the clinical setting. The reality of busy clinical practices oftentimes limits the physician in time spent with their patient, and prevention may only receive a minute or less during the course of a clinic visit [35]. It is also highly unlikely that physicians will ever have more time to devote to counseling their patients around health behaviors due to the high cost of physician time and the time pressures under which they do their work [36]. As such, many barriers exist for providers to effectively and efficiently incorporate advice and access to follow-up programs and, as a result, this practice occurs far too little. Barriers related to addressing healthy lifestyles in care delivery include, among others [37,38]

- Lack of time to provide counseling
- Lack of financial reimbursement
- Lack of training and background in subject matter (nutrition, physical activity, obesity, etc.)
- Lack of training in counseling techniques
- Lack of organizational support to deliver the services
- A perception that patients do not want the service
- A perception that intervention does not change patient risk or behavior
- A perception that intervention is not the clinician's job
- Lack of confidence to deliver the service
- An overwhelmingly large number patients that need these services
- Perceived lack of referral services in the community
- Perceived lack of scientific evidence that lifestyle interventions are effective
- Lack of commitment to deliver the service

Yet, given the relative importance of healthy lifestyles on outcomes of both prevention and treatment effects of many chronic diseases, it would behoove providers, and especially patients, to engage more fully in such practices. Patients are known to appreciate receiving dietary advice, help in setting realistic goals, and exercise recommendations from their physician [39]. Furthermore, when the goal is to achieve the IHI Triple Aim as delineated earlier and depicted in Figure 111.2, the integration of lifestyle medicine becomes paramount in clinical practice.

The Purchaser

In considering health care coverage, two major purchasers are considered: employers and the government. Certainly, promoting health among the employee (and dependents) population has become a major interest of employer groups in the past few years. Whereas worksite health promotion was recognized over 2 decades ago for its health- and cost-management potential [3], it took longer to generate the data that substantiate the promise of improved health and reduced costs. Major reviews on this topic have painted an increasingly clear picture over the past several decades that worksite health promotion programs improve health and productivity, reduce health care expenditures, and create a positive image for the company that offers them [9,17,40–45]. However, despite enthusiasm and interest in such programs, according to the most recent national survey in 2004, only 6.9% of all worksites in the United States have actually implemented a comprehensive worksite health promotion program according to standards as defined by Healthy People 2010 [46]. Based on the literature, components associated with success include screening and assessment with appropriate feedback and follow-up, health education programming, supportive social and physical environment, integration of the program into the organizational structure, and linkages to related programs such as employee assistance programs (EAPs), work-life balance resources, and others [44,46]. In short, comprehensive multicomponent programs that offer individuals access and choice and are implemented at multiple levels of the company, may be considered informed by evidence of effectiveness [9,44]. In supporting employers in efforts to develop effective programs, the National Institute for Occupational Safety and Health (NIOSH) created a list of 20 essential elements of effective workplace programs and policies ([47]; Table 111.1).

The second major purchaser (also a payer), the government, has traditionally focused on coverage of treatment for disease and clinical preventive services. Disease prevention through support for healthy lifestyle behaviors has not been a focus until the Patient Protection and Affordable Care Act ("the ACA") was passed in 2010 [48]. A major prevention provision of the ACA is the new Medicare Annual Wellness Visit. A fundamental and statutorily mandated component of the Annual Wellness Visit is administration of a health risk assessment (HRA), which is used to gather and analyze much of the information referenced in the statute's menu of elements (e.g., family and medical history, behavioral risks) prior to the office visit, allowing clinicians to spend the bulk of their time during the visit on a personalized and comprehensive conversation about the patient's risk profile and the steps the patient can take to modify that risk. The law specifies that Medicare will cover, without cost to beneficiaries, an Annual Wellness Visit that includes an HRA. Table 111.2 identifies the elements that may be included as part of the Annual Wellness Visit. Despite its appropriateness and comprehensiveness, the preceding list of required procedures and screening activities is not likely to be easily implemented within the context of a time-limited office visit appointment.

TABLE 111.1
NIOSH List of Essential Elements for Effective Workplace Programs

Organizational culture and leadership	
1.	Develop a "human-centered culture"
2.	Demonstrate leadership
3.	Engage mid-level management
Program design	
4.	Establish clear principles
5.	Integrate relevant systems
6.	Eliminate recognized occupational hazards
7.	Be consistent
8.	Promote employee participation
9.	Tailor programs to the specific workplace
10.	Consider incentives and rewards
11.	Find and use the right tools
12.	Adjust the program as needed
13.	Make sure the program lasts
14.	Ensure confidentiality
Program implementation and resources	
15.	Be willing to start small and scale up
16.	Provide adequate resources
17.	Communicate strategically
18.	Build accountability into program implementation
19.	Measure and analyze
20.	Learn from experience

For additional information and a complete description see: http://www.cdc.gov/niosh/TWH/essentials.html

TABLE 111.2
Elements of the Medicare Annual Wellness Visit as Directed by the "ACA"

- Establishment of a beneficiary's medical/family history
- Establishment of a list of current providers and suppliers who are regularly involved in providing medical care to the beneficiary
- Measurement of an individual's height, weight, BMI (or waist circumference, if appropriate), blood pressure, and other routine measurements as appropriate, based on the beneficiary's medical/family history
- Detection of any cognitive impairment that the individual may have
- Review of the individual's potential (risk factors) for depression, including current or past experiences with depression or other mood disorders, based on the use of an appropriate screening instrument for persons without a current diagnosis of depression, which the health professional may select from various available standardized screening tests designed for this purpose and recognized by national medical professional organizations
- Review of the individual's functional ability and level of safety based on direct observation, or the use of appropriate screening questions or a screening questionnaire, which the health professional may select from various available screening questions or standardized questionnaires designed for this purpose and recognized by national professional medical organizations
- Establishment of a written screening schedule for the individual, such as a checklist for the next 5–10 years, as appropriate, based on recommendations of the United States Preventive Services Task Force (USPSTF) and the Advisory Committee on Immunization Practices (ACIP), as well as the individual's health status, screening history, and age-appropriate preventive services covered by Medicare
- Establishment of a list of risk factors and conditions for which primary, secondary, or tertiary interventions are recommended or are underway for the individual, including any mental health conditions or any such risk factors or conditions that have been identified through an Initial Preventive Physical Examination (IPPE), and a list of treatment options and their associated risks and benefits, Furnishing of personalized health advice to the individual and a referral, as appropriate, to health education or preventive counseling services or programs aimed at reducing identified risk factors and improving self management, or community-based lifestyle interventions to reduce health risks and promote self management and wellness, including weight loss, physical activity, smoking cessation, fall prevention, and nutrition

ACA, Patient Protection and Affordable Care Act.

Community Context

The proposed framework (Figure 111.2) recognizes the community context in which the stakeholders operate. This context is represented by the local, regional, national, and global community representing an environment in which not only local (site-based, townships, cities, etc.) policies and protocols influence activity but also the larger aspects of civil society, the competitive marketplace, the relative influences of a community's health and welfare, and the context of global forces that influence the health and well-being of a population. In the context of community, multiple determinants of health should be considered—not only those that may be considered in the context of health care or health systems.

Clearly, there are more to health than health care alone. In fact, most of a population's health status is not determined by the health care sector [23,24]. Whereas access to health care is in itself an important determinant of health, other determinants, such as the social gradient, early-life experiences, education, employment, poverty, access to transportation, clean air, clean water, and a built environment conducive to healthy living, represent factors that, when acted upon, are of vital importance to population health improvement [49]. Gross inequalities in society influence the opportunities that people have and the choices that they make. These opportunities and choices, in turn, have a direct impact on the health of the population—to quote the Commission on Social Determinants of Health's report: "Social injustice is killing people on a grand scale" [50]. Furthermore, health inequalities significantly impact costs to society associated with managing the ill-health effects of such disparities. As a result, health disparities negatively impact the economic prosperity of society and addressing them improves not only population health but also the economic vitality of communities,

regions, and the nation as well. As outlined by Dr. Joseph Stiglitz and colleagues, the establishment of healthful natural and built environments and equitable social and economic policies and institutions not only ensure happiness and harmonious relations among the population but also address security among people [51]. Hence, nonmedical determinants of health extend their impact beyond health-related outcomes alone and reach economic, interpersonal, and safety outcomes and experiences. These important nonmedical determinants cannot be assigned to a medical diagnoses code or tied to reimbursement, and they are not mentioned in the list of most important clinical preventive services [21]. Even so, they must be addressed as part of an integrated multisectoral health policy agenda.

Approach to Healthy Lifestyle Integration

Based on the early work of Dr. Michael O'Donnell [52] and adapted to reflect a more contemporary context, an approach for the integration of lifestyle medicine in health systems may be organized around four components: (1) awareness, (2) engagement, (3) behavior change, and (4) supportive environments. These four components provide a powerful organizing principle to improve the health of populations since together they can act complementarily, additively, or synergistically. One component by itself may have some success, but only by taking them together can optimal impact be achieved. In particular, the creation of supportive environments is paramount since this level of programming will enable and support individuals to adopt and maintain changes in behavior.

Awareness

Awareness programs are designed to increase a person's level of knowledge, awareness, or interest in a certain health topic. Whereas these programs may affect an individual's belief, attitude, and knowledge on the topic, they usually do not result in significant increases in the desired behavior. Hence, awareness programs by themselves are not effective. However, they improve outcomes when offered in conjunction with programs that engage people in health actions and behavior change. This issue has been clearly demonstrated by the recent worksite reviews conducted by the Task Force on Community Preventive Services [16,45]. The assessment of health risk with feedback (AHRF) may be considered an awareness program as it is defined as the collection of health information, translation of this information into a risk status or category, and the provision of such risk information to the participant. The Task Force found insufficient evidence to determine the effectiveness of AHRF when implemented by itself as a primary intervention. However, the Task Force found sufficient or strong evidence that AHRF plus health education programs generates significant health outcomes in the areas of tobacco use, alcohol use, physical activity, seat belt use, dietary fat intake, blood pressure, total cholesterol, summary health risk scores, number of lost days from work, and use of a variety of health care services.

Engagement

Whereas awareness programs relate to a person's knowledge and interest in a health topic, engagement goes deeper and refers to the degree of motivation and participation in health actions. Engagement is a necessary step in bridging the gap between awareness and successful behavior change. Individuals need to try new behaviors, model those behaviors in their own environments, and adapt to such new situation in a positive manner. Indicators of engagement may include participation, time spent in the health activity or new behavior, degree of interest expressed in feedback, general satisfaction with the program, and willingness to refer others into the program, among others.

Health systems have direct relationships with individual members and those members also represent patients in the clinical setting. Members may also be employees in the workplace setting. The effective use of benefit design, communication methods, incentives, and behavioral economics [53] has the potential to spur people into action and create supportive environments in the clinical, occupational, and economic environments of the member.

Behavior Change

Adoption and maintenance of new lifestyle behaviors is a challenging task for most people. The successful and long-term adoption of new behaviors such as nonsmoking, regular exercise, healthful eating, or to discontinue harmful drinking requires personal motivation, support from others, continued reinforcement, and positive feedback. Despite such challenges and difficulties, population-based programs designed according to identified success factors have shown to positively move the entire population to an improved level of health status over the short-term as well as over the longer-term. Edington [54] has shown a natural flow of risk transitions over the course of 3 years—the natural flow is negative in that an increase in health risks are experienced over time in the absence of health-promoting interventions. Loeppke et al. [26] used a similar risk transition format to describe the intervention effect of a prevention program and reported a net improvement in population health level of 13.5% as compared to the natural flow expected based on Edington's model, which would have been −7.1%. Another population-based example of a multiyear program reported a net improvement of 6.1% in modifiable behaviors over the course of 3 years of intervention although this change model used different parameters than the Edington model and they can therefore not be directly compared [27]. One of the strongest reports providing evidence that it is possible for populations to improve their level of health through lifestyle modification comes from the diabetes prevention program [55]. In this study, conducted as a randomized controlled trial, a lifestyle intervention of 3 years induced 5.6 kg of weight loss, and 58% of the group had increased their levels of physical activity enough to meet guidelines for health benefit. The result was a 58% reduction in risk for type 2 diabetes.

Supportive Environments

Supportive environments are critical for adoption and maintenance of healthy lifestyle behaviors. Physical and social environments are the context in which individuals work, play, and live their lives. Humans are affected by characteristics of their physical, cultural, social, and economic environments. When the environment makes healthy choices the easy choices, it is more likely that larger numbers of people succeed in living healthfully and, thereby, successfully prevent or delay premature morbidity and mortality. The food that is eaten depends largely on the food that is available and accessible—it is not merely a matter of personal preference. Food preference is very much related to marketing and pricing and how people perceive its value [56]. The level of physical activity is related to the environment, too, not only to an individual's intention to be active. Prolonged sitting, an emerging independent health risk factor, is largely a result of the continued decline in occupational physical activity over the past 50 years [57]. Tobacco use has decreased dramatically since policies were instituted that banned smoking from public places, including worksites [16,31]. Hence, attitudes, beliefs, and value are affected by the macroenvironment in which individuals live. When this macroenvironment remains a barrier to the adoption and maintenance of healthful living, programs aimed at influencing individual behaviors may be expected to have little impact. Figure 111.4 represents the concept that individual efforts made toward optimizing one's health potential are supported, or hindered, in large part by the public policies that shape the physical, social, and economic environments of communities.

Health systems have many opportunities to create supportive environments. Examples include health benefits designs that create incentives for individuals to engage in their own health, employers (purchasers) to promote health, and providers to focus on health. Prompts that come from the plan to remind people to come in for their clinical preventive services (these may be sent electronically using secure web-mail or as a simple mailing), reminders regarding access to services to support smoking cessation, enhance physical activity levels, or achieve a healthy weight.

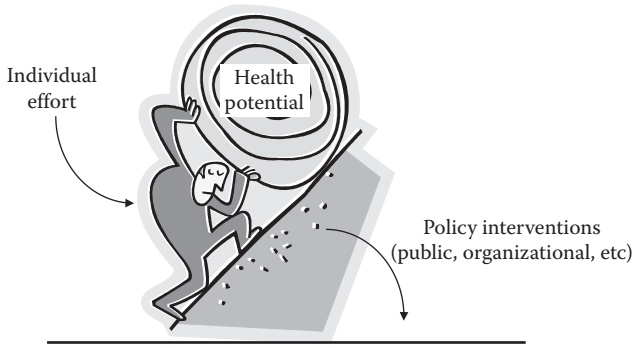


FIGURE 111.4 Making healthy choices the easy choices.

STRATEGIES AND TACTICS

Framework for Action

One component of the National Physical Activity Plan is a framework for promoting physical activity in the business and industry sector [58]. This framework has been adapted here to reflect a focus on health in general and an introduction of example tactics. The result is depicted in Table 111.3. Horizontally, the factors outlined ensure that health improvement can happen, is likely to happen, and may be adopted and sustained by considering the notion that it is possible for individuals and groups to improve health, recognize that they are incented to do so, and connecting the efforts to ongoing activities within the larger community. Vertically, the framework recognizes the importance of action at multiple levels. Strategies to promote, adopt, and maintain healthy lifestyle behaviors long-term need to be supported by specific tactics that can be implemented at the level of individuals, groups, organizations, and the environment (physical, social, economic, etc.). It is important to carefully select individual, team, organizational, and environmental-tactics in order to ensure a balanced approach to successful implementation. In the words of Sun Tzu, "Strategy without tactics is the slowest route to victory. Tactics without strategy is the noise before defeat." [59]. Taken together, strategies and tactics create a powerful method to generate successful outcomes of initiatives to improve the health of the population. Considering the grid outlined in Table 111.3, several specific tactics are inserted in the cells of the grid which may be helpful to envision how this framework may be used to create a strategic and tactical plan.

The framework outlined in Table 111.3 also serves to connect the tactics to the overall strategic approach depicted in Figure 111.2. In order to successfully implement programs that simultaneously generate an exceptional experience, population health, and a positive return on investment (i.e., achieve the Triple Aim), the process of implementation should be carefully considered since participation in health improvement programs is paramount to successful outcomes. In the absence of participation, nothing happens to population health. Without population health, any economic outcomes observed cannot be attributed to health promotion efforts. As such, to paraphrase Elliot Freidson [60], "the process used to improve health constitutes a dimension quite as distinct and fully as important as the outcomes it generates."

Program Mix

Besides the process used, the choice of interventions also needs to be carefully considered. Here, it is important to consider multiple program topics that address a variety of health needs, to provide choices for individuals, to deploy multiple modalities for program implementation, and to select those interventions that show the highest likelihood for success.

TABLE 111.3
Framework to Support Connecting Strategies with Tactics to Improve Population Health

		Make Being Healthy …						
		Possible	**Simple**	**Socially Rewarding**	**Financially Rewarding**	**Personally Relevant**	**Organizationally Relevant**	**Community Connected**
Level of influence	Individual	Easily accessible program options		Individuals recognized for achievement		Choice of program tailored to personal need		
	Inter-individual			Groups recognized for achievement				
	Organizational						Health system analyses indicate lower cost as health improves	
	Environmental		Opt-out design facilitates exposure and engagement		Participation linked to preferred health benefit differential			Health actions include community resources

Note: Examples of tactics are inserted for illustrative purposes only.

Evidence-Based Approaches

When it comes to implementing health promotion programs, following evidence-based practices is increasingly recognized as a prudent way to optimally use scarce resources. Many programs have been identified as being "evidence-based" and health systems should take full advantage of available resources that outline such programs. In general, when faced with resource allocation decisions, preference should be given to those interventions that come with evidence of effectiveness versus those that do not. Decisions to apply resources toward programmatic solutions are often challenged by demands and cycles of accountability within the political context that are based on a need to satisfy short-term demands or interests. Many health systems, however, have already built evidence-based principles into their decision-making processes that relate to clinical care delivery. Since 1984, the U.S. Preventive Services Task Force (USPSTF) is a well-known reference for that purpose [61]. When considering community preventive services, the Task Force on Community Preventive Services [31] systematically reviews the evidence of effectiveness for interventions in the realm of health promotion and disease prevention. The Task Force on Community Preventive Services leads the development of the Guide to Community Preventive services ("the Guide") and makes its recommendations and reviews available via the web (see: www.thecommunityguide.org), publications, presentations, and other tools, products, and services. Other institutions that provide excellent recommendations based on systematic reviews of all the scientific literature related to a given intervention include the National Institute for Health and Clinical Excellence in the United Kingdom (see: www.nice.org.uk) and the Cochrane Collaboration (see: www.cochrane.org).

Program Topics

Depending on the setting in which the health system supports the implementation of programs, selection of program topics and interventions needs to be carefully considered. For example, if a health system partners with an employer group, a comprehensive, multicomponent, and multilevel program tends to be most likely to generate successful outcomes [58]. On the other hand, if the health system implements a direct-to-member strategy to improve health, a more tailored or topic-specific approach may be preferred. As such, topics for health improvement may be selected from a long list, and a wide variety of activities may be associated with any given topic. Topics may include physical activity, tobacco cessation, weight management, sleep hygiene, stress management, resilience, healthy nutrition, rethinking drinking, preventive services, and medication adherence, among others. Within each topic, activities may range from pedometer walking programs to half-marathon training programs for physical activity or pay-for-performance programs for care delivery to reduce tobacco use among members to supporting referral to state quit lines for tobacco cessation.

From a health system's perspective, it may make sense to focus on those topics that are most strongly related to member health burden, avoidable health care costs, and for which effective interventions exist. Physical inactivity, poor diet, heavy alcohol consumption, and cigarette smoking have been identified as actual causes of death in the United

States since they cause type 2 diabetes, cardiovascular disease, stroke, elevated blood pressure, certain cancers, back pain, high cholesterol, and other chronic conditions [3]. Occurring in clusters, these behaviors are responsible for approximately 40% of all deaths, nearly 80% of chronic diseases, and, through their association with chronic disease, are related to nearly 75% of all medical care expenditures in the United States [62,63]. Simultaneous adherence to these four lifestyle behaviors is associated with lower mortality from cardiovascular disease and all-causes in both men and women [64,65]. Furthermore, among adults, adherence to these four behaviors is associated with short-term, 2-year incidence of chronic disease in a dose–response manner [66], and also correlates with indicators of emotional health [67]. Whereas these associations are certainly bi-directional, messaging around the adoption of a lifestyle that is physically active, where an individual does not use tobacco, misuse alcohol, and eats five servings of fruits and vegetables daily is very much common sense. Simply put, adherence to one of these four is better than none, more is better than some! Alternatively, a "just add one!" message would be right on target.

PATIENT PROTECTION AND AFFORDABLE CARE ACT

At the time of this writing, health systems, employers, care delivery organizations, and a host of other organizations dealing with health care in the United States are working to understand the implications and changing to ensure compliance with the PPACA [45]. When considering the opportunity for health promotion and modifiable lifestyle behaviors to be addressed in the health systems setting, a lot will depend on the incentives that will drive the actions of each of the 4-Ps identified as the four stakeholders in this chapter. Alignment of their incentives around health objectives or, perhaps more importantly, around the Triple Aim, will present opportunities for health promotion strategies to be deployed. Whereas cautious optimism exists that this may be the case, it is too early to tell and it remains far from clear to delineate how this may happen.

One promising development delineated in the ACA is the introduction of Accountable Care Organizations (ACOs) in the community. The ACA requires the secretary of health and human services to establish a shared savings program for groups of health care providers that join forces, with or without hospitals or health plans, to form legal entities that agree to take responsibility for the quality, cost, and overall care of a population of patients [68]. In case the savings of such a program will be related to the "total cost of care" related to a defined group of people receiving services from an ACO, it would make a lot of sense for such ACOs to ensure that the healthy people of this population stay healthy, those who are ill receive high-quality care, and those at risk for costly care receive close monitoring to prevent avoidable hospitalizations.

SUMMARY

This chapter has presented an overview of the opportunities that reside within health systems to integrate modifiable lifestyle behaviors into their products and services, their relationships with other stakeholders, and the potential benefits that may be gained by doing so. An economic rationale has been presented supporting this approach, and frameworks that may guide this work have been introduced. In order to position health promotion as an integral part of what heath systems do, the incentives need to be aligned with those of several other key stakeholders, most importantly the providers of health care, the purchasers of health benefits, and insured persons. As health care in the United States moves into its next iteration, integration of health promotion remains understated in its importance to help achieve the central objectives of cost containment and improved population health. Yet, in this age of dramatic change in the health care industry, health systems are uniquely positioned to draw upon the potential health promotion offers to align the stakeholders and generate outcomes of mutual interest.

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112 Financial Impact of Worksite Health Management Programs and Quality of the Evidence

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CONTENTS

Introduction 1325
Financial Impact of Disease Management Programs 1327
Bottom Line: More Research and Better Methodology Are Needed to Evaluate Programs 1328
Literature Review on the Financial Impact of WHM Programs 1328
Disease Management 1328
Lifestyle Management 1330
WHM Evaluation Methodology Challenges 1331
WHM Evaluation Methodology Recommendations 1332
Methodology Overview 1333
Eligibility 1333
Base Period and Reporting Period Timeframe 1333
Trend and Cost Assumptions 1333
Regression Models 1333
Discussion 1334
References 1335

INTRODUCTION

This chapter reviews the financial impact of worksite health management (WHM) programs and the quality of the evidence in light of the utilized study methodology. The authors will provide a brief overview of WHM and then focus the majority of the chapter on a review of the literature demonstrating the financial impact as well as the issues associated with evaluating such programs. WHM can be understood as a type of population health management focused on the worksite. Pronk[1] defines population health management at the worksite as "the strategic and operational processes used to generate the health outcomes of a defined group of individuals collectively associated with a company's health improvement efforts." WHM has been in place for several decades. As an example, O'Donnell's first textbook on WHM was published in 1984.[2] WHM has gained increasing popularity over the past 5–10 years as noted by the Mercer National Survey of Employer-Sponsored Health Plans findings on program prevalence. The 2010 Mercer National Survey of Employer-Sponsored Health Plans is the longest running survey of its kind and indicated increases in prevalence of health risk assessments, disease management, and lifestyle management programs of employers with 500–20,000 employees[3] (see Figure 112.1).

The rationale behind the increasing implementation of WHM programs involves several factors. One of the most common motivations among employers to implement WHM program is in an effort to mitigate increasing medical costs. While the overall rate of increase in medical costs has varied over time, trends are consistently two or more times greater than the Consumer Price Index (Figure 112.2).

Another reason for WHM promotion as a cost management strategy is that employers realize cost shifting is a short-term strategy and that eventually they will have to stop placing additional costs on the employee. Furthermore, with the U.S. health care reform phasing in, employers cannot shift costs too much or they will violate regulations around plan affordability, and if overall premiums become too high, employers face an excise tax. Therefore, given the limitations to cost shifting and the constraints of health care reform, more employers will continue to seek WHM strategies. In addition to the health care cost containment issues, WHM activities have impact on health care outcomes such as absence and productivity[4–10] serving as another piece in the business case rationale.

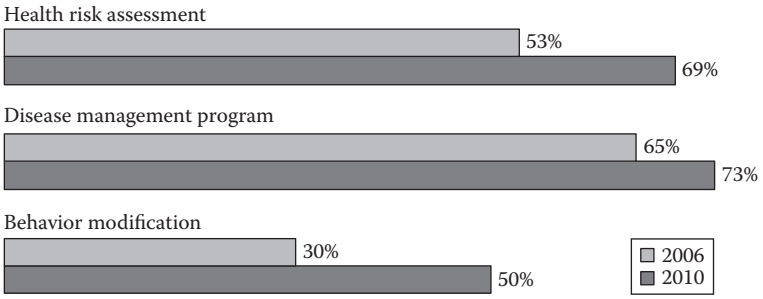


FIGURE 112.1 Rate of growth in WHM activities.

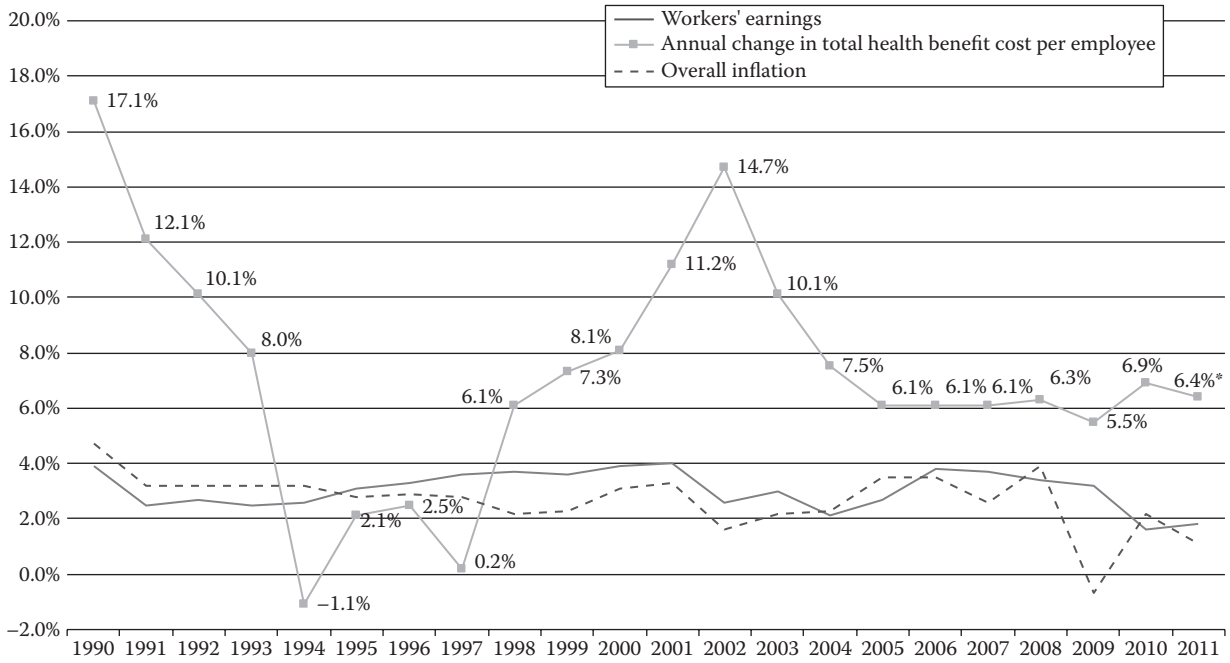


FIGURE 112.2 Health care cost trends and benchmarks. Source: Mercer's National Survey of Employer-Sponsored Health Plans; Bureau of Labor Statistics, Consumer Price Index, U.S. City Average of Annual Inflation (April to April) 1990–2010; Bureau of Labor Statistics, Seasonally Adjusted Data from the Current Employment Statistics Survey (April to April) 1990–2010.

Finally, the worksite is an ideal location for population health management interventions because it provides a(n)

- Cohesive audience
- Ability to modify physical environment and organizational policies such as tobacco use
- Opportunity for repeated exposure
- Chance to influence behavior through incentives and cultural norms

While there is a healthy skepticism by some business leaders as to the value of WHM, there has been a tremendous amount of knowledge accumulated over the past 30 years to help employers implement effective programs.[4,6,7,11] For example, one researcher with a long-term historical perspective, talks about the past 25 years in health promotion and the positive results of programs in both commercial and public sector.[12] However, some skepticism stems from poor past experiences potentially related to ineffective programs that were not implemented according to best practice approaches or that did not have a chance to benefit from more recent advances in the industry. There have been a number of articles that document WHM best practices.[13–16] One research study describes the relationship between identified best practice characteristics of WHM programs with increase program engagement and greater reduction in health risk.[16] Nine best practices were identified: comprehensive program design, integrated incentives, integrated comprehensive communication plan, strong senior management support, dedicated on-site staff, multiple program modalities (phone, mail, online), population-based awareness building activities, biometric health screenings, and vendor integration.

The Health Enhancement Research Organization (HERO, www.the-hero.org) Scorecard is another example of quantifying best practice approaches and benchmarking among employers. The scorecard is a tool that assesses WHM programs on the following dimensions: corporate culture and leadership commitment, strategic planning,

communications/marketing promotion, program components, benefit design, incentives, program coordination, data management, and evaluation. Each area is given a score and weighted to combine for an overall score. Participating employers can compare their scores with other employers as well as use the tool as a planning guide. Other organizations, such as the National Committee for Quality Assurance (NCQA, www.ncqa.org), URAC (formerly the Utilization Review Accreditation Commission; www.urac.org), and the National Business Group on Health (NBGH, www.wbgh.org) also have tools to review program quality and whether the programs meet standards associated with a higher probability of success.

Understanding best practice approaches helps program evaluators determine whether the reason for the lack of program outcomes was a result of a truly faulty program design or due to poor implementation. In many cases, poor outcomes and lack of return on investment (ROI) are a product of less than best practice implementation rather than a flaw in the WHM science and rationale. As an example of strong best practice implementation and outcomes, one can note the programs that qualified to win the C. Everett Koop Health award. Those winners all report impact on both health improvement and health care cost savings. Likewise, the Centers for Disease Control and Prevention (CDC) funded research on WHM best practice approaches and found few companies take advantage of key practices toward assessing the need for services, attracting participants, using behavioral theory as a foundation, incorporating multiple ways to reach people, and making efforts to measure program impact.[17]

FINANCIAL IMPACT OF DISEASE MANAGEMENT PROGRAMS

It is important to remember the initial definition of WHM as we consider the research on the financial impact of these programs. The definition is general in nature and encompasses programs that range in scope from focusing on chronically ill populations for disease management to those at risk for illness by virtue of lifestyle, as well as wellness populations that need to be reinforced for healthy behaviors. WHM programs may include some or all of these programs and target some or all of the population described. This variation in program offering and population target can add to the complexity of comparing research. For example, research conducted by Goetzel et al.[18] on disease management is an important follow-up to the Congressional Budget Office study that found limited positive financial evidence supporting disease management programs,[19] although they did find evidence showing programs improved clinical and process-related measures. This study focused on research with financial impact measures of disease management programs and more specifically, those articles where an ROI was calculated or could be calculated based on the data presented. The study covered asthma, congestive heart failure (CHF), diabetes, and depression.

The authors' review indicated an overall positive ROI for CHF programs and programs covering people with multiple conditions. Evidence for diabetes seemed to indicate a positive ROI, but studies on asthma and depression looked as though they might cost more than they save. Although the authors' conclusions are consistent with the data reviewed, they acknowledge that the analysis is highly limited as noted in the following list:

1. The number of studies reviewed was small and generally 2001 or earlier.
2. Sample sizes tended to be small.
3. There was tremendous variation in types of programs implemented. Most programs were not "population based" as there were any number of exclusion criteria used in the analysis.
4. Age and gender of the population varied across studies.
5. Studies' designs and evaluation methods were very limited and subject to bias such as regression to the mean, selection bias, poor financial metrics, and lack of baseline or appropriate comparison group.
6. Review methodology grouped studies according to whether they were randomized clinical trials (RCTs), controlled before and after studies, or descriptive before and after studies. There were very few RCTs that reflect the current implementation models.

General skepticism on limited impact might also be fueled by another review of disease management[20] until one notes several key points regarding the article:

1. The author's main theme is that there are inconclusive published data available to determine the savings impact of disease management programs.
2. Methodology used by researchers is not rigorous or sensitive enough to detect financial program impact.
3. The author only found three large-scale published studies to review. Two studies focused only on diabetes and did show net savings. The third study covered multiple diseases and showed improved care and lower increases in the participant group but no net savings.
4. The other studies reviewed tended to be small demonstration projects focusing on high-risk groups that don't easily generalize to commercial populations.
5. The study was a review of reviews, so there may have been something lost in the translation.
6. The dates of the studies go back to 1990, which are not representative of today's approach.
7. There were no long-term studies available. One year was the typical study period.
8. Key findings:
   a. Improved quality of care and disease management process
   b. Net savings in two of the three large studies
   c. Inconclusive evidence, to date, to "prove" disease management yields net savings

Bottom Line: More Research and Better Methodology Are Needed to Evaluate Programs

If the program can improve the clinical process, we assume that the outcomes will also improve. Disease management programs seem to improve the process (i.e., quality of care) for those engaged in the program. Contacting, reaching, enrolling, and engaging identified populations are major challenges for disease management. The cost associated with the engagement process can outweigh the benefit if only a few members are engaged. More effective outreach and incentives for participation will help drive a positive ROI at the population level.

Interestingly, these articles are focused on disease management, which is sometimes generalized to WHM, but there is more evidence for positive savings for wellness programs than for disease and case management. Furthermore, it is very important to note that the disease management studies rarely report net positive savings in year 1. Disease management studies occasionally report positive impact in years 2 and beyond, which is consistent with what the theoretical models would suggest (i.e., uncovering problems, which generate short-term increase in utilization but avoidance of high cost services). As further support of the disease management model, Mattke et al. note that depression disease management increases costs and utilization, which is exactly what they are designed to do in the short term.[20] In that way, they reduce costs for other comorbid disease states as well as mitigate any long-term catastrophic costs.

One major challenge to determining the impact of WHM programs is the limited number of published studies on program impact within the past 5 years. This is an understandable phenomenon given most WHM programs are implemented by employers with a business motive to contain costs and improve productivity. While employers want to measure their program impact to justify program investment, they have limited motivation to publish the findings in peer-reviewed journals. Most studies on WHM are conducted by academics, vendors, and the rare employer willing to invest in the cost of conducting a rigorous analysis. Therefore, given the limited number of studies available on the topic, this section of the chapter will recap the literature reviews in the field and then discuss several studies conducted within recent years to give a start to what will be the basis for a critical mass of evidence for modern best practice programs as well as further documentation of health management financial impact.

LITERATURE REVIEW ON THE FINANCIAL IMPACT OF WHM PROGRAMS

There has been an increasing need for a review and synthesis of the impact of WHM programs given the growing interest by employers and policy makers to use WHM as a primary health care cost containment and productivity enhancement strategy. There have been a number of literature reviews conducted in the past 10 years that tend to focus on the wellness programs within WHM and some have included disease management as well.[4,6–8,18,20–22] The problem is that with few new studies being published, these reviews tend to review the same studies, include reviews in the review, and cover commercial (WHM) and public sector (Medicare and Medicaid) populations in the same review without differentiating the very different program challenges present in the varying populations. One review that conducted a meta-analysis did not take into account the quality of the evaluation being conducted, the difference in program scopes, or the variation in populations.[21] Other reviews reported out the study findings in an objective format, but again took the findings on face value. One review attempted to weight the study findings by research design quality and convert the outcomes to total population metrics such as impact on total health care costs.[22] Those researchers looked at health promotion programs separately from disease management programs as well as combining the two (Table 112.1).

TABLE 112.1
Health Care Cost Impact and ROI from WHM Programs

	Health Promotion		Disease Management		Employee Health Management	
	Low Range	High Range	Low Range	High Range	Low Range	High Range
Average savings (% impact on medical costs)	2.20	2.76	1.01	1.27	3.22	4.02
Average ROI	3.0:1.0		2.0:1.0		2.5:1.0	

The earlier review of reviews indicates consensus of positive ROI and health impacts based on reviews that span at least two decades. Research still needs to refine these program impacts over time, program types, populations, and settings. While not being reviewed here, there have been some studies on the relationship of organizational culture and program impact that have also showed a powerful effect of factors beyond program services.[16,23]

The following is a review of recent studies that demonstrate strong methodology, analyze a specific program intervention, and provide evidence for program impact. They also reflect the latest best practices and program innovations in a rapidly evolving program landscape. Few studies are conducted of comprehensive interventions but most address the total population in one way or another.

DISEASE MANAGEMENT

Review of recent studies in the disease management arena has revealed several interesting studies, but as a review by de Bruin et al. indicates, the evidence is inconclusive.[24]

There are studies that demonstrate impact on specific programs. For example, one recent study conducted by Wennberg et al. provides strong evidence for the impact of telephone-based coaching for those with chronic conditions.[25] This study used a randomized control design to document the incremental benefit of enhancing the standard care disease management approach to predictive modeling, outreach, and frequency of contacts. The intervention arm of the studied termed "enhanced care," which entailed outreach to a larger portion of the population by lowering the threshold for eligible participants, was compared to an existing commercial program. The findings indicated that in the population with the enhanced care, average monthly medical and pharmacy costs per person were 3.6% ($7.96) lower than the population with the usual support ($213.82 vs. $221.78, $P = 0.05$). A 10.1% reduction in annual hospital admissions ($P < 0.001$) accounted for the majority of savings. These findings may seem modest but are compared to those in standard disease management who may also be experiencing savings. The authors did not compare the enhanced care group to population of individuals with chronic conditions who did not receive some level of treatment. In addition, the savings are presented "per member" not per participant. Given roughly, 10% of the members have a chronic condition, and only a portion participated; the savings per participant would be significantly higher. The authors indicate the cost of this intervention program was less than $2.00 per person per month and therefore provides a strong return on the investment. Again, it is important to note that the price is per all members, not just those with a chronic condition. This raises another complexity when comparing research—the measurement of savings is not consistent. Savings are reported in a variety of ways including per member, per identified, and per participant. When comparing results, it's important to be aware of these nuances.

Another disease management study that looked at cost of care, utilization, and quality used a strong evaluation approach in a fee-for-service environment and also included complex care management as part of the intervention.[26] The evaluation of the difference in utilization was based on the difference in the cost per-member-per-month (PMPM) in a 1 year measurement period, after adjusting for differences in fee schedules, case-mix, and health care benefit design. After adjustments for both case-mix and benefit differences, the study group was $63 PMPM less costly than the comparison population. Interestingly, the effect increased with age. Cost differences are largest in the 55–64 years and 65 years and above age groups. The study group was $115 PMPM lower than the comparison population for the age category of 65 years and older.

Most of the published research included in literature reviews tends to be on either mail- or phone-based delivery channels. A rapidly growing program modality involves the web-based delivery of disease and lifestyle management programs. This study examined the impact of a web-based disease management program on medical cost among health plan members.[27] The study used a matched cohort design in a retrospective quasi-experimental approach. The sample size was 413 participants and 360 nonparticipants, all members of the same health plan. The web-based program was a rigorous program requiring ongoing engagement and program interaction, all within a broader health management context that, in some cases, included telephonic support. The researchers considered participants, only those members who completed all requirements of the program and for whom claims were available during the evaluation period. The results yielded significant financial impact of $757 per year less for participants as compared to matched nonparticipants. Authors indicate this is a ROI of almost 10:1. It is important to note that self-management web-based program may not be applicable to all members, but of those that engage in them, there appears to be a significant impact although this type of return is considerably greater than those typically reported and may be a function of the methodology used to assess program impact.

Another form of medical management involves the process of medical claims monitoring and alert systems. While technically not a disease or lifestyle management program, these activities often serve as the basis of outreach for disease management nurses and provider compliance programs. The interventions tend to involve direct communication with providers and, in some cases, the employee or health plan member. The intent is to increase provider and patient compliance with evidence-based medicine. One study done in 2005 and then a follow-up in 2008 used a claims data-based sentinel system to improve compliance with clinical guidelines.[28,29] The evaluation used a randomized prospective design and found among those in both intervention and control groups who triggered recommendations 19% fewer hospital admissions in the intervention group compared with the control group ($P < 0.001$). Health care charges among those whose recommendations were communicated were $68 PMPM lower among controls compared with the baseline values ($P = 0.003$). Paid claims for the entire intervention group (with or without recommendations) were $8.07 PMPM lower than those for the entire control group. The authors note that the intervention cost $1.00 PMPM, suggesting an eight-fold ROI. In a follow-up study, the researchers analyzed the effect of a decision support tool designed to help physicians detect and correct medical "missteps." The key findings were that the new information technology lowered average charges by 6% relative to the control group. This area of intervention has grown into what is also known as "gaps in care" interventions and is often used as a basis for how programs prioritize care management plans.

The focus of this chapter is on financial impact; however, it seems relevant to acknowledge the clinical basis upon which the financial impact is said to follow. In addition to the aforementioned studies on increasing compliance with evidence-based guidelines, a study conducted by Pimouguet et al. reviewed the effectiveness of disease management programs specific to diabetes that focused on improving glycemic control in adults found consistent results.[30] Programs on average provided about 0.51% reduction in hemoglobin

A1c levels. One theme of this meta-analysis was that they found a positive relationship between program impact and patient contact. A second and recurring theme throughout the literature was the relatively modest clinical impact of the programs.

LIFESTYLE MANAGEMENT

Lifestyle management programs address behavioral risk factors typically identified and targeted through screenings and health risk assessments. Lifestyle management has been a core element of WHM programs for more than a decade. Targeted programs aimed at those members at moderate and high risk is thought to be an effective approach to population health management. One review of the research on the impact of using health risk assessments and follow-up feedback indicated a positive impact on health risk change but did not evaluate financial impact.[9] However, a study by Naydeck et al. assessed the impact of a comprehensive WHM program for Highmark employees on health care costs over a 4 year period.[31] The study used an external control group to compare the participant change versus similarly matched nonparticipants. The results of the multivariate *models estimated health care expenses per person per year as $176 lower for participants. Inpatient expenses were lower by $182. Four-year gross savings were $1,335,524 compared with program expenses of $808,958, therefore yielding an ROI of $1.65 for every dollar spent on the program. This study contributes to the limited data on evaluations of multiyear programs. Another study of a program that has been in place for 30 years looked at the past 6 years of program impact on health care costs.*[32] *The evaluation measured the participant company's, Johnson & Johnson, health care cost experience* against similar large companies. Johnson & Johnson experienced average annual growth in total medical spending that was 3.7% points lower than the similar large companies. Company employees benefited from meaningful reductions in rates of obesity, high blood pressure, high cholesterol, tobacco use, physical inactivity, and poor nutrition. Average annual per employee savings were $565, producing an ROI equal to a range of $1.88–$3.92 saved for every dollar spent on the program. The most recent study available on a comprehensive population health management program was conducted for three years of program operation and included lifestyle and disease management as well as nurse line (Serxner et al. 2012).[33] The authors used multivariate regression to control for selection bias and understand the independent as well as incremental contributions of each program to the overall cost impact. While the ROI in year 1 was not positive, the following 2 years were positive which yielded an overall 3 year ROI of $2.45:1. By year three the participant health care cost increase was 8% compared to increases for the non-participants of 11.4%.

Further evidence for positive impact of WHM programs comes from the Healthy Lifestyle Incentive Program conducted with Salt Lake County, Utah, government employees over a 5 year period.[34] That comprehensive program, aimed at improving health behavior as well as preventing and controlling chronic disease, showed that over a 5 year study period, the cost savings in lower prescription drug and medical costs was estimated to be $3,568,837. A study of health promotion in a health plan population looked at the impact of health assessment, biometric screening, follow-up counseling, and online lifestyle management programs. The results of this 4 year evaluation showed that participants incurred consistently lower costs than risk-matched nonparticipants. Predictive modeling of upward cost trajectories relative to actual health care costs for participants and risk-matched nonparticipants indicated a savings of $350 per participant per year. These four studies, Johnson & Johnson,[32] Highmark,[31] Salt Lake County,[34] and HMSA,[27] combine to show a promising trend for sustained long-term program impact on health care costs.

A study by Nyman et al. found significant savings for disease management but not for lifestyle management.[35] Only small savings were detected for reduction absence with disease management participation. Interestingly, they only found disease management impact on the "big 5" conditions (asthma, diabetes, coronary artery disease, CHF, and chronic obstructive pulmonary disease), not all 11 conditions for which they had programs. In the case of musculoskeletal conditions, there was an increase in cost. Also of note was while the second year of program participation produced cost reductions, they were lower than the first year. Participation in the general disease management program over 2 years was associated with significant reductions in expenditures (approximately $1000 per year per participant averaged across conditions and various analyses), as was participation in programs for certain specific diseases. No consistently significant absenteeism or lifestyle management effects were found. Overall, the program (combined disease and lifestyle management) did not generate a positive ROI.

As noted earlier, a rapidly growing intervention modality is web-based programming. A 2011 study by Williams and Day attempted to assess whether an insurer-provided web-based wellness program resulted in cost and utilization improvements.[36] The web-based programs ranged from disease condition topics to self-care to lifestyle risks such as stress and smoking. The evaluation involved comparing participating employees to nonparticipants using generalized linear mixed models to study changes in costs and utilization while matching for differences between the two groups. Costs of program participants showed a lower rate of increase in 2004 and then dropped below those of the nonparticipants for the duration of the study. Between 2003 and 2007, the increase in medical expenditures of the participant group was significantly less than that of the nonparticipant group (31% vs. 46%). In addition, the participant group showed a lower increase in professional service expenditures and greater utilization of preventive services. The authors conclude that web-based insurer-provided wellness programs may decrease health care costs and encourage preventive service utilization. Another web-based WHM program looked at the effects of an incentive-based physical activity on health care costs.[37]

The employer (IBM) analyzed a matched sample of participants and nonparticipants on medical and pharmacy costs prior to program participation against program years. The results showed that participants average annual health care costs increased by $291 compared with an increase of $360 for nonparticipants ($P = 0.09$). Participants had significantly lower inpatient hospital costs as well as cost related to hear disease and diabetes. It appears that web-based WHM programs and disease management programs may have a positive impact on reducing health care costs.

In addition to telephone, mail, and web programming, there has always been on-site programming since the advent of WHP. Historically, on-site clinics focus on occupational issues and dealt with regulatory health surveillance and workers' compensation issues. More recently, the role of the on-site clinic has evolved to become more prevention and primary care oriented. Employers see on-site programming as a way to further engagement their population as well as reduce time away from work for medical visits. One study examined the impact of on-site nurse practitioner program on employee health care costs.[38] The researchers evaluated the program using two methods. One method compared actual to projected claims and the second method looked at nine major diagnostic areas accounting for almost 90% of the total claims. The first method yielded 8.7:1 ROI and the second yielded a 2:1 ROI. Taking a conservative perspective and adding any reduction in time away from work would indicate that the program provided a worthwhile benefit to the employee and employer.

Based on the earlier selected review of studies, there seems to be continued evidence that WHM does provide financial savings and a positive ROI, albeit modest in many cases.

WHM EVALUATION METHODOLOGY CHALLENGES

While the earlier review has served to provide a good context for estimated program impact, the discussion only briefly noted the methodological considerations that go with those study findings. This section will highlight major challenges involved with evaluation of WHM programs and make recommendations for enhanced approaches. One factor contributing to the limited number of published WHM outcomes studies is the degree of difficulty in conducting a rigorous program evaluation study. Another key factor is the applied nature of the environment in which the intervention occurs. This applied context poses a number of challenges as compared to a more controlled environment. The following are a few examples:

- *Interventions can change during the measurement period*—Employers are more concerned about results, employee experience, and budget than maintaining a consistent intervention to preserve study quality. Often employers will modify the intervention during the study period to improve participant experience, drive improved results, or be more efficient with limited resources.
- *Carriers/provider change*—Based on pricing, contracts, business relationships, and perceived or demonstrated performance, employers may change one or more of the vendor partners providing the program and services. This change introduces data issues as well as program continuity issues.
- *Data quality/access*—Financial impact studies of comprehensive WHM programs are data intensive requiring multiple years of data and involve many variables (demographic, program participation and outcomes). Each set of data may be located in with a different vendor and when located with a data aggregator may still have data integrity issues. Gaining access to multiple sources of data and linking them to a unique identifier require significant effort to assure data quality while maintaining individual-level confidentiality. Additionally, health care claims data can take months to mature, which can delay reporting and analysis.
- *Employee tenure*—Most outcomes studies involve some form of cohort design. However, in the worksite setting the members are constantly coming and going. Organizations experience varying degrees of turnover and even have different turnover rates within divisions. Employee tenure can introduce bias in the study and must be addressed in the analysis as well as in the extrapolation of findings.
- *Business environment*—The business environment is the overriding context in which the WHM program and evaluation occurs. If the business needs to shift priorities toward increasing production, containing costs, or marketing products, they may increase or decrease the workforce, reduce the WHM budget (and interventions), postpone the interventions, or limit the evaluation budget. All of the issues can affect the nature of the intervention, the study design, and the ability to conduct a rigorous analysis.
- *Benefits mentality*—WHM programs are provided as an employee benefit and as such are made available to all eligible employees/members. Withholding services is inconsistent with that philosophy and a general sense of fairness, all of which makes random assignment difficult or not an option in most worksites. Without random assignment, a number of threats to validity, such as selection bias and regression to the mean, require solutions.

Supporting data must also be considered as context to understanding findings on program savings and ROI. Often program impact and savings will be presented without information on the number of participants identified, targeted, enrolled, and engaged in a given program. Without information on the "participation cascade" the link to gross savings is difficult. Credible outcomes require having measures on leading indicators such as program engagement, risk reduction, and health service utilization. Furthermore, generalizability

analyses comparing the study sample to the total employer population must be conducted in order to understand the validity of extrapolating the savings from the study sample to the broader employer population.

Other challenges in WHM program evaluation and determining an ROI have to do with incorporating broader measures to address productivity and absence. In many organizations, quality absence data are not available and self-report productivity measures are viewed with less credibility by many employers. Productivity is acknowledged as a key impact of WHM programs, but employers are reluctant to include productivity savings in the ROI calculation. The focus tends to be impact on total medical and medication spending.

Working with claims data is a specialized skill set in addition to those required to conduct program evaluation analyses. Health care claims tend to be highly skewed with a large portion of the distribution having zero or small claim and a small portion of members having very large claims. Analysis needs to account for both ends of the distribution by addressing outliers as well as the skewed distribution. This topic will be addressed in the recommended methodology section of this chapter.

Two other issues that can introduce variation across studies are how key metrics are operationalized and the employers vary in terms of populations and programs, which can make generalization of findings difficult. One example of the operationalization issue is that of defining participation. Is an individual considered a participant if they register for a program, take one call with a coach, two calls or "graduate"? Employers, program providers, and researchers have no standard definition of participation for interventions or by modality such as what constitutes participation in web-based or mail-based programs. These definitions have important implications since many studies compare participants to nonparticipants, but if in one study, a participant is someone who simply enrolls and in another study a participant must graduate, comparing the two analyses would be challenging. Likewise, the control groups will be very different since the nonparticipant group might include some "participants" in one study but not in another.

WHM EVALUATION METHODOLOGY RECOMMENDATIONS

The discipline of WHM promotion has evolved dramatically of the past two decades. Probably one of the most important additions is that of disease management programs. With the advent of disease management programs, WHM began a full population health management approach; however, the disease management industry used very different evaluation and reporting approaches than the health promotion management industry. Most notably is the wide application of a trend-based evaluation for disease management compared to a statistical or health impact model for the health management industry. As the prevalence of disease management grew so did the interest in documenting ROI and the concern with the credibility and accountability of the standard practice methodology. To further the concerns of employers, as programs began to cover the health continuum, multiple program providers were implementing programs and claiming savings, which lead to a double counting or overestimation of savings. Recently, there has been movement in the industry to raise the standard of methodology. Several major program providers have started to adopt more rigorous approaches.[39] One of the industry organizations, the Care Continuum Alliance (formerly the Disease Management Association & America), has issued version 5 of their outcomes guidelines that provide a broad review of best practices that include a statistical approach to WHM program evaluation but make no specific recommendation on which methods provide the most credible evaluation results under which circumstances.[40] At least one major benefits consulting firm has been promoting an individual-level multivariate approach over the population-based trend methodology.[41]

Individual-level multivariate analysis—The following description of WHM evaluation guidelines is an enhancement to work published by Serxner et al.[42] Some of the key enhancements are the focus on using a two-stage regression approach to address selection bias. The recommendations discuss various options for creating a matched case control or using the propensity score in a regression model to predict "difference in difference" health care costs, utilization, and productivity changes. This approach is based on creating an individual-level database that includes detailed program participation information, demographics, and outcomes. The analysis involves using non-participant-derived financial outcomes compared to participant-derived financial outcomes prior to program implementation and for program years. The difference between this approach and the comprehensive population-level trend approach is that this approach involves using multivariate statistics analyzing individual participation records to document the program experience of each member, and then linking that intensity of participation with outcomes measures such as medical costs, prescription drug costs, and productivity measures. In addition to creating unique categorical participation variables, demographic variables such as age, gender, plan type, and geographic location should be part of the individual member record and controlled for in the analysis. For organizations that have detail participation data, this approach assesses the independent contribution of each discrete program component and eliminates any overlap in savings calculations or "double counting." A dose-response type of relationship can then be established to determine the incremental or additive benefit of each program component. The following is a description of the recommended approach; however, each evaluator will have to adapt the methodology to the specific situation based on available data, programs being evaluated, and the nature of the claims and participation data. Therefore, the following are guidelines to help evaluators and reviewers of literature determine the most rigorous approach for each context.

This approach is for a two-stage individual-level, multivariate analysis to measure the savings estimate for the ROI calculation. Outlined in the following is an overview of the methodology that the program evaluator will use to conduct the annual analysis. The proposed multivariate methodology assumes, through the use of statistical matching or propensity score weighting methods and covariates (e.g., adjusting the groups for differences in age, gender, and health risk burden), that the analysis can create a statistically valid (i.e., no statistically significant differences between participant and comparison groups on key variables) comparison model for nonparticipating and participating members.

Methodology Overview

The methodology compares nonparticipant outcomes to participant outcomes prior to program implementation and for each program year. Multivariate statistics are used to analyze the relationship between individual participation and outcome measures such as medical and prescription drug claims over time. Stage 1 of the process involves creating a comparison group using one of several methods (i.e., multi-pass matching, propensity score matching, propensity score weighting, or propensity score as a covariate). Stage 2 regression analysis involves comparison of participant and nonparticipant groups on financial, utilization, and productivity outcomes along with a robust covariate selection to control for differences that may not have been fully addressed in the matching process (i.e., stage 1). Through these methods, a quasi-experimental design will be constructed based on variables related to significant differences between the participant and nonparticipant groups controlling for selection bias as well as regression to the mean and other threats to validity. The final design and operationalization of the methodology should be mutually agreed upon by the parties in writing.

Eligibility

1. Eligibility should be defined in an identical manner between the Base Period and Reporting Period based on client benefits eligibility or program specific guidelines.
2. Individuals will be included in the analysis only if they have 6 months or more of continuous eligibility in both the Base Period and Reporting Period. In addition, an individual must be identified for inclusion in the program during the Reporting Period for at least 3 months.
3. The Base Period and Reporting Period group eligibility should be a minimum of 12 months. Individual eligibility requirement should include a minimum of 6 months of eligibility in both the Base Period and Reporting Period. Additionally, exposure (i.e., months identified for inclusion in the active care management portion of the program) should be included as a primary covariate in the analysis.
4. Analysis will be on active members between the ages of 18 and 65 years.
5. Individuals may be excluded entirely from the analysis for the following reasons:
   a. Coverage through Medicare carve-out
   b. Retired persons
   c. Certain procedures or conditions such as:
      i. Diagnosed with end-stage renal disease
      ii. Diagnosed as HIV positive or have AIDS
      iii. Received an organ transplant
6. Active participation in any program results in qualifying as a participant.
   a. Participation in any year qualifies as participating in that year
   b. In order to be considered as a participant in a program, the participant must engage in one or more counseling calls with a nurse/coach and meet the eligibility requirements listed earlier (note: definition of program participation may vary by vendor).

Base Period and Reporting Period Timeframe

One year of eligible member level claims costs (major service areas such as inpatient, outpatient, emergency room visits, professional services, and prescriptions for at least 6 months) prior to program launch will form the base period. Reporting population claims included should be symmetrical with the 12 month base period and reporting period eligibility. Baseline and measurement periods may be conducted on a calendar year or indexed basis (i.e., based on the participation engagement date). In general, indexing is preferred.

Trend and Cost Assumptions

Participant medical and pharmacy costs will be converted into an average per PMPM cost.

Regression Models

1. *Stage 1*: Comparison group: Using a multipass or logistic or multinomial regression process, an equivalent nonparticipant group will be developed. Results of the regression (propensity score) may be used to create a matched group or as a weighting variable that can be applied to eliminate differences between participant and nonparticipant groups.
2. *Stage 2*: Independent variables: The following variables are not meant to be a comprehensive list of factors to be considered and instead a subset of those most likely to be included in the multivariate model.
   a. *Participation*: Mutually defined in non-overlapping mutually exclusive categories
   b. *Demographics*: Age, gender
   c. *Clinical profile*: Including, but not limited to, disease state, level of comorbidities, health risk level, clinical standards of care compliance

   d. *Utilization history*: Including count of inpatient stays, outpatient visits, and emergency department utilization. Additionally, ICD-9 and CPT utilization, both the specific occurrence of and combination of
   e. *Participant risk*: Risk score derived from proprietary predictive models, episode risk score, resource utilization band, weighted average comorbidity index, or similar proxy
3. *Dependent variable*: Total and PMPM medical and prescription drug claims costs, utilization (inpatient, average length of stay, emergency department visits, etc.), and productivity measures.
4. *Modeling fundamentals*: Since the analysis involves repeated measures or longitudinal data, panel data and models appropriate to the distribution of the data (e.g., generalized estimating equations with gamma distribution) will be used. The inclusion of both participant and nonparticipant data within the same econometric model and the effect of the program by the parameter estimate for the interaction of group membership and time will be valid if the participant group and nonparticipant group are shown to be balanced on key demographic and cost variables.

As noted earlier, program evaluations have adopted the two-stage regression approach and the use of propensity scores to address the potential selection bias between participants and nonparticipants. The use of matching, weighting, or the score as a covariate has potential merits. The key enhancement to prior individual-level multivariate analyses is that the evaluator be able to demonstrate that process was employed that equalize the two groups on critical variables such as demographics, baseline costs, and health service utilization prior to conducting the second-stage regression analysis to determine impact on outcome measures of interest. Additionally, the second-stage regression should take into consideration the distribution of the data on their original scale (i.e., without logging the dependent variable, which presents retransformation issues) and the correlation of data over time, where appropriate.

DISCUSSION

Reviewing the studies of WHM seems to provide general consensus that these programs tend to provide a positive ROI. However, the results of any WHM study need to be considered within the context of detailed understanding of the exact nature of the program and the methodology used for evaluation. For example, the programs reviewed in this chapter ranged from medical data surveillance to lifestyle management. Some programs were delivered telephonically and others used web-based technology. Even within a given program area, such as disease management, there is tremendous diversity in the frequency, content, and quality of coaching calls across different program providers and worksites. The point is that sweeping generalizations about whether WHM has a financial impact can be misleading since the category of programs is broad, and the variability within program offerings can be significant. Additionally, evaluation methods do matter and have a dramatic effect on results. While enhanced two-stage statistical models have been accepted as the standard in the peer-reviewed literature they have not been widely adopted in the program provider community. Lack of consistency in programs offered and methods for evaluation creates a major challenge in summarizing the state of the art in WHM program impact.

Given the cautions about understanding the nature of the programs being offered and the methods used for evaluation, there was a theme across many of the programs reviewed. Overall, the programs provided positive but modest impacts. For example, a. 5% reduction on H1c means that an individual with a 10 only brings her level to a 9.5 when the target for most diabetics is 7 or less. The study on disease management by Wennberg et al. reported a 3.6% cost reduction in the participant group, but savings where limited to only five conditions.[25] The modest savings reported in many of these studies for participants or for a select group of participants need to be spread across the total program cost to justify the investment.

The business decision with regard to whether to invest in WHM programs is complicated and as with most business decisions involves weighing the costs against the opportunity. The level of rigor involved in this decision varies by organization, but in the case of WHM is also constrained by the lack of available quality studies on the topic. Estimated savings opportunity can be assessed by reviewing prevalence of risk and chronic conditions in a population, but estimating the probability for having an impact is more difficult. In addition, there are new considerations in calculating the cost of WHM programs. For example, recently, many programs include incentives for members to participate in WHM programs. Incentives have evolved from simple gifts to cash to lower health care premium contributions to richer plan designs. It can be difficult to assign a specific cost to the later incentives and many studies neglect to include any incentive costs in the ROI calculations. Other costs that may be overlooked are the costs of changing a culture by engaging leadership, implementing robust communications, and modifying the physical environment. Also difficult is assessing the potential success in changing the culture and, in turn, the effect that may have on driving positive program outcomes.

There are limitations to the published literature on the WHM that go beyond those of methodology or consistent program implementation. One such limitation is termed the "file drawer effect" of the phenomenon whereby only studies with positive results are published creating a publication bias in the literature. It is unclear how many unsuccessful program evaluations have not been disseminated, but clearly, this absence of balanced findings adds to the challenge of estimating program impact. One other challenge in deciphering results is that each analysis uses a different unit of analysis (e.g., per member, per identified, per participant, per employee but with spouse costs included as employee costs). The different units of analyses make it difficult to compare savings when the savings basis changes dramatically across studies.

WHM is growing in prevalence and continues to be considered a valuable method for improving population health as well as managing costs. Reported results of these programs have varied widely and, in some cases, been met with skepticism. The challenge for WHM is translating science into practice and in turn into a viable value proposition for business. The science of WHM draws on public health, psychology, economics, and many other disciplines. The multidisciplinary science used to develop programs that help people make positive behavior change serves as the framework for WHM but can be difficult to operationalize or provide programmatically on a population-level scale. The field of WHM has evolved over the past few decades to serve larger and more diverse populations through leveraging data, enhanced technologies, multidisciplinary training for practitioners, and robust clinical systems. However, there is still tremendous variability in WHM program design, implementation, and quality. All these factors provide a challenge when comparing one program to another. Continued program measurement and monitoring against best practice targets can begin to yield light on which programs and components are providing the most impact to support the credibility of the value proposition being made to business.

Going forward, quality and consistent implementation will be the key to participant engagement and ultimately to driving positive outcomes. Programs need to be data driven and science based to yield the highest probability of success. As worksites solve engagement issues through the combination of incentives, communications, and culture, the focus will increasingly be on quality and efficacy of the WHM programs. Commitment to quality measurement methodology and the resources required for the evaluation will serve providers by helping them improve their programs and generate a credible basis for their value proposition while at the same time serving the participant by providing relevant quality programs that ultimately help to improve their health.

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113 Future of Health Promotion in the Twenty-First Century

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CONTENTS

Executive Summary 1337
A Tale of Two Stories 1337
First Story 1338
Second Story 1338
Considering the Past and Present of Health Promotion 1339
Brief History of Health Promotion 1339
Business Problem and Solution of the Twentieth Century 1340
Twentieth-Century Health Promotion Solution 1341
Transition: Setting the Stage for a Transformation 1341
Changing Landscape in the Twenty-First Century 1341
Major Transitions in Health Promotion 1341
Business Problem and Solution of the Twenty-First Century 1342
New Century, New Decade, Changed World: New Journey 1342
Twenty-First-Century Health Promotion Solution 1342
Challenge Is to Grow Champion Companies or Remain on the Periphery 1342
Using Three Learnings from Successful Business Strategies 1343
Best Practices or Next Practices 1343
Keep a Good Customer or Go Find a New One? 1343
Strategic Systematic, Systemic, and Sustainable Strategies 1344
Future of Worksite Health Promotion in the Twenty-First Century 1344
Population Health Management: Next Assumptions 1344
Framework for Health Promotion in the Twenty-First Century 1344
Implementation of the Next Practices for the Twenty-First Century 1344
Create the Vision 1345
Create a Supportive Environment and Culture 1346
Develop Self-Leaders 1347
Recognize Positive Actions 1347
Measure and Share all Strategies and Outcomes 1348
What Will We Be About in the Twenty-First Century? 1348
References 1348

EXECUTIVE SUMMARY

A Tale of Two Stories

This chapter is our view, as told through two stories: the twentieth century maturing of health promotion and the twenty-first century transformation of health promotion into a serious mandate for creating positive health and high-performing populations. At the University of Michigan Health Management Research Center (HMRC), the two stories represent our focused research direction first from 1978 to 2010 and second from 2006 to present.

A focused research direction (story) begins with an intuitive or simplistic concept based on previous data and proceeds through the complexity of verifying (or not) the original concept and emerges on the back end as a simple easily understood conclusion. As Einstein said, "… if you can't explain it in simple and easily understood terms, you don't understand it well enough …."

The two stories are related in that they cover the development of the past and future of healthy and high-performing workplaces, workforces, and countries worldwide. Our prediction is that healthy and high-performing workplaces and workforces will be the competitive and cooperative advantage of the twenty-first century, whereas labor costs were the competitive advantage during the past three decades. Anything less than healthy and high-performing workplaces

and workforces in the twenty-first century will threaten sustainability of the organization and put the future of that population (workforce, community, and country) at risk of becoming irrelevant.

First Story

This story extends from the early formulation of worksite health promotion programs in the late 1960s and early 1970s, with their initial objectives of disease prevention, to their maturation in the early years of the twenty-first century. Health promotion programs at the worksite have traditionally focused on the reduction of health risks and improvements in healthy behaviors defined as the opposite of the precursors to disease. These precursors to disease were formulated by the early population studies at Framingham, MA [1]; Tecumseh, MI [2]; and other large-scale studies. The recognition of the complexity of the risks and behavior precursors and formulation of the Health Risk Appraisal was by an Indianapolis physician, Dr. Lou Robbins, after observing his own patients and the results of the population studies; the work in Canada; and the further development of algorithms and computerization by the Centers for Disease Control and the Carter Center in the United States [3].

The details of the first story can be found in the first section of *Zero Trends: Health as a Serious Economic Strategy* [4]. Table 113.1 documents the progression of understanding about three critical concepts: the natural flow of a population, the development of the business case for health promotion (worksite wellness), and the beginnings of transformational strategies for the twenty-first century.

Second Story

The second story arose out of the serious questioning of the outcomes and fundamental approaches developed by the practitioners of health promotion during the 30 years captured in the first story. In February 2008, we asked a team of experienced analysts, "Other than the precursors to disease, what could be the determinants of a healthy and high-performing workplace and workforce?" The answers we got were then pursued in the scientific literature to satisfy four criteria: can it be measured; is it connected to short and long-term costs to an employer; is it suitable to a questionnaire; and can it be reduced to one or two questions (for a paper questionnaire). If so, we included that determinant in the draft of the next-generation HRA. This work took 3 years. In the fall of 2010 and spring of 2011, we asked a similar question to every group we encountered, "If you worked for a very high-performing organization, how would you describe the workplace and workforce." In every case, we got the same responses we heard in early 2008. We feel these expanded health and business determinates of health plus a systematic, systemic, and sustainable business strategy will dominate the future of health promotion in the twenty-first century.

TABLE 113.1
University of Michigan Health Management Research Center Progression of Learnings: 1980–2010

Timeframe	Learnings
1980–1990	Establish the integrated data warehouse and databases for several companies
	Implement health risk appraisals
	Move from mortality to utilization and cost outcomes
1991–1992	High-risk persons are high cost by individual and/or cumulative risk (0–2, 3–4, 5 or more)
	Absenteeism shows same relationships to risks as medical costs
1993–1994	Excess costs are related to excess risks
	Cost changes follow risk changes (medical and pharmacy)
1995–1996	Risk combinations are the most dangerous predictors of cost
	Low-risk maintenance
	Resource optimization—targeted, specific risk combinations drive change in costs (Trend Management System)
1997–1998	Benchmarking by wellness score and company health score
	Participation relates to risk and cost moderation
	Program opportunities: preventive services, low-risk maintenance, high-risk intervention, and disease management
1999–2000	Presenteeism as a measure of productivity and influenced by risks and disease
	Total value of health defined to the organization
2001–2002	Natural flow established for risks and costs (the do-nothing strategy)
	Cluster identification
	Focus on the person, not risk or disease
	Cost changes follow risk changes
	Time away from work respond the same as medical costs
2003–2004	Improved population health status results from employer sponsored programs
	Proof of concept must bend the cost trends
	Health Management Scorecard: 90%–100% participation; 75%–85% low risk; and 85% stay low risk over time
2005–2006	Preretirement participation influences postretirement participation
	Presenteeism cost changes follow risk changes
	Interventions have severe "stepdown" participation
	Zero trends as an outcome
2007–2008	Don't get worse
	Help healthy people stay healthy
2009–2010	Zero trends: health management as a serious economic strategy
	Champion companies
	Culture of health
2010–2012	Best practices to next practices
	New cultural and community assessments
	Next-generation healthy life assessment

The purpose of this chapter is to introduce the reader to a transformation in the way health promotion approaches a positive healthy and high-performing workplace and workforce in America and across the world. The things we have done in the past fell short of an optimal outcome measures capable of fulfilling the promise of worksite health promotion. Therefore, we need an expanded transformational strategy if we intend to impact the health, well-being, and performance levels of the workplace and workforce around us. First, we'll briefly review the field of health promotion so we can determine why all of our efforts yielded limited positive results. Then we'll discuss the changing landscape of the twenty-first century. Finally, we'll describe the strategic systematic, systemic, and sustainable model that will drive the future of health promotion into the coming decades of the twenty-first century.

CONSIDERING THE PAST AND PRESENT OF HEALTH PROMOTION

Brief History of Health Promotion

Before we discuss the future of health promotion, it is important to recognize the history of this field. While health promotion efforts existed in even the most ancient of civilizations (such as devising methods to provide clean drinking water or dispose of sewage), we will limit our discussion to the modern efforts of health promotion, which began in the 1950s as the medical profession became aware of how health behaviors were linked to health risks, disease, morbidity, and mortality through studies such as the Framingham Heart Studies [1].

The World Health Organization currently defines health promotion as "the process of enabling people to increase control over their health and its determinants, and thereby improve their health" [5]. This broad definition encompasses many different facets of health promotion, while our discussion will mainly be restricted to the efforts of organizations such as corporations, municipal organizations, health insurers, and care providers.

As noted earlier, the Framingham Heart Study and others like it were the first indicators that our lifestyle as Americans might be contributing to early morbidity and mortality. In the initial stages of this field, it was thought that as soon as individuals were educated about how their health behaviors might negatively impact their health, they would take steps to change those behaviors. This was the driving force behind early efforts, which mainly consisted of health education. The health risk appraisal (HRA) tool was conceived by Louis Robbins [6] and further developed by Canadian and the U.S. Centers for Disease Control [7] as the primary source for gathering health risk information in a given population. Usually, a report was returned to the participant that acted as a principal health education tool. Corporations, health insurers, physicians, municipalities, and other groups began to offer health education classes, activities, or printed information to further edify individuals. These programs typically focused on individual health risks. Weight management classes were recommended to an overweight individual, while smokers were encouraged to attend cessation programs, for example.

Several theories of behavior change were proposed in the early decades of health promotion research. Examples include the Health Belief Model [8], the Theory of Reasoned Action [9], the Social Cognitive Theory [10], and others. There was no shortage of ways to explain why and how people might change their behaviors. One of the most popular was (and continues to be) the transtheoretical model of behavior change, also called the Stages of Change model [11]. This theory states that for any single behavior, individuals exist along a continuum of six stages of change ranging from precontemplation to contemplation, preparation, action, maintenance, and termination. Behavior change was adopted as the intuitive health promotion strategy and was the dominate strategy for several decades. As diagramed in Figure 113.1, behavior change was positioned as the central strategy for changes in lifestyles, healthier individuals, better employees, and gains for the organization. But if we've learned anything from these models, it's the fact that changes in behavior are very complicated; just like the people who are making, or not making, them.

Since corporations were the main payers of health care in the late twentieth century in the United States, they often led the efforts to provide health promotion activities for employees. While there were altruistic motives for instituting these programs, a chief goal was also health care cost control. Some of the landmark studies were those that established the link between health risks measured by commonly used HRAs and economic outcome measures such as health care costs, pharmacy costs, and productivity costs [12–15]. The evidence for this association justified the cost of providing health promotion activities for employees and also provided ways to measure the success of those efforts.

Health Maintenance Organizations (HMOs) have a long history [16] but really caught the attention of employers

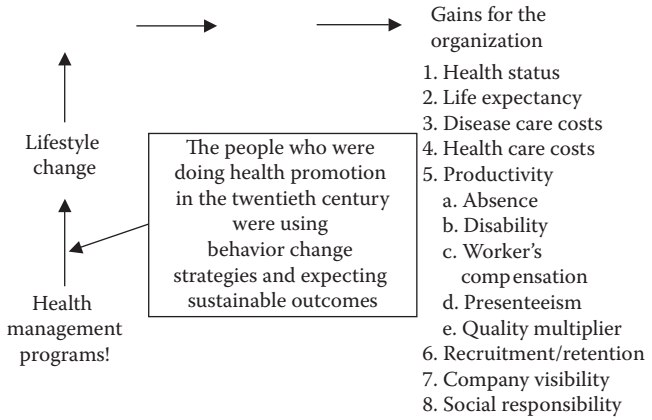


FIGURE 113.1 Health promotion using behavior change as the dominate strategy in the twentieth century.

in the late 1980s and early 1990s. They are prepaid health plans that enroll members and provide care through a designated provider network. HMOs marketed themselves as being prevention-oriented and a better way to help people stay healthy rather than waiting to treat them until they were sick. By the end of 1996, about a quarter of the U.S. population was enrolled in one of the more than 600 HMOs. However, participant dissatisfaction with managed care led insurers to alter their key cost-containment strategies such as closed panels of doctors, primary-care gatekeeping, and preadmission authorization [17]. Furthermore, HMOs abandoned their original goals of providing wellness management rather than simply sickness care in favor of strategies to directly control costs.

During this same period, corporations made concerted efforts to improve workplace safety and return-to-work programs as strategies to lower accident rates and disability leave costs. These programs generally achieved great success. The Occupational Safety and Health Act of 1970, which created the National Institute for Occupational Safety and Health and the Occupational Safety and Health Administration, likely, were the impetus for improvements that many companies made [18]. A literature review supports the concept that employee safety training creates hazard awareness and safe work practices at a wide variety of worksites [19].

Outcome measures that were used to gauge the success of health promotion efforts in the 1970s through the year 2000 were prevalence of health risk factors, avoidable deaths, mortality rates, infectious disease rates, incidence of disease, injury rates, environmental hazards, preventive services compliance, and disease management process measures. As programs progressed and the research base was established, organizations were able to move toward the use of economic outcomes to measure the success of their health promotion efforts. These measures included health care costs, productivity costs, cost-effectiveness of interventions, pharmacy costs, recruitment, and employee morale. Return on investment (ROI) research compared the cost of programs with the avoided cost of disease and showed some promise in a few cases, but evidence of widespread success was still lacking [20–22]. This deficiency of evidence was caused by many factors but primarily by a lack of understanding of the impact of the individual as a complex interrelated system rather than a collection of single risk factors that could be addressed one by one.

Despite the efforts of government, corporations, and other organizations in health promotion and safety, health spending as a percentage of total compensation increased from 5.6% in 1987 to 8.3% in 2003 [23]. Household spending on medical care as a percent of adjusted personal income also rose during that time from 4.8% in 1987 to 5.9% in 2003 [23]. The United States has experienced double-digit increases in health care spending for many years [23] with only occasional decelerations in the growth of health services spending [24,25].

So, why did the efforts of health promotion and managed care make little to no impact on rising health care costs? The medical community has always focused on sickness care. "Good health" has typically been defined as the "absence of disease." A strategy of waiting for people to become sick and then treating them is unsustainable, however. What is needed is a shift in thinking. True wellness is achieved when individuals have a high level of health, vitality, resilience, and performance, not simply the absence of disease. Behavior change and risk reduction strategies had only modest success as the cost of medical care escalated. Not only did few individuals participate in these programs, but if someone was able to make a change, it was only a short time until recidivism occurred. Thus, we observed a continual march toward increasing numbers of Americans who were obese and not physically active, as well as increases in the number of individuals with metabolic disease such as diabetes.

Five important lessons were learned from the history of health promotion thus far [4]:

1. One cannot solve a fundamental problem by waiting for defects and then attempting to fix the defects.
2. Only the actions that are rewarded are the actions that are sustained.
3. Anyone in business knows that you take care of your champion customers before going to find new ones.
4. One cannot put a changed person back into an unchanged environment and expect the change to be maintained.
5. Successful health promotion systems require continuous improvement through immediate and strategic quality assurance metrics.

A paraphrase of Einstein was finally heard: "The level of thinking that got us into these unsatisfactory results is not the level of thinking that will get us out of the situation." It is clear to us that the future of health promotion will be dependent on finding a framework or systems approach rather than the relatively isolated programs that attempt to fix defects one risk or disease at a time. These important learnings will propel health promotion to the top of strategies used to achieve and maintain high health status and performance in our corporations, towns, and countries, worldwide.

Business Problem and Solution of the Twentieth Century

Another line of thinking got us to a similar conclusion as in the previous paragraphs. The universal business problems of the final two decades of the twentieth century and first decade of the twenty-first century were the continuously increasing and unsustainable costs related to medical and pharmaceutical utilization, time away from work, worker's compensation, and other issues that led to lower performance and productivity.

Twentieth-Century Health Promotion Solution

The solution presented by the health promotion field was predominantly an ever increasing number of independent and single-focused risk reduction programs such as weight reduction, smoking cessation, physical activity, safety belts, and stress reduction. Behavioral change was the predominant tactic delivered one-on-one, telephonic, or via the Internet. By the first decade of the twenty-first century, the health promotion field was adding additional programs, looking for additional delivery methods to present behavioral change, and searching for the lowest-cost methods of delivery but continuing to emphasize single-focused risk reduction programs. Evaluation methods continued to be focused on the ROI methodologies.

It is clear to us that the assumptions and methods of the twentieth century will not be the solutions for the twenty-first century. We contend that Einstein and Covey would suggest, "… more of the same level of thinking that got us into this unhealthy and low performing situation will not be the level of thinking that will get us out of it … and we are also insane if we continue to do the same. …" Health promotion needs a transition from the past to the future and eventually a transformation from "best practices" to "next practices."

TRANSITION: SETTING THE STAGE FOR A TRANSFORMATION

Changing Landscape in the Twenty-First Century

Whereas the prevailing theme for medicine and wellness in the twentieth century was to wait for defects and then fix them, the prevailing theme for the twenty-first century will be to fix the systems that lead to the defects.

Whereas the prevailing strategy for wellness in the twentieth century was individual behavioral change, the prevailing strategy for the twenty-first century will be population health through supportive cultures and environments.

Whereas the standard of program efficacy in the twentieth century was evidence based and best practices, the standard in the twenty-first century will be evidence-based next practices.

Whereas the competitive advantage in the last half of the twentieth century was discovering ways to find lower costs of materials, production, labor, and other factors, the competitive and cooperative advantage of the twenty-first century will be with those organizations that can develop and maintain a healthy and high-performing workplace and workforce.

Finally, "What's the point?" This is a question that we raise with every audience we have the opportunity to address. Of course, the point is cost control in the organization and health and performance for individuals. But far beyond those, we believe the next practices of the twenty-first century will be "… our promise to provide each member of our organization and their families and work group an equal opportunity to obtain the highest possible level of health and performance. …" It is the right thing to do for the individual, their family, their work group, their organization, their community, and eventually their country.

Major Transitions in Health Promotion

As we noted in the previous section, during the twentieth century, health promotion, as identified by behavior change and risk reduction strategies, had only modest success, while the cost of medical care continued to rise and with only marginal improvements in quality of health care. In the early 2000s, health promotion stakeholders demanded more rigorous outcome measures and methods. Steps were taken to quantify the "total value of health" to organizations and communities. This includes a combination of several outcomes such as health care costs, pharmacy costs, productivity costs, absenteeism, presenteeism, job effectiveness, recruitment, turnover, morale, and socioeconomic measures. Programs were evaluated for ROI, but little for cost-effectiveness of interventions.

Other changes were taking place in companies and communities during these years of transition. These included a decrease number of jobs in the manufacturing sector as more jobs were created in knowledge-based work. Furthermore, many workers began telecommuting, and workforces became widely dispersed rather than concentrated at a single worksite. These changes presented challenges to the field of health promotion as it tried to reach people in new ways and through new technologies.

Going forward, corporations will continue to be the major stakeholders in defining the value of a healthy and high-performing workplace and workforce. Corporate and community leaders are only beginning to make the assessment that delaying the initiation of care to when sickness or high risks become apparent is an unsustainable strategy. It is in the employers' best interest to convince health plans to address the health status issues that lead to sickness. When insurance companies shift their sole focus from illness to, at least, considering wellness, they transition to a health plan and able to partner with purchasers of health benefits (companies) by having aligned incentives. Communities also have begun to realize the economic advantage of healthy and high-performing populations. The recession of 2009–2010 altered the pace of this transition and possibly delayed it due to acute budgetary consideration resulting in more short-term thinking.

However, the problem remains that health promotion and the entire medical establishment is focused on fixing sick people and addressing high risks. It is certainly a bad situation for the United States and many other countries of the world when one of the largest and fastest growing industry sectors is devoted to taking care of sick people. The implications for society as we know it is not good.

One physician has correctly stated that "Medicine (U.S.) has become a pig trough" and that trough is a reimbursement system that pays on a fee-for-service basis using a diagnostic and procedural coding system [26]. There are many examples that demonstrate this assertion. Gallstones are one example. Generally, in the absence of complications, patients

should be educated about the condition and encouraged to modify their diet. After those changes are made, a gallstone may dissolve on its own or shrink so that it no longer causes symptoms. However, the choice to operate immediately has become increasingly more common. There are several reasons for this. Operating increases revenue, satisfies patients' desire for action, and reduces the need for patients to make changes in their own behaviors. Even if a physician does not explicitly realize the reasons for his or her choice, the incentives are stacked up in a way to immensely encourage the decision to operate.

A second example would be diabetes. The insurance system will reimburse a hospital for amputating a limb afflicted with gangrene caused by diabetes complications. But it pays little or nothing to help a patient avoid developing diabetes in the first place, which obviously would have prevented the amputation. Billing occurs at the individual patient level and reimburses for services and procedures, a reflection of what the system presently values. This is like watching a soccer match through a pinhole: you see a single player in isolation, but you are blind to the strategy and dynamics of the larger picture. Similar economic models fit for health promotion as it is now practiced.

The future of health promotion must be redefined. Waiting for people to get sick and then working to make them better is a failed strategy if the objective is to take the population to a healthy and high-performing society. We can transition the twentieth century conversation about health and productivity for organizations to the twenty-first century conversation by considering the following five transitions:

1. From health as the absence of disease to disease as the absence health
2. From only caring for the sick to enabling healthy people to stay healthy
3. From the cost of health care to an investment in the total value of health
4. From individual participation to population engagement
5. From behavior change to a culture of health

These transitional conversations will help focus health promotion for the twenty-first century.

Business Problem and Solution of the Twenty-First Century

If one continues to ask the same or similar questions and can't get to a solution, then it could be that it is time to change the question. The unsustainable cost part of the twentieth-century business problem remains the same, but it is now complicated by a more competitive world and competition for high-performing people and, perhaps more importantly, competition for healthy and high-performing populations. Unsatisfactory results plus expanding or changing the questions clearly requires a new level of thinking.

Going forward, the competitive advantage for companies, communities, and countries will be healthy and high-performing individuals and populations working in healthy and high-performing workplaces and living in healthy families and communities. The health promotion field will struggle unsuccessfully if it continues to rely on twentieth-century solutions and maintains a continual emphasis on independent and stand-alone single-focused programs targeted at high-risk individuals with a behavior change solution.

New Century, New Decade, Changed World: New Journey

New world economics will require organizations to grow and maintain a healthy and high-performing workplace and workforce if they are to meet the economic challenges of the worldwide competitive marketplace. This awaking and new journey is alive in all countries of the world. The world now needs a few leading edge companies to begin to focus on achieving zero growth in their costs and an increase investment in a highly engaged and resilient workplace and workforce. Not only will the aforementioned costs be lowered but the clinical measures will also be improved, for example, fewer new cases of chronic diseases such as diabetes and heart disease.

It is clear we need a transformational change in the way we take care of healthy people and the environments and cultures we establish to maintain their health and to welcome others back into a healthy and high-performing quality of life. The outcomes from the past 40 years of twentieth-century health promotion should have taught us it is time for a transformation and it is only a matter of commitment within the organizations (and communities) to allow this new way of doing business to flourish in our lives.

Twenty-First-Century Health Promotion Solution

The solution for the twenty-first century must be created by strategically applying systematic, systemic, and sustainable business and economic viable solutions. Almost all organizations (public and nonpublic) take their lead from senior management balanced by agreement throughout the organization and bottom-up feedback (systematic). The process is continuous and sets the expectations and "rules" on how all members feel and act (systemic). The final (sustainable) part of the process comes through immediate and appropriate feedback to each level in the organization and movement in the outcome metrics.

Challenge Is to Grow Champion Companies or Remain on the Periphery

We are totally convinced that either the effort in creating healthy and high-performing workplaces and workforces will be carried into the core business strategy of organizations or this field will be left irrelevant and on the periphery of business success, only providing a series of single-focused programs, which touches only a very small percentage of the population.

Going forward into the twenty-first century, we see four levels of engagement for organizations to select as their desired state:

- Level 1. A do-nothing company
- Level 2. A traditional company doing health assessments, lunch and learn programs, and risk reduction programs
- Level 3. A comprehensive company doing Level 2 plus additional programs and some measurements related to ROI
- Level 4. A champion company recognizing health as a serious business and economic strategy and employing strategically implemented systematic, systemic and sustainable strategies.

Using Three Learnings from Successful Business Strategies

Best Practices or Next Practices

C.K. Prahalad, one of the world's most influential business leaders, used a concept attributed to Peter Drucker that often innovation and advances in business comes about by "seeing what is not visible." This advice is similar to hockey great Wayne Gretzky's advice: "go to where the puck will be." Prahalad advocates spotting opportunities and inventing "next practices."

Best practices are important if one wants to stay abreast of the competition and to move within the inherent limits of current circumstances. Best practices do not advance innovation or continuous improvement except at the margin. If the goals of business are relatively static, the results of its efforts are 100% achieved, and if nothing changes in the business or social environment, then best practices may be the right objectives. However, as we all know, these assumptions within the context of worldwide competition are far from realistic in the business (or society) equation.

It seems clear to us that to achieve continuous improvement in bringing about healthy and high-performing workplaces and workforces, the current best practices are not the road to innovation and success going forward. The primary component that is lacking in those who base their strategy on best practices is a vision of the future: "seeing what is not visible" and "going to where the puck will be." They also find that when they achieve the best practices, "someone moved the cheese," as described by Spencer Johnson [27].

The current best practices in the health and wellness field are built upon a series of individual interventions that one assumes will magically bring about a healthy and high-performing population. The degree of success over the past 30 years is marginal at best and when one uses population metrics as the measure of success one finds nearly no success. Our friend Albert Einstein would again remind us, "… if the current level of thinking is continuing to produce unsatisfactory results, more of that same level of thinking will not lead to satisfactory results." Thus, it is time for a higher level of thinking.

As a solution, Deming, Prahalad, Blanchard, and Drucker advocate the integration of individual strategies into systems thinking. In our opinion, this transformation creates a powerful approach where everything in the organization is focused on a common objective: a healthy and high-performing organization. In this approach, the healthy workplace and workforce become one with a healthy and high-performing organization.

System thinking is what drove the creation of the transformational approach advocated in *Zero Trends*. The system that leads to a healthy and high-performing organization begins with the vision of senior leadership connected to the mission of the organization; handing off to operations leadership to create the environment that begins to lead to a culture that allows the vision to come alive, continuing to manage expectations and creating consistent messaging at every touch point; providing resources for each and every employee to grow to all they can be, including family members; providing various forms of recognition for positive actions; and maintaining a quality assurance real-time process to measure, evaluate and provide for decision support at each point in the system.

The operational nature of a system is that the output of one part of the system is the input into the next part of the system. In no other way can each part be working together to move along the journey to a healthy and high-performing organization. It is the "next practices" that we should seek.

Keep a Good Customer or Go Find a New One?

The field of health promotion has been focused on ignoring the good customers and solely focused on those individuals with high risks. Although this seems intuitively correct, it violates one of the learnings of the "natural flow" of populations and one of the learnings of any business: take care of your good customers first, utilizing exceptional customer service.

It seems to us that the "low-risk, low-cost, and high-performing" individuals are the good customers and champions. Why ignore them and focus all of the health promotion efforts on the high-risk, high-cost, and poor-performing customers? The problem becomes how to identify the good customers and find a supportive process to help them remain in the good customer cohort.

There are at least two strategies that work to help achieve this goal. First, reward the positive actions taken by the individuals through intrinsic and extrinsic recognition of those actions. Second is to create an environment (structure and culture) that supports the desired behaviors and supports those who change from high risk to low risk, high cost to low cost, and low performers to high performers.

Recognition of positive actions is a fundamental precept of behavioral science: what is recognized and rewarded is the action that is sustained. Blanchard and Johnson in the One Minute Manager emphasize the point of "… catching people doing something right …" and the thought is that if one catches someone doing something right and then recognizes and rewards that behavior, it is likely they will do

it again [28]. Not only should the individuals be recognized and rewarded for positive actions but recognition and rewards can also be effective at the unit level: workgroup, department, division, location, etc. There are opportunities to reward groups that are even more sustaining than that of individual recognition.

Tom Golaszewski and Judd Allen have led the way in describing the influence of the environment on the workplace and the workforce [29]. The environment can be somewhat artificially separated into structure and culture and each has a complementary impact on the environment. The effectiveness of the structure and culture interventions is likely the most impactful on creating and maintaining the high-performing champions and in creating a best place to work company.

Strategic Systematic, Systemic, and Sustainable Strategies

We are convinced that there is a major disconnect between the high level of expectation and potential of health promotion programs and the current performance of these programs in workplace settings. Our 30 years of work at the University of Michigan's Health Management Research Center collaborates the high promise of the wellness strategy; however, the programs are under delivering on that promise.

The missing component to the twentieth-century health promotion programs is a business strategic strategy and an operational framework that results in a serious business and economic approach. After learning from our 30 years of work, we formulated such an approach in *Zero Trends: Health as a Serious Economic Strategy:*

The focus of the systematic framework is to incorporate the vision of a healthy and high-performing workforce into the systemic part of the organization. That is, incorporate wellness into the environment and culture of the organization. Most organizations already have incorporated Safety and Quality into the culture of the organization. These two examples provide a roadmap for us to do the same with a healthy and high-performing workplace and workforce.

Once high-performing workplace and workforce are systemic, then the culture is set to make it sustainable. After all, if any initiative in not sustainable, it will likely die out of the organization within a few years. This is not necessarily a major organization development issue; it is just follows the teachings of [28,30,31], and many other leaders of systems and leadership thinking. The strategic systematic, systemic, and sustainable strategy will move us beyond "fixing defects" and get us to "fixing the systems that lead to the defects."

Einstein gave us the framework to solve the safety and quality issues that troubled American businesses in the past with the next level systems thinking and that same systems level thinking will help us solve the overpromising and underperforming medical and wellness promises. In addition, systems thinking will allow behavior change to finally reach its full potential, so that we have supportive environments and cultures for changed behaviors to be sustained.

FUTURE OF WORKSITE HEALTH PROMOTION IN THE TWENTY-FIRST CENTURY

Population Health Management: Next Assumptions

Most current wellness or health promotion programs are based on the theories that corresponding risk-related behavior change will lower the chance of disease which, in turn, decreases health care, disability, and productivity costs. These theories seem reasonable; however, their real-world application to impact the health of a population (worksites or communities) have led to strategies proven to be largely ineffective—witness the increased percentages of the population with diabetes, obesity, other chronic diseases, and unhealthy risks and behaviors.

The current assumptions will still hold in the twenty-first century. However, other and more advanced assumptions related to population health and a framework for implementation at the worksite will be needed. The fundamental question for the twenty-first century is, "What are the major individual and social determinants of health for individuals and populations?" We project that the most influential assumptions for the twenty-first century will revolve around individuals, workplaces, workforce, family and friends, communities, and the overall impact of the environment and culture.

Framework for Health Promotion in the Twenty-First Century

In the first decade of the twenty-first century, the field of health promotion as applied to populations was more appropriately called wellness. It became clear to us in 2006–2009 timeframe that wellness, as defined by low-risk lifestyles, is insufficient to describe a healthy and high-performing individual and especially a population such as a workforce or citizens of a community. Either a redefinition of the current describers or another name needs to be found or created to represent a higher level of health and performance. Well-being, positive health, or health and well-being and other descriptors are being tested in several countries to represent a higher level of performance for individuals. Population health is a reasonable term to use to describe the health of a population.

Implementation of the Next Practices for the Twenty-First Century

We are convinced that the future of health promotion depends on finding a remedy for the five important twentieth-century learnings discussed previously (see p. 7). The obvious solution for worksites is to integrate health status into the organizational environment and culture. Our research over the past 30 years has provided us with the transformational framework: five fundamental pillars that support a culture of health in an organization and enables workplaces and their total workforce to maximize the potential of optimal health and performance.

The five pillars are designed to

1. Drive the vision from the level of senior and strategic leadership
2. Create a supportive environment via the operations leadership
3. Formulate the objectives through employee self-leadership
4. Reward and encourage positive actions that promote self-leadership
5. Provide quality assurance measures for the purpose of assessing and improving the success of the objective

In the worksite setting, the ultimate objective is to facilitate a high-level positive health status and high performance for all members, which benefit both the individuals and their employers. Figure 113.2 shows how the behavior change strategy diagramed in Figure 113.1 has been replaced with the strategic strategy (the five pillars). Behavior change remains a key tactic, especially in Pillar 3, but it is no longer the only or dominate tactic.

The strategic strategy has the potential to engage the total population and enable companies, health promotion practitioners, and individuals to capture the total value of health. A positive healthy and high-performing champion organization will have the features listed in Table 113.2, which create and support a culture of health.

We've touched on how the future of health promotion will change from focusing on individuals and individual health risks to a population-level approach. What does this mean exactly? Population-based programs are those which impact the entire spectrum of an organization or community. They offer something for everyone, not just the high-risk individuals. And, population-based programs are the only way to avoid the continuing development of high-risk individuals. This is accomplished by helping low-risk people stay low risk, helping others not get worse, encouraging all employees to develop a winning attitude, nurturing the champions,

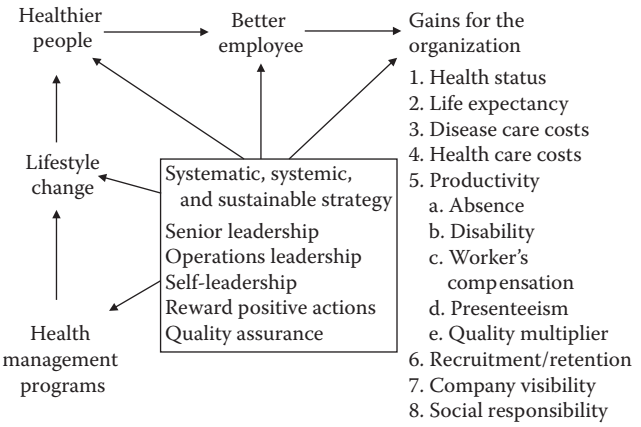


FIGURE 113.2 Health promotion using integrated and strategic systematic, systemic, and sustainable strategies as core business in the twenty-first century.

and beginning to engage higher risk individuals in the culture of health.

The systematic solution and framework represented by the five pillars are discussed in the following sections.

Create the Vision

It is fitting that this first pillar was illustrated in the publication of an article coauthored with Ken Blanchard: "Averting the Collision between Rising Health Care Costs and Corporate Survival" [32]. The message of the article is that CEOs have to recognize that health and health care are core business and economic survival issues in these times of global competition. If CEOs and other senior executives do not recognize this and do not create environments where they grow healthy and high-performing companies, someone else in the world will and they will lose competitive advantage as well as their overall way of life.

In the future, CEOs will provide a vision for organizations and people where everyone shows up for work, regardless of their work location, on time and with high energy, enthusiasm, creativity, optimism, resilience, and vitality; they are high performers during the whole work period; and, when they finish their work period, they leave with high energy, enthusiasm, creativity, optimism, resilience, and vitality. These employees will then apply that same energy and high performance to their home life and to their community. In addition, they will show up at work the next day with renewed energy enthusiasm, creativity, optimism, resilience, and vitality and the other traits that fit the company's vision of a positive, healthy, and high-performing workplace and workforce.

The earlier description is what we consider an ideal vision for the future work situation where the workplace and the workforce act synergistically to produce a high-performing organization that will be able to compete in an increasingly highly competitive local and worldwide marketplace. Currently, there are only a few organizations that create and sustain this type of workplace. In fact, many organizations are set up to create a workplace where employees arrive with energetic characteristics but leave the workplace with an empty tank of energy, even if they are well paid.

The gap between these two work situations focuses the question: "How will organizations create a workplace that expects and supports healthy and high performance from employees?" The enlightened employers will realize that they have to give energy back to the employee to allow those daily high-energy–high-performance work characteristics to be renewable and sustainable over time. This renewable and sustainable energy will create a work environment that feeds high performance and often exceeds all expectations of the company.

The role of the CEO and other senior leaders will be to create the vision, similar to that describe earlier; connect the vision to the business strategy; be the role models they want the employees to see; provide adequate resources; engage all senior leaders in a visible participating role; and have the ultimate courage to support the vision throughout the implementation of the strategy.

TABLE 113.2
Health Promotion Program Features of a Champion Organization

Senior Leadership	Operations Leadership	Self Leadership	Reward Behavior	Quality Assurance
Emphasizes the role of senior leadership in creating the vision	Emphasizes the role of operations leadership in impacting the culture	Emphasizes self leadership among employees	Emphasizes rewarding positive behaviors and developing the culture of health	Engages in quality assurance activities to get to results-driven programming
Vision connected to company strategy and people	Brings integrated health policies into alignment with a healthy culture	Provides for a health assessment system, including coaching and wellness activities for all	Rewards the champions	Understands the distinction between data, measurement, information, and decision support
Senior leadership is visible and committed	Brings all policies and procedures into alignment with a healthy culture	Provides educational programs for understanding of the value of health management to the company and to the employee	Cultivates individual respect, care, and growth	Tracks the percent of total population engaged and the percent of the total population at low risk
Senior leadership delegates and then transitions to cheerleaders	Modifies benefit design to focus on company values	Offers appropriate resources to all employees, including dependents, if possible	Corporate culture emphasizes an abundance mentality that engages the total population	Compares the program results with the expected natural flow of risks and costs
Provides adequate funding for programs	Integrates management of disease, crises, absence, disability and workers' compensation, and other resources		Incentives follow actionable items	Tracks employee and company satisfaction indicators
Assigns responsibility for implementation	Emphasizes branding of the program and direct marketing to the employee Encourages meetings with all managers and employees to manage expectations Provides incentives for all, including the low-risk individuals Engages external partners (health enhancement companies, health plan, benefit consultants, pharmaceutical companies, primary-care physicians, health systems, and communities) in accordance with vision			Examines the trends of the relevant outcome measures

Create a Supportive Environment and Culture

The vision will not be implemented without a planned and integrated strategy initiated at the senior leadership level and seamlessly implemented by the operations or local leadership. The vision from the senior level will come alive in the environment created by the operations people (typically human resources). The combination of vision and environment/culture will be the heart and soul of a champion company and will create the structure and culture of a healthy and productive great place to work.

The structure part of the environment will include fair wages, integrated and well-designed value-based health care, resilience training, self-leadership training, and healthy choices throughout the worksite. The culture piece of the environment will start at the top and permeate throughout the organization as positive role models, peer support, supervisor support, mutual trust, positive norms, and positive expectations. The culture will need local champions listening at the employee level for success stories or sometimes barriers to success and feeding that de-identified information up the

organizational structure for consideration. This bottom-up communication will complete feedback loop cycle.

Once everyone in the organizations understands the vision realizes the intent of the environmental factors and sees and feel trusts the individual and organizational support, the culture will reach a point where individual and corporate energy is renewable and sustainable. Although the concept of addressing cultural issues in health promotion is not new, the identification of a workplace health initiative as a cultural phenomenon departs dramatically from the long-standing intervention practices of the twentieth-century health promotion efforts. This new focus, i.e., creating a culture of health, represents a major breakthrough in both evaluation and intervention design.

Creating a supportive environment and culture will require a major effort to communicate the message throughout the organization (managing expectations), align and integrate all internal policies and procedures, align and integrate all external partners to be consistent with the organization's objectives, brand the vision where everyone in the organization recognizes the vision and the objective, and engage all members (employees and dependents) in the vision.

The transformation to a twenty-first-century vision of a champion company's health promotion strategies will require a new set of tools: next-generation health risk assessments, which include components related to positive health and well-being components and issues related to the workplace, community, and family environments and cultures. The transformation will require a move from best practices as the standard to "next" practices, which incorporate a higher level vision and more organizational strategies.

Develop Self-Leaders

Champion companies are going to need self-leaders in order to be competitive in the twenty-first century. This will be accomplished by additional recruitment criteria and on-the-job training. The organization will need to create a supportive environment and opportunities for employees to become winners; help employees not get worse; and help the low-risk and healthy employees stay low risk and healthy.

The needed tactics will include communications to manage expectations at all levels of the organization; special orientation and training opportunities (learning modules) centered around the characteristics of positive, healthy, and high-performing individuals; low-risk maintenance programs; and some of the common twentieth-century risk reduction programs.

One of the tactics for all employees (population-based program) will be the completion of core modules illustrating the basic concepts of self-leadership, consumerism, resilience, change, and self-efficacy. In addition to the modules, health promotion coaches will need to be trained in motivational interviewing (advanced form of the twentieth-century strategy) including coaching for low-risk individuals and how to develop self-leaders.

We've touched on how the future of health promotion will transform from focusing on individuals and individual health risks to a population-level approach. What does this mean? Population-based programs are those which impact the entire culture of an organization or community. They offer something for everyone, not just the high-risk individuals. Population-based strategies are the only way to avoid the migration of individuals with low-risk health status to high-risk status. In the future, this will be accomplished by helping low-risk people stay low risk, encouraging all employees to develop a winning attitude and nurturing the champions. This low-risk strategy will be supplemented by enhancements of the more traditional high-risk reduction programs that were used in the twentieth-century health promotion programs.

An example of a population-based approach where everyone can win includes a goal of walking 1000–3000 steps a day, a campaign to learn your blood pressure and cholesterol numbers, and an agreement to maintain body weight (just don't get worse!). Every individual or preferably every work group will earn the recognition because everyone can do these activities (or get appropriate substitutes). The organization can now celebrate its winners. What's next? The next step might be to ask individuals what they would like to undertake for the next 6 months. Perhaps it will be 4000 steps/day, still don't gain weight, and still just know your numbers. The organization will continue to be on the journey to more positive health and high performance, which benefits each person in the organization and the organization itself.

A health-oriented environment and culture will reinforce the population-based strategy and engage everyone in skill development and motivational opportunities. In the twenty-first century, strategic positive, healthy, and high-performing workplaces and workforces will be recognized as an integral part of a high-performing champion company. A highly productive employee is not only healthy but one who also has competitive skills for their job and is highly motivated to be a champion within the champion company. In addition to the "don't get worse" challenge, more traditional risk reduction programs are needed for those who decide they want to undertake more intense self-improvement.

Recognize Positive Actions

When companies in the twenty-first century take the important step of making a healthy and high-performing workplace and workforce a core business strategy, as a first incentive, they may only choose to pay for health care only for those employees who engage in the self-leadership program. Employees who decide not to engage will pay for their own health care benefits. This significant incentive (positive reward or recognition) will be discussed with all employees, and the options openly explained during preprogram meetings. The purpose of these meetings is an attempt to manage company and employee expectations.

Once motivated by the initial incentive, the workplace and workforce will need another series of rewards, or more preferably recognition, to maintain corporate and employee interest and engagement. This second level of positive recognition is necessary because initial activity in the twentieth

century often took place at the time of benefit selection and was focused only on increasing participation. An emphasis on self-leadership must continue throughout the year in order to reach the desired outcome of a positive healthy high-performing individual working in an environment and culture that supports positive and healthy actions. Constant communication and work group recognition keeps the momentum going and keeps participants engaged, either maintaining their health status or making improvements. Another effective recognition strategy will be to have activities in the current year lead to a qualification threshold for the recognitions for the following year. Regardless of the type of motivation that will be used, it is crucial that they are not viewed as entitlements: that is, effective incentives will follow positive actions such as an investment for future returns.

Measure and Share all Strategies and Outcomes

The quality assurance pillar involves data-driven decision making and performs the critical function of integrating a positive healthy high-performance workplace and workforce into the culture of the organization. The highest level objectives are those organizational and individual traits identified in earlier parts of this section. The senior leaders and the leaders of each of the pillars will have identified three metrics they each need to give them confidence of the progress of moving the organization toward a champion company and moving individuals toward self-leadership.

There will be a need for preliminary and intermediate objectives (early indicators) of company and individual engagement, such as program participation rates or the prevalence of health risks or gaps in communications. A champion company, however, will take the major steps of measuring, evaluating, and making decisions process to a much higher level of company performance. The data sources needed to create the metrics are unlimited and could include employee satisfaction, changes in the environment and culture, management and alignment of policies and procedures, employee progress on completing the learning modules and coaching, employee engagement, maintenance or reduction in health risk status, family and community involvement, shift from a focus on costs to a focus on investments, beating the natural flow, bending the cost trend lines, relevant company productivity measures, and less utilization of medical, absence, and disability claims.

Each company, regardless of size or industry sector, will measure accomplishments and successes through the creation of a real-time quality assurance system. The data systems will be integrated to create data information systems from which the appropriate metrics will be provided upon request in order to facilitate effective and timely decision support.

WHAT WILL WE BE ABOUT IN THE TWENTY-FIRST CENTURY?

The twenty-first-century health promotion programs will have learned from the first 40 years of experience that the only strategy that addresses the fundamental positive health and high-performance objectives is a strategy of fixing the culture and environment of the workplace and the self-leadership needs of the workforce. The outcome of this transformational approach will result in all of the economic cost outcome measures approaching a zero trend line and the investment outcome measures approaching an optimal productivity of the company. However, companies and other organizations will not be able to solve the fundamental issues by themselves. They will need integrated help in public policy from the federal government, state governments, optimal company products and services, communities, families, and individuals. In addition, the quality and cost of a high-performing workplace and workforce will be within reach but it will require an equal effort of both sides of the economic and social equations. It will take a synergistic set of strategies for each company or country to remain on track to fulfill its promises to its clients, employees, and citizens for effective positive, healthy, and high-performing systems.

We've covered a lot of ground and presented numerous ideas and concepts about our view of the future of health promotion strategies and outcomes. The take-away message is that health promotion has evolved at the margins over the past 40 years, but now there is an urgent and passionate need to generate a major transformation if health promotion is going to remain relevant and effective. The lessons learned from the less than optimal approaches in the twentieth century can be put to good use augmenting the transformational and effective methods necessary for the optimal future of health promotion.

Following the organizational strategy of a strategic systematic, systemic, and sustainable strategy will help organizations transform themselves into champion workplaces and help individuals live positive, healthy, and high-performing lives in their families, workplaces, and communities. The vision of the future will only come alive by a transformation in our thinking to a new and higher level of thinking. Only the view from that level will create the positive, healthy high-performing future workplace and workforce. Twenty-first-century health promotion will show that the "investment in doing something" (successfully) is less than the "cost of doing nothing."

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Part XXI

Exercise Psychology

Steven J. Petruzzello, PhD

114 Taking Stock of Where We Are in Understanding Mind/Body Interactions in the Exercise Domain

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CONTENTS

"Windows into the Thinking Mind" 1354
"Windows into the Feeling Mind" 1356
Anterior Hemispheric Asymmetry 1357
Transient Hypofrontality 1357
Dual-Mode Theory 1358
"Looking Through 'Strained'-Glass Windows" 1358
Cleaning Our Windows/Looking for the Patterns 1362
Closing the Window 1362
References 1363

In the previous edition of *Lifestyle Medicine*, I (S.J.P.) wrote a chapter on mind-body understandings [1]. Given that more than 10 years have passed since that chapter appeared, we thought it might be interesting to see how far things have (or have not) progressed since that publication. What follows is a revised and updated accounting of that 1999 chapter, but rather than presenting more generic studies, we have focused primarily on what has evolved in the exercise domain since that time.

The Latin phrase "Mens sana en corpore sano"—a sound mind in a sound body—was (and perhaps still may be) the mantra for exercise psychology. It clearly suggests that mind and body are intimately related to one another. Careful consideration of the available literature, however, often leads to the conclusion that mind and body are distinct entities, with the latter serving only as a place within which the former resides. Since the early seventeenth century, science has operated on the notion that mind and body can be separated. As Melnechuk [2] put it,

> Back then, dualism made the body, as a ghost-free machine of mere meat, a permissible object of empirical investigation at a time when the Inquisition was dangerous to scientists, as shown by the contemporaneous trial of Galileo. In modern times it reinforced the biomedical avoidance of studying emotions as factors in health and disease. (p. 183)

This dualistic thinking still permeates much of science, and particularly exercise science, although it is difficult to defend the position that mind and body are separate. What results from the continued distinction are physiologists studying physiological processes as entities with no influence from the mind and psychologists (or other "mind scientists") studying psychological processes as though they were distinct from physiological sources. Consider the following: "All social cognitive approaches are based on a constructionist metatheory, where cognitively based variables such as intentions, attitudes, and self-efficacy are nonmaterial psychological constructions and not observable in the physical world" [3, p. 1396]. This is a perfect illustration of what Morgan [4] meant when he wrote "… those who rely on cognitive psychology, seem to believe that the head does not have a body" (p. 100).

A more tenable philosophical approach to examining mind-body issues is monism, a central tenet in psychophysiological approaches to understanding human behavior (i.e., perceptions, thoughts, emotions, and actions) [see 5, p. 20, Note 2, for full description]. At its essence, the monistic identity thesis holds that there is a counterpart in the physical domain for every psychological or subjective event. This leads to the realization that events taking place at any level in the individual occur simultaneously at all levels [6]. As such, intentions, attitudes, and self-efficacy are *not* nonmaterial constructs and *can be* observed in the material world. The monistic identity thesis holds then that events of the body are simultaneously events of the mind. Thus, "A mental perception or idea and the initial physical event (brain cells firing, neurotransmitter molecules moving) are not two separate things, but two different ways of describing the same event. An initial mental change *must* entail corresponding physical change…" [6, p. 9]. Indeed, Joseph LeDoux, a prominent neuroscientist, has stated that "your self, the essence of who

you are, reflects patterns of interconnectivity between neurons in your brain. Connections between neurons, known as synapses, are the channels of information flow and storage in the brain" [7, p. 2]. If one espouses such a philosophy, then examining mind-body issues becomes potentially more fruitful. It becomes the challenge of science to find these corresponding physical changes. As Cacioppo et al. [8] noted, at least in most other areas of "psychological" science,

> Monism has replaced any lingering notions of dualism, as psychological states are more likely to be conceived as represented in and acting through cortical, limbic, and brain stem regions, with influences on autonomic, neuroendocrine, and immune activity, which in turn serve to modulate crucial cellular and molecular processes. Afferent information, in turn, travels from the peripheral to the central nervous system to influence the brain and behavior in social contexts. (p. 2)

Unfortunately, dualistic thinking continues to pervade much of exercise psychology. Ekkekakis [9] nicely outlines several instances where this has occurred (and continues to occur) in the field, usually in conjunction with some of the most deeply revered theories and models. Rather than viewing psychological events as embodied phenomena, exercise psychologists instead hold to a disembodied philosophy. This allows investigation at a single level of organization (e.g., psychological) without concern for how such phenomena might extend to other, adjacent levels (e.g., physiological, social). When it is considered, the body is devalued, reflecting what the philosopher Leder referred to as onto-valuational dualism [9,10]. Cacioppo et al. [11; see also 12] have stated,

> Traditionally, investigators have emphasized single levels of analysis of social psychological phenomena with survey and self-report measures being the most common methods used to investigate the mechanisms underlying these phenomena. The predictable yield from isolated research on discrete determinants of multiply determined social psychological phenomena is a portfolio of fact lists and disparate microtheories. These microtheories each provide a limited account for the phenomenon of interest and are at best pieces of a larger conceptual puzzle. Even determinants of a phenomenon that account for a modicum of variance are noteworthy if the goal is to achieve a comprehensive theory of the psychological phenomenon rather than a microtheory of the determinant. In addition, knowledge of the body and brain can usefully constrain and inspire concepts and theories of psychological function, because there are any number of ways in which a particular outcome might be achieved. Knowledge about the functional organization of ordered and disordered mental or social activities, however, can also usefully guide the study of the underlying brain processes because the nature of the particular physiological mechanisms and events could be suggested by the observed mentation, behavior, or interaction. Although there are neurophysiological processes that are affected, for instance, by human association and which underlie the associated psychological and social phenomena, these phenomena shape physiological events in ways that may not be evident from studies of the physiology isolated from the social context in which they manifest. (p. 74)

To be fair, it should be noted the problem cuts both ways. The physiologist, often viewed as reductionistic, typically ignores the influence of psychological and social factors. To once again quote Cacioppo et al.,

> … it [reductionism] undermines multilevel, integrative analyses, alienates scientists working at "unchosen" levels of organization who might otherwise contribute relevant data and theory, and renders it acceptable to ignore relevant theory and data on a phenomenon of interest simply because they were not born from one's preferred level of analysis. [11, p. 75]

While such approaches to viewing the world and answering questions about it are certainly valuable in their own right, the obvious point is that a much greater understanding of phenomena can be gained by examining *across* levels of analysis (i.e., psychological and physiological) [13].

Thankfully, there are seedlings of change cropping up (e.g., transient hypofrontality hypothesis (THH) [14], dual-mode theory (DMT) [9,15,16]). There continues to be a growing effort to uncover the physical events that correspond with psychological phenomena. As way of illustrating the interconnectedness of mind-body, the remainder of this chapter will examine findings from different areas of research, which clearly show the linkages between mind and body or between body and mind. Intriguing findings have come from scientists focusing on cognitions and emotions using a mind-body perspective.

"WINDOWS INTO THE THINKING MIND"

Cognitions and cognitive function have historically held a prominent position in psychophysiology. Cognitive function involves the ability to concentrate, divide attention among several things, learning and memory, action planning, effective execution of that plan, self-regulation of activities, object recognition, to evaluate, to construct in one's mind, logical thinking, and problem solving. Of note, executive control processes [17] constitute a set of cognitive processes oriented toward goal-directed behavior [18]. Such processes include scheduling, planning, working memory (being able to retain relevant information in memory for relatively short periods of time), interference control (dealing with distraction), task coordination, and multitasking; such tasks do not become automatic over time or with practice [19]. Furthermore, they have been shown to decline substantially with advancing age, as do regions of the brain known to support them (e.g., prefrontal cortex (PFC)).

Researchers in motor behavior have long been interested in cognitive function, beginning with the systematic examination of reaction time (RT), or how long it takes an individual to respond to a stimulus presented in the environment (e.g., visual, auditory). This response is assessed behaviorally by measuring the amount of time that elapses from the time a stimulus is presented until the subject makes some overt response (e.g., button press). However, this reveals little

about the how the response comes about. More information is gained if the motor system is examined using electromyography (EMG) recordings, but this still reflects a delay from the time the stimulus is processed by the nervous system to when a response is initiated. In other words, behavioral (i.e., RT) and motor system responses (i.e., EMG) still provide only a limited window through which to "view" the thinking mind (as an aside, some more recent studies are combining behavioral and neuroimaging techniques like functional magnetic resonance imaging (fMRI) to determine the level of convergence between methods).

Fortunately, several other options are available for potentially "better" views. Perhaps the analogy can be expanded to a window with multiple panes, with each pane representing a different way of viewing the thinking brain. Measures of brain activity have been used as "windows on the mind (i.e., cognitive functioning)" [20] for quite some time. Work with such imaging techniques (e.g., electroencephalography [EEG], fMRI) has been able to demonstrate partial information transmission, preparation of the motor system for action of some kind, and processes involved in the inhibition of responses [20]. Perhaps we can think of these different techniques (along with structural MRI) as separate panes of the window, each of which gives a particular view of the brain. What is needed is to get to a point where we are looking through the window as a whole, using mixed methods to determine if we are finding a common picture of what is going on or if we just have these fragmented panes.

Over the past 10 years, there has been an explosion of interest in how exercise might influence cognitive functioning. Much of the credit for this interest is owed to the pioneering work of Waneen Spirduso (examining physical activity/fitness and RTs) and the psychophysiological approach applied to this work by Robert Dustman (see subsequent sections). The effect of exercise on cognitive processing has been primarily examined in older adults and preadolescents given that these are milestones on the developmental continuum where cognitive processing is either in decline or in development, respectively. Thus, these become time points in the lifespan when exercise (if it influences cognitive processing at all) would potentially have its most robust effects.

Psychophysiological measures of brain activity, like EEG, have been useful in examining central inhibition capacity. The ability of the central nervous system (CNS) to inhibit unwanted/undesirable responses typically deteriorates with advancing age. A decrement in inhibitory strength would thus adversely influence physical and cognitive functioning [21]. EEG waveforms have been shown to be more homogenous across electrode sites (i.e., cortical coupling) in older than in younger adults [22], reflecting a loss of inhibition. Greater cortical coupling values are often seen in diseased states (e.g., Down's syndrome, dementia) and with advancing age. Because cortical coupling reflects the degree to which distinct cortical regions function independently from one another, an increase in cortical coupling with age would "suggest that aging is associated with a loss of functional autonomy of brain areas such that the older brain responds in a more homogenous or global manner" [21, p. 146]. Interestingly, physically fit older adults have been shown to be similar to young adults on measures of such functional autonomy (i.e., cortical coupling values), suggesting that endurance exercise can modulate excitation/inhibition relationships.

A more contemporary measure of regional brain functioning is EEG coherence, which measures the similarity between two EEG signals at different brain regions. Like cortical coupling, it is thought to reflect structural and functional coupling of those brain regions [23]. As coherence values approach unity, this reflects increasingly similar responses between different brain regions. Like Dustman's work with cortical coupling, data from our laboratory have shown that older, active individuals had lower mean coherence values than their older, sedentary counterparts [24]. Further elaboration is needed in order to determine how such differences might be manifested at the psychological level (i.e., cognitive function).

Event-related potentials (ERPs) have also been effectively used in the exercise literature as a methodology for indexing cognitive function [25]. Most prominent among the various ERP measures available are the P300 and the event-related negativity (ERN). The P300, or P3, is so labeled because it is a positive-going waveform occurring approximately 300 milliseconds after the presentation of a stimulus. It is thought to reflect the allocation of attentional resources, which can be thought of as the amount of brain activity needed to attend to the task and the updating of memory. Thus, the amplitude of the P300 (i.e., the magnitude of the deflection in a positive direction) reflects the proportion of attentional resources the brain needs to engage in a particular task (i.e., a larger amplitude means the allocation of more attentional resources). The latency of the P300 is a measure of the speed with which a stimulus is classified (i.e., longer latency means longer time to process the stimulus by the CNS). The ERN provides an index of the evaluation and self-monitoring of one's own actions, also referred to as response-monitoring associated with the evaluation of conflict. Thus, the ERN component is thought to reflect the conflict between what a stimulus dictates the response should be and the response that is actually made. Studies have shown the ERN component is generated by the anterior cingulate cortex.

Using exercise as an avenue for providing windows into the thinking mind, early work by Dustman et al. [26] compared ERP measures in younger and older higher and lower fit individuals. Young and old individuals who were more fit had earlier visual evoked potential latencies (i.e., perception of visual stimuli occurred more quickly) and shorter P300 latencies (i.e., they processed information more rapidly) than did their less fit counterparts. In addition, the older fit individuals were similar to the younger subjects in terms of P300 latency, suggesting that maintenance of aerobic fitness may offer some immunity against functional loss often seen with "normal" aging. Similar findings have been reported by numerous investigators since Dustman's work in preadolescents, adults, and older adults [e.g., 17,27–31], although not always [e.g., 32]. Similarly, with the ERN, studies have

shown higher fit younger adults have smaller ERNs after making an error than do their unfit counterparts [33]; this is thought to reflect more efficient allocation of conflict monitoring processes. Behaviorally, this is seen in greater accuracy on trials immediately following an error, something fit individuals exhibit to a greater extent than their less fit counterparts (this finding is consistent with fMRI data showing a less active anterior cingulate cortex in physically active and/or fit individuals—see subsequent sections).

Beyond electrophysiological measures, newer imaging technologies allow views from different panes into the "thinking mind" from slightly different windows. One of the reasons given for the change (often decline) in cognitive function, which is typically seen with advancing age, is the age-related loss of both gray and white matter in the brain, particularly in anterior brain regions (e.g., frontal, prefrontal, and temporal regions). The structural loss itself may not be the absolute reason for cognitive degeneration; however, such losses many times are associated with deafferentation of neurons of closely related structures and the subsequent functional changes that result [34,35]. Kramer and Eriksen [36] noted a relative dearth of studies that have examined the effects of physical activity interventions on the brain itself, more specifically on the structure of the brain and how it operates. Cross-sectional work using high-resolution structural MRI scans of the brains of older adults has shown that in spite of substantial declines in tissue density in the frontal, temporal, and parietal regions of the brain, fitness served to offset (i.e., substantially reduce) these declines [37]. Others have shown that the volume of the hippocampus, a subcortical area of the brain known to influence memory function (i.e., spatial memory) was positively associated with fitness; greater fitness and hippocampal volume were associated with better spatial memory performance [38].

Intervention studies of sedentary but healthy older adults have shown significant increases in brain volume (both gray and white matter) as a function of aerobic training [39]. These results were thought to show that fitness provided a "sparing" effect on brain tissue, an effect confirmed by others [40]. Another study [28] compared the effects of cardiovascular training, which resulted in a significant improvement in aerobic capacity (10% increase), to a non-training control group (stretching and toning; 3% increase) on brain areas implicated in different aspects of executive control and the attentional network (e.g., superior parietal lobule, attentional selection, resolution of response conflict; anterior cingulate cortex, sensitive to response conflict). Consistent with previous research, the aerobic group had significant improvement from pre- to postintervention in reducing their conflict time (11%); the control group essentially did not change. fMRI revealed significantly greater activity in the attentional control areas of the brain (e.g., superior parietal lobule) and significantly less activity in the anterior cingulate cortex in the exercise training group relative to the non-training control group. These results were again interpreted as evidence that exercise training can enhance executive control functioning, even in older adults.

Thus, it appears that regardless of which window or window pane one chooses to look through, physical activity, fitness, and exercise seem to provide the foundation for a "sound thinking mind." It is actually quite striking how consistent the findings generally are across the various levels of analysis.

"WINDOWS INTO THE FEELING MIND"

> Probably more than any other class of behavior, emotion often involves frank biological changes that are frequently perceptible to the person in whom the emotion arises as well as to an observer. [41, p. 361]

It has been suggested by numerous individuals that understanding affect is a necessary task for understanding human behavior. Davidson has been instrumental in advancing what he has termed "affective neuroscience" [42,43], a field of inquiry that certainly captures the essence of multilevel integration. As highlighted by Petruzzello [1], studies using measures of muscle activity (i.e., EMG) [44,45], eyeblink (using EMG [46]), and temperature [47–52]) have demonstrated, and continue to demonstrate (e.g., pupil diameter [53,54]), links between affective responses and physiological measures of such responses. Similar methodologies and paradigms have been extended to the exercise domain to examine a variety of potential explanations for affective change (e.g., temperature [55,56] and eyeblink, again using EMG [57]).

A strong case can be made for the importance of the brain in furthering our knowledge about human affect and affective function, but it is important to note that emotions are not just "in the head" either [58, p. 130]. It is clear that how we feel has direct effects on our central and peripheral physiology; changes in our physiology also influence how we feel. As LeDoux [59] has noted, "understanding emotions in the human brain is clearly an important quest, as most mental disorders are emotional disorders." (p. 19). Much of what is known about affect, particularly in the exercise domain, is often based on self-reports of emotions (e.g., anxiety) or feeling states as a function of manipulations hypothesized to change how we feel. As noted by Davidson and Sutton [43], "Inferences about emotion can be made on the basis of changes in behavior and physiology, and need not rely upon conscious introspective report." (p. 217). Davidson [58] further commented that consideration of the physiological perspective, specifically the brain, could help constrain psychological theory regarding emotion and affect. A similar point was raised by Petruzzello [60] in terms of recognizing what is currently known about the neurophysiology of the CNS and our knowledge of the transactions between the individual and the environment to better understand human emotional behavior. Psychophysiological investigations of affect have provided a much greater understanding that could have never been achieved from an exclusively self-report perspective. Davidson [58] actually refers to the reliance of studying only from a psychological perspective as one of the "seven sins in the study of emotion" (p. 129).

Perhaps as much as any other area within the exercise domain, we have gained much better "views" into the feeling mind over the past 10 years. This is due in no small part to better measures and methodologies, both of which have evolved from better theoretical perspectives to help guide the inquiries. One of the important developments in this domain has been the paradigm shift to examining affective responses from a dimensional perspective rather than what had been the dominant categorical perspective [61]. This led, among other things, to consideration of the activation/arousal and valence (e.g., pleasure/displeasure) dimensions of affective responses to exercise rather than continuing to rely on distinct emotional states (e.g., anxiety, depression), particularly in individuals who were not anxious or depressed. What follows is a summary of some of these theoretical perspectives and some research exemplars that have either directly tested them or indirectly supported them. As Ekkekakis [62] pointed out, there are at least three theoretical propositions that we are in a position to address from a psychophysiological perspective within the affective domain of exercise: anterior hemispheric asymmetry, transient hypofrontality, and the DMT.

Anterior Hemispheric Asymmetry

A rich literature has developed over many years examining the role of the brain in affective responsivity and affective regulation [63,64], a primary measure of which has been the EEG.

> In an era where functional neuroimaging methodologies, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have seen an exponential increase in the study of emotion and psychopathology, one might question whether there remains a role for frontal EEG asymmetry in the study of emotion, motivation, and psychopathology. Aside from the obvious advantages of EEG as a measure that is less invasive, less expensive, and more widely available than many neuroimaging modalities, frontal EEG asymmetry has established— by virtue of the nearly 100 studies using this measure— a sizable literature that embeds the measure in a network of psychological and behavioral constructs, thus bestowing frontal EEG asymmetry with sizable construct validity as a measure of an underlying approach-related or withdrawal-related motivational style… As such, frontal EEG asymmetry has greater construct validity as a measure of this motivational style than does any neuroimaging measure to date. [63, p. 1]

EEG, particularly in the alpha frequency range, has been a particularly useful measure in work with humans, specifically in the investigation of affective responses, and has been utilized in a growing number of exercise studies as well. Evidence from numerous fronts has led to the proposal that the anterior regions of the cerebral cortex are particularly important in affective behavior and experience. Davidson has proposed that the right and left anterior regions of the brain are specialized for withdrawal/aversive and approach/appetitive processes, respectively [41,65]. Not only does evidence show that brain activation (as indexed by EEG) changes in response to affect-eliciting events (i.e., state-dependent) but resting anterior EEG asymmetry has also been shown to be a state-independent index of an individual's propensity to respond affectively [for reviews, see 42,66–73].

Exercise has been suspected as an affect-eliciting stimulus for some time, often resulting in reduced negative and/or enhanced positive affect. The perspective espoused here is that the physical changes, which occur with exercise, are intimately linked with these affective changes. Generally, studies that have examined EEG-exercise relationships before and after aerobic exercise have reported an increase in EEG activity (operationalized in a variety of ways) following aerobic exercise, particularly in the slower frequencies (i.e., delta, theta, and alpha) [74]. In addition to its predominantly atheoretical nature, however, this literature has been plagued by numerous methodological shortcomings that make its interpretation difficult. In a programmatic examination of this relationship, we have shown that regional brain activation can predict affective responses to exercise [75–80]. Overall, these studies suggest that both the duration [81] and intensity of exercise may influence the relationship between resting frontal asymmetry and affective responses to that exercise [see 82,83]. When low-to-moderate intensities of exercise are used [walking at a self-selected pace [75]; cycling at 55% VO_{2max} [80]; or cycling at 60% predicted VO_{2max} [84]] frontal EEG asymmetry does not predict affective responses following exercise. However, at higher intensities (cycling at 70% VO_{2max} [80]; running at 70% VO_{2max} [79]; running at 75% VO_{2max} [78]; and graded exercise to exhaustion [76]), frontal EEG asymmetry has been predictive of affective responses, and this relationship appears to be influenced by fitness [78].

While EEG remains a more readily accessible technology in this domain, other emerging technologies could provide even greater insights into the link between physiological processes and affective responsivity. Ekkekakis [62] has described near-infrared spectroscopy (NIRS; see also [85]) as a technology that can provide a better understanding of "what the brain 'does' during exercise" (p. 505) and thus "help reformulate, refine, or place important boundary conditions" (p. 505) on the questions we pose. Basically, NIRS allows an assessment of oxygenation of tissue (including cortical tissue) with evidence indicating an increase in oxygenation (i.e., increased activation) at low-to-moderate levels of exercise intensity and decreases in oxygenation (i.e., decreased activation) during strenuous exercise. Perhaps one of the greatest advantages of NIRS over EEG would be the ability to monitor PFC activity during exercise without the movement artifact concerns present with EEG. Furthermore, understanding the during-exercise affective responses has become an important practical and theoretical issue [16].

Transient Hypofrontality

The second theoretical question noted by Ekkekakis [62] is the THH [14,86,87]. The THH proposes that exercise exerts an inhibitory effect on activation of the PFC, thus providing a possible explanation for both the impairment of certain

cognitive processes during exercise as well as the anxiolytic and antidepressant effects of exercise. There is some behavioral evidence to support the basic tenets of the THH [e.g., 88,89]. However, there is also evidence that does not support it [e.g., 90,91]. Brümmer et al. [90] examined the effects of increasing exercise intensity on EEG current density (measure of brain activity) in the primary sensory and motor cortices and the PFC during the exercise itself. In keeping with the THH, activity in the primary cortex increased in conjunction with increasing intensity, but activity in the PFC (and primary sensory cortex) remained stable throughout. A particularly interesting study was designed to examine whether single bouts of exercise could reduce cravings for cigarettes [92]. Imposing temporary nicotine abstinence on the participants, a substantial reduction of brain activation (assessed via fMRI following exercise or no-exercise control conditions) was seen in the dorsolateral PFC following 10 min of moderate-intensity cycling exercise (compared with scanning done during no-exercise control). In contrast, other areas of the frontal cortex showed increased activation following exercise. van Rensburg et al. [92] pointed to the THH as a potential explanation for their finding. While several psychophysiological methodologies could be used to examine the THH, Ekkekakis [62] makes a cogent argument for the use of NIRS because of its potential application across a range of exercise intensities and its general ability to withstand movement artifact, thus allowing its use during exercise. Coupled with appropriate measurement of ongoing cognition and/or affect, NIRS could be invaluable in furthering our understanding of mechanisms underlying such changes.

Dual-Mode Theory

The final theoretical question concerns what has been called the DMT. Ekkekakis [15,16,62] proposed the DMT as a way of explaining affective responses occurring in response to exercise, taking into account both the evolutionarily adaptive significance of, and the physiological basis for, such responses. Essentially, the DMT proposes that affective responses to exercise are influenced by both cognitive (e.g., self-efficacy) and interoceptive factors (e.g., muscular, respiratory cues). The relative influence of cognitive to interoceptive factors is hypothesized to depend on the intensity of the activity itself. At exercise intensities below the ventilatory threshold (VT), cognitive factors are hypothesized to influence affective responses to a greater extent; at intensities near or above the VT, interoceptive influence becomes increasingly dominant. Such a theoretical perspective would allow psychophysiological examination of affective responses guided by theory, something that has not happened to any great extent in the exercise domain [93]. Evidence to date has been largely supportive of various aspects of the DMT [e.g., 15,94].

As noted by de Geus and de Moor [95] and echoed by Ekkekakis [96], two questions that have puzzled exercise scientists are (1) why exercisers exercise and (2) why non-exercisers don't. de Geus and de Moor presented an interesting case for genetic influence for such individual differences in how exercise might influence affective responses. "We suggest that the genetic make-up of exercisers tips the balance of the appetitive and aversive effects of exercise in favor of the appetitive effects, whereas in non-exercisers the aversive effects may prevail" [95, p. 57]. A tool has been developed to address such individual differences by assessing intensity preferences and intensity tolerances [97]. Defining intensity preferences as "a predisposition to select a particular level of exercise intensity when given the opportunity (e.g., when engaging in self-selected or unsupervised exercise)" and intensity tolerance as "a trait that influences one's ability to continue exercising at an imposed level of intensity even when the activity becomes uncomfortable or unpleasant" [97, p. 354], studies have shown support for both constructs [98,99]. Clearly, with documented large individual differences in the magnitude of exercise-associated affective changes [93,95] and even in the direction of affective responses (positive, negative, and no change to the same exercise stimulus), continued study of individual differences is crucial to developing better exercise prescription so that perhaps even non-exercisers will adopt and adhere to regular exercise programs.

Thinking of affect in terms of both activation/arousal and valence dimensions, examining affective responses during exercise in addition to before and after exercise, and considering individual differences have been productive approaches in examining the role of exercise intensity [93]. Furthermore, the move toward guiding such investigations from theoretical perspectives has yielded, and will continue to yield, noteworthy insights and has provided clearer views through the windows. Yet again, the point is that "mind" issues (i.e., affect/emotion) are intimately rooted in, and inseparable from, "body" issues.

"LOOKING THROUGH 'STRAINED'-GLASS WINDOWS"

Life in the latter half of the twentieth and beginning of the twenty-first centuries has been characterized by ever-growing levels of stress. One of the consequences of this increasingly stressful lifestyle is a concomitant increase in stress-related diseases (e.g., heart disease, cancer, depression, ulcers, irritable bowel syndrome). Sapolsky [100], in a very accessible text, describes how we respond to acute physical crises, chronic physical challenges, and psychological and social disruptions.

An influential framework in the development of our understanding of the stress response involves two related yet distinct neuroendocrine axes: the sympathetic-adrenal-medullary (SAM) axis and the hypothalamic-pituitary-adrenocortical (HPA) axis. The SAM axis response to a stressor results in sympathetic outflow (via the splanchnic sympathetic ganglion) to the adrenal medulla, resulting in the release of catecholamines (norepinephrine [NorE] and epinephrine [E]) into the bloodstream. The HPA axis response involves the release of corticotropin-releasing hormone by

the hypothalamus into hypothalamic-pituitary circulation, which then stimulates the pituitary gland to release adrenocorticotropic hormone into the blood, ultimately stimulating the adrenal cortex and resulting in the release of glucocorticoids (e.g., cortisol in humans). Both axes are involved in the stress response, with the SAM axis responding more rapidly and the HPA axis requiring longer recovery time. As described by Sapolsky, catecholamines (NorE and E) act "within seconds; glucocorticoids back this activity up over the course of minutes or hours" [100, p. 30].

It is a popularly held belief that exercise can act as a buffer against the stress response [101]. Indeed, plenty of anecdotal evidence exists that exercise can help alleviate stress. One basic premise for how exercise could buffer the deleterious effects of the stress response is referred to as the cross stressor adaptation hypothesis (CSAH). Noting that exercise itself is a stressor that invokes many of the same physiological paths as psychosocial stressors but in a beneficial fashion, the CSAH comes from the idea that these beneficial adaptations from exercise manifest themselves when experiencing a psychosocial stressor. Because the exercise-induced adaptations are more positive, they help to attenuate the negative effects of the stressor [102]. As with examination of the affective impact of exercise, an ever-increasing literature has evolved documenting the impact of "body" interventions (i.e., exercise) as a way of buffering the effects of psychosocial stressors. This research has taken the form of studies examining the effects of fitness on various stress indices (e.g., ranging from self-report to cardiovascular to immunological) and studies examining the effects of both acute and chronic exercise on stress. In an oft-cited initial review, Crews and Landers [103] quantitatively summarized the results of 34 studies examining the effects of aerobic fitness on the psychosocial stress response. A variety of stress indices, including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), self-report, and catecholamines (NorE, E), were included. The basic question was simple and straightforward: Do individuals possessing greater levels of aerobic fitness have an attenuated stress response relative to less fit individuals? Crews and Landers concluded that, regardless of the stress index used, more fit individuals had a significantly smaller stress response compared to unfit individuals.

In terms of cardiovascular reactivity to stress, three other reviews of the fitness-stress reactivity literature offer a much less optimistic picture. Forcier et al. [104] examined the effects of fitness on cardiovascular reactivity (HR, SBP, DBP) and recovery from psychosocial stressors. Although their results favored a fitness effect, it was much more muted than that reported by Crews and Landers. Forcier et al.'s analysis essentially showed that physically fit individuals have a smaller HR and SBP reactivity response to psychosocial stressors, estimated at 15%–25%, and also have a faster HR recovery when such stressors are over relative to unfit individuals. In contrast to both investigations, Jackson and Dishman [105] concluded that the evidence does NOT support the hypothesis of reduced reactivity to stressors in more fit individuals. They, like Forcier et al., did find evidence for a slightly faster recovery following stressor offset in more fit individuals, but noted such an effect was rather small. Finally, Hamer et al. [106] reviewed 15 randomized controlled trials that examined the acute exercise effect on blood pressure (BP) responses to psychosocial stressors. The overall effect showed the equivalent of 3.7 and 3.0 mmHg reductions in the SBP and DBP responses, respectively, compared to controls. Hamer et al. concluded that the benefits of regular exercise might come from the fact that the regular exerciser is likely to be in a favorable postexercise window more often when experiencing a daily stressor.

Beyond acute bouts of exercise, it has also been assumed that exercise training would have stress-buffering effects. However, there is no consensus on this assessment. For example, Peronnet and Szabo [107] stated, "Examination of these longitudinal studies suggests that there are no clearly identifiable changes in sympathetic response to psychosocial stress after physical exercise training as revealed by direct sympathetic indices, such as circulating catecholamines" (p. 206). They also suggested that the mechanisms responsible for the sympathetic aspect of the psychosocial stress response are different from the response to exercise stress. Further, Buckworth and Dishman [108] noted that there was little support for the hypothesis that exercise training and/or high levels of cardiovascular fitness translate into a reduced psychosocial stress response, pointing to the lack of evidence demonstrating an effect of exercise training on a reduced sympathetic response (i.e., plasma levels of NorE and E; sympathetic nerve activity). The sympathetic response has been shown to be reduced after exercise training, but only at absolute exercise intensities (i.e., all participants train at the same workload regardless of fitness level); when similar relative intensities are examined (i.e., exercise workload is adjusted based on fitness, age, gender, etc.), the sympathetic response is similar. In other words, "exercise training seems to increase the capacity of the sympathetic nerves to respond to maximal exercise, but does not change their responses to exercise of the same relative strain as before training" [108, p. 83].

While these criticisms may ultimately be true, some research does suggest that aerobic fitness may confer buffering effects to psychosocial stressors. For example, in a cross-sectional comparison, Boutcher et al. [109] found a lower absolute HR response to psychosocial stress (i.e., mental arithmetic, Stroop tasks) in aerobically trained individuals. Utilizing what may be a very important distinction, Boutcher et al. distinguished between absolute reactivity (i.e., the absolute value of HR during stress) and relative reactivity (i.e., a change in HR during stress from a baseline value). As Boutcher et al. noted, the lower absolute HR during stress could be due, at least in part, to a lower resting HR [109]. It has been argued that a lower resting HR is a reason for the smaller reaction to stress in more fit individuals [108]; in reality, their reaction is similar in magnitude to the less fit person. Boutcher [110] argues instead that the lower resting HR and absolute HR during stress may be cardio-protective, an effect resulting from exercise training. More specifically,

he suggested that the lower HR effectively results in the more fit person spending a greater amount of total time in a more "stable" state during the BP cycle (i.e., during diastole, that portion of the cycle when there is less change in the rate of blood flow and when blood flow itself is primarily unidirectional).

As noted by Holmes et al. [102], exercise-stress research is still fairly immature, largely because of a lack of "conceptual sophistication" (p. 501), poor methodological quality, timing of assessments, and the selection of stress indices. For example, "simply" focusing on HR and BP responses has been the norm rather than the exception in the majority of the literature. In addition to his thoughts on the lower HR response to stressors in more fit individuals, Boutcher [110] noted that a reduced absolute HR response may be due to greater dominance of the parasympathetic system at rest, combined with a smaller sympathetic response during the stressor. Using HR variability (HRV), a measure which provides an indirect assessment of parasympathetic influence on the heart, it has been shown that the HR response to a stressor is due more to parasympathetic withdrawal and less to increased sympathetic activity in trained individuals [109,111]. This parasympathetic withdrawal effect has potential importance in terms of catecholamine sparing. That is, if the elevated HR response is due to a withdrawal of parasympathetic influence more so than an increase in sympathetic activity, fewer catecholamines will be released in response to the stressor.

Another example highlights the more real-world nature of the fitness-stress relationship. King et al. [112] examined the effect of a 12 month exercise intervention (compared to a year-long nutrition education program) on cardiovascular stress reactivity in initially sedentary women. These women, who were caring for a relative with dementia, had HR and BP reactivity assessed in response to a 6 min period during which they were asked to discuss those "aspects of her caregiving experience that she found to be most frustrating or disturbing" (p. M29). The assessment was done at the beginning and end of the intervention. Participants in the exercise intervention had significantly smaller SBP and DBP reactivity (4–9 mmHg smaller, approximately twice that reported in the Forcier et al. 2006 meta-analysis [104], following the intervention than did their nutrition education counterparts, reflecting an improvement in the relationship between chronic stress and cardiovascular pathology.

While most exercise–stress research has tended to focus on cardiovascular and catecholamine reactivity, some research has examined the HPA axis response to psychosocial stressors. The stress response has wide-reaching effects and has been shown to have a potent impact on immune function. Several disciplines have developed as a result of such inquiries, including psychoneuroimmunology (PNI). PNI research examines the interplay among a variety of mind-body systems, particularly the nervous and immune systems. Furthermore, and more importantly, special attention is given to psychological and social/environmental factors and the effects these have on mind-body function. To follow up on the work of Davidson [70] presented in the previous section, he and his colleagues [113] have shown that individuals with greater relative right anterior brain activation, as opposed to relative left anterior activation, had significantly lower basal levels of natural killer (NK) cell activity (a measure of immune function), reflective of immunosuppression. The same right-activated individuals showed a greater decrease in NK function in response to a significant stressor (i.e., final examination). Similar results were found earlier in a study by Kang et al. [114], consistent with the framework that greater relative right anterior brain activation is reflective of a vulnerability to negative affective responsivity and dispositional negative affect.

In groundbreaking work in the exercise domain, LaPerriere et al. [115] examined the impact of exercise training as a way of buffering stressors. In a group of asymptomatic men at risk for acquired immune deficiency syndrome (AIDS), LaPerriere et al. showed that those who exercised for 5 weeks prior to receiving notification of their human immunodeficiency virus type 1 (HIV-1) status had little change in psychological and immunological measures when they were notified of testing positive for HIV-1. A control group of men who did not exercise showed significant immunologic changes indicative of reduced immunocompetence (i.e., decreased NK cell activity) along with significant increases in anxiety and depression following positive HIV-1 notification. Thus, the relatively brief exercise training provided, at least in part, significant buffering of the stressful influence of a real-life stressor (i.e., discovering that one has the virus that causes AIDS), both psychologically as well as immunologically.

More recently, Traustadottir et al. [116] examined the CSAH. They examined whether adaptations known to occur within the HPA axis in response to physical stress (e.g., blunted cortisol response to exercise performed at the same absolute intensity, greater maximal capacity of the adrenal glands) also occur in response to psychosocial stress and whether aerobic fitness influenced that response. To examine these questions, Traustadottir et al. had 10 young (19–36 years old) and 26 older (59–81 years old) women perform a battery of psychosocial stressors. All of the younger women were classified as unfit; roughly half of the older women were also classified as unfit, while the other half were classified as fit. The battery of tests was referred to as the Matt Stress Reactivity Protocol (MSRP), which lasted approximately 30 min. It consisted of the Stroop Color Word Test, mental arithmetic, an anagram task (a series of letters needing to be unscrambled to form words; time urgency usually stressed), a cold pressor task (subjects placed their hands in buckets of ice water for as long as they could, up to 3 min), and an interpersonal interview, in that order. HR, BP, and plasma cortisol were assessed 45 min prior to beginning the protocol, at the conclusion of each of the tasks, and during recovery from the protocol.

Whereas the MSRP resulted in significant elevations in cardiovascular and endocrine responses, the cortisol response

was modified by fitness. Older fit women had significantly lower cortisol responses to the MSRP than their older unfit counterparts. This difference in response to stress occurred in spite of there being no significant baseline differences between the groups. It is worth noting that even during the recovery time period, cortisol responses were still elevated above baseline values for the older unfit group. Although the cortisol effects were pronounced, no differences existed for adrenocorticotropin-releasing hormone response, or for any of the cardiovascular measures, between both groups. Thus, aerobic fitness blunted the stress response in the older women. This was interpreted as evidence that aerobic fitness can influence sensitivity to stress, ultimately affecting the HPA axis in the direction of a reduced cortisol response to psychosocial stress [116].

The conclusion reached by Traustadottir et al. has been confirmed in at least two other studies. An initial study by Rimmele et al. compared highly trained (i.e., elite sportsmen) to otherwise healthy but sedentary men in response to a 10 min psychosocial stressor challenge. The Trier Social Stress Test (TSST) consisted of a 5 min public speaking task; in this case, participants had to engage in a mock job interview, followed by a 5 min mental arithmetic task involving serial subtraction. Oral responses were given during the serial subtraction task, and both tasks were performed in front of two evaluators (unfamiliar to the participants). Previous research had shown that the TSST significantly alters both HPA axis and cardiovascular responses. Rimmele et al. [117] found the elite sportsmen had significantly smaller reactivity (i.e., smaller increase) in both HR and salivary cortisol compared to their sedentary counterparts. It could be argued that one reason for the different response was simply due to the fact that elite sportsmen are exposed to socially threatening situations more often through competition and thus have different responses due to this. A follow-up study [118] replicated and extended these findings. Similar groups were tested (elite sportsmen vs. sedentary men), but a third, intermediate group was added—amateur sportsmen. Thus, these participants would likely have the same exposure to the socially threatening situations, but do not train at the same level as the elite sportsmen. The participants were again subjected to the TSST, and the results were similar for the elite sportsmen compared to the sedentary group (i.e., reduced HR and cortisol reactivity during the stressor task). The amateur sportsmen had a similar cortisol response as the sedentary group, but a HR response that was similar to the elite group. Thus, the overall findings from both studies were consistent with the Traustadottir et al. work, namely that physical activity seems to have a blunting effect on the HPA axis (i.e., appears to support the CSAH). Furthermore, it appears that physical activity has more rapid effects on the sympathetic nervous system as both groups of sportsmen showed less reactive HR responses to the stressor.

To further examine the effects of exercise and/or fitness on psychosocial stress exposure, Hamer and Steptoe [119] assessed the association between fitness (estimated from a submaximal test), parasympathetic control of the heart (via HRV), and immune function responses to mental stress. Participants completed two mental stressors (5 min Stroop task, 5 min mirror tracing task), and blood samples and HRV were collected at rest and 45 min post-stressor tasks; HRV was also assessed during the stressor tasks. Measures of immune function [interleukin (IL)-6, IL-1 receptor antagonist] were significantly greater during recovery. Further analyses indicated that, after accounting for several other baseline factors (e.g., age, body mass index, gender, baseline levels of immune function), exercise HR was related to IL-6 and tumor necrosis factor (TNF)-alpha responses to the stressor tasks; exercise HR was also related to the HRV response to stress. Furthermore, higher SBP during exercise was predictive of TNF-alpha responses to the stressors. Hamer and Steptoe noted that a lower exercise HR (an index of greater fitness) was associated with smaller immune response, specifically a smaller inflammatory response, to acute mental stress. This response seems to be mediated, in part, through parasympathetic pathways, a mechanism which may offer an explanation for how fitness buffers against cardiovascular risk.

As mentioned earlier, Holmes et al. [102] have commented on the lack of "conceptual sophistication" (p. 501), poor methodological quality, timing of assessments, and the selection of stress indices. A key issue in this regard, one that has been typically overlooked in exercise research, is the examination of the recovery from the stressor once it has stopped, as opposed to reactivity to the stressor. Gal and Lazarus [120] noted that emotional arousal in response to a stressful event might not be reflected in the magnitude of the hormonal response but rather in how long the response lasts (i.e., the duration). They cite data from a study of combat soldiers, noting that while an "attacking" company had a more marked rise in corticosteroids (i.e., cortisol) in response to combat than a "defending" company, the defending company took much longer to recover from the combat than the attacking company (13 vs. 6 days). This finding not only fits with their thesis that participating in physical/motor activity of some sort, as opposed to being passive, helps to cope with a stressor, but also highlights the importance of recovery from a stressor compared to the actual reactivity to it.

Spalding et al. [121] showed lower HR and rate pressure product (the product of HR × SBP) levels during recovery from a psychosocial stressor in a group of aerobically trained individuals compared to weight-trained or non-trained individuals. Likewise, Traustadottir et al. [116] found elevated cortisol levels in older unfit women during recovery from a stress battery compared to a group of older fit women. Thus, while the evidence for a stress-buffering effect of exercise may not be particularly compelling at present, evidence suggests that fitness or exercise training may provide a more rapid recovery from the stressor once it is no longer present. This shorter duration stress response could have the effect of reducing the overall wear and tear on the mind-body. Again, in this case, better timing of assessments [102] may yield greater clarity of findings.

CLEANING OUR WINDOWS/ LOOKING FOR THE PATTERNS

As one examines mind/body research, it is clear that there is certainly incredible potential to increase our understanding of human functioning. If researchers can be convinced to examine such functioning from multiple levels, as we have argued at the beginning of this chapter, this will most certainly be a step in the right direction. However, human functioning is not going to be easily understood. One need only examine the work of Cacioppo et al., summarized in Cacioppo [122]. In examining neuroendocrine responses to a stressor, he and his colleagues could have easily stopped with the finding that a psychological stressor activates the SAM axis (increased NorE and E) but not the HPA axis (no change in cortisol). However, when these responses were examined within high and low HR responders (i.e., from an individual differences perspective), a different picture emerged. High HR responders had higher levels of cortisol in addition to the elevated catecholamine response; low HR responders did not. As Cacioppo [122] also points out, classifying an individual as a high or low HR responder ignores the origin of this reactivity. For example, high HR reactivity could be due to elevated sympathetic reactivity, vagal withdrawal, or reciprocal activation of both sympathetic and vagal input to the heart. The point is, simply including measures from different levels of analysis alone is not sufficient. There is also the need to look for patterns or profiles of responding as opposed to expecting simple relationships to be found between mind and body measures.

"An integrative, interdisciplinary approach across levels of organization and analysis can add unique perspectives because different levels of analysis *can reveal distinct patterns of order in data* …" (emphasis added, p. 26, [123]). Cacioppo et al. [8] make a logical case for how to examine these multiple measures from the physiological and psychological domains and put them together in a manner that allows us to make sense out of the chaos. They argue that it is probably not realistic to expect to find simple one-to-one relationships between a psychological event and a physiological event (e.g., to expect that HR will give us a physiological measure of anxiety). Such an assumption inevitably leads to frustration because consistent correspondence between such measures will rarely be found. Cacioppo et al. argue instead for examination of patterns or profiles of response. As an illustrative example, they present how two autonomic measures, skin conductance and HR, can be used to infer different psychological processes. The orienting, defense, and startle responses all share a relationship with skin conductance and HR, which would normally preclude the ability to infer the psychological processes from the physiological signals. Such inferences can be made, however, when the patterns particular to each response are examined. The orienting response is associated with a phasic skin conductance response coupled with a deceleration in HR. Both the startle and defense responses can be inferred from a phasic skin conductance response and an acceleration in HR. However, both are differentiated by the fact that the startle response involves an abrupt acceleration in HR while the defense response involves a lingering acceleration in HR. The point is, it is only through the examination of patterns of responding or response profiles that we can uncover the complicated relationships between "body" measures and "mind" constructs. The cost of such an approach isn't cheap, but the payoff is infinitely great.

CLOSING THE WINDOW

Although certainly not exhaustive, the evidence presented in this chapter would make it difficult to argue against the idea that "mind" and "body" are intimately linked and inseparable from each other. Much more information is gained by simultaneously examining human functioning from a mind-body perspective at multiple levels (i.e., psychophysiological, physiological, and social/environmental) than could ever be obtained by looking at mind and body as separate entities and/or from single levels of analysis. It is also worth pointing out that "… in such matters technical progress is likely to outpace refinements in perspective; indeed, technical advances are likely to shape perspective" [124, p. v]. Thus, while it would be foolhardy to discount the advances to understanding that may come from new technologies (e.g., fMRI, NIRS), it would be equally foolhardy to rely on such techniques and technologies without constraining the findings to a theoretical perspective or, at the very least, to the research paradigm that was used to derive the findings. For example, Robinson et al. [125] pointed out that there are numerous factors that could potentially influence the patterning and magnitude of emotional responding in an fMRI paradigm, all of which can lead to different definitions of the phenomenon being examined or to interpretations of the data garnered from such investigations. Another issue with these newer technologies is that the number of participants studied is often rather small (e.g., <10 participants), sometimes only examining one sex, and very often minimizes individual differences (i.e., examining group averages). We know from a growing number of studies [e.g., 97,126] that ignoring such individual differences can lead to erroneous conclusions and the same holds for studies using new techniques.

The major point here is that, as a field, we need to be careful not to get too caught up in the tools that we have available, but to begin with solid research questions that inform innovative research designs. Hopefully this will not lead to a large number of disparate studies with disjointed findings, but instead to a greater likelihood of uncovering patterns and meaning in the relationships between mind-body.

It is our hope that such information will stimulate readers to examine their research questions more thoughtfully and to begin to explore phenomena of human functioning from a multilevel perspective. It is no longer enough to assume that the only reality that matters is that which the individual constructs for her/himself. Such perspectives are important but incomplete. The corporeal basis for such realities will aid in

how we come to understand human behavior. The following quote from Miller [127] sums it up well:

> The body is the medium of experience and the instrument of action. Through its actions we shape and organize our experiences and distinguish our perceptions of the outside world from sensations that arise within the body itself. (p. 14)

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115 Genetic Influences on Regular Exercise Behavior

Marleen H.M. de Moor, PhD and Eco J.C. De Geus, PhD

CONTENTS

Introduction 1367
Definitions of Regular Exercise Behavior 1367
Prevalence of Regular Exercise Behavior 1368
Twin Studies on Exercise Behavior 1370
Extended Twin Family Studies 1374
Gene-Finding Studies 1374
Conclusions and Future Research 1376
Acknowledgments 1376
References 1376

INTRODUCTION

Regular exercisers have lower risks for cardiovascular disease, obesity, and type 2 diabetes than non-exercisers [1–3], and the percentage of people at risk because of inactivity is higher than those at risk because of hypertension, smoking, and cholesterol [4]. Despite these well-documented benefits of physical activity, a large proportion of adults in the Western world do not engage in exercise activities on a regular basis [5–7]. As a consequence, a sedentary lifestyle—and the accompanying risk for obesity—remains a major threat to health in today's society. This is reflected in public health recommendations, which unanimously include an encouragement to a more active lifestyle [8].

To increase the success of intervention on this important health behavior, much research has been devoted to the determinants of exercise behavior. The bulk of these studies have attempted to explain low exercise prevalence in terms of social and environmental barriers. These include, among others, poor access to facilities [9], low socioeconomic status [6,10], non-Caucasian race [11], high job strain [12], subjective "lack of time" [13], inadequate health beliefs [6], and low social support by family, peers, or colleagues [13,14].

Although social factors are important, they explain only a small part of the individual differences in regular exercise behavior. In this chapter, we review the evidence that genetic factors play an important role too. Broadly, the genetic research on regular exercise behavior can be classified into twin (family) studies and gene-finding studies. We will summarize the evidence presented by each of these types of studies. As the exact definition of the phenotype might influence heritability estimates, we will first review the different definitions of exercise behavior that have been used across studies.

DEFINITIONS OF REGULAR EXERCISE BEHAVIOR

A first important distinction between studies on regular exercise behavior is whether they query regular exercise activities that are confined to leisure time or whether they count all physical activity (TPA). Leisure-time exercise activities are often specifically aimed to improve cardiorespiratory health such as jogging, exercising at fitness clubs, and participation in team or individual sports [15]. TPA is not limited to these activities and also incorporates occupational physical activity, bicycling to school/work, and household activities.

Even when we restrict ourselves to leisure-time exercise behavior, definitions can differ across studies. Some studies explicitly focus on all "pure" exercise activities (jogging, exercising in the fitness center, and all individual or team sports), while others also include leisure-time behaviors such as gardening, dancing, and walking/bicycling. The differences in the definitions of exercise behavior are further complicated by the varying methods of assessment. Most of the studies on exercise behavior have been survey-based, but rather different questions have been used. Some studies used surveys with only a single YES/NO question [16], whereas others asked about specific exercise activities [7,17] and still others allowed all exercise activities to be reported [18]. The type, duration, frequency, and intensity were sometimes but not always assessed in great detail. This makes it difficult to either pool or compare the prevalence of exercise behavior across survey studies.

Two regular exercise phenotypes are nonetheless easy to define and resemble each other quite well across studies. Sedentary subjects simply do not engage in any type of leisure-time exercise activity, whereas vigorous exercisers perform leisure-time exercise activities above the intensity and frequency thresholds required to maintain a continued

increase in aerobic fitness above their sedentary level. To achieve such an increase, vigorous exercisers engage in large muscle dynamic exercise activities requiring more than 50% of their maximal oxygen consumption for at least three times a week for 20 min or more per occasion [8,19].

Measures of regular light to moderate exercise behavior, i.e., all exercise levels in between sedentary and vigorous exercise, are much harder to compare across studies. Studies use different criteria for the minimum frequency and the minimum intensity that is required to classify participants as "regular exercisers." Criteria for frequency have varied from once per 2 weeks [6,20,21] to five or more times a week [22]. In some studies, the exercise activities were coded for intensity and had to meet a certain minimal intensity to be counted [23–25], whereas in others, no minimum intensity was specified [6,20,21].

In the next paragraph, we describe the prevalence of three different measures of exercise behavior that have been consistently measured in the same way in a large community-based sample from the Netherlands Twin Register (~30,000 subjects) [26]. We compare the prevalence of regular exercise behavior in the Netherlands to the prevalences obtained in five other large studies conducted in industrialized societies [6,7,20–22].

PREVALENCE OF REGULAR EXERCISE BEHAVIOR

Within the Netherlands Twin Register, data on exercise behavior have been collected through surveys in large numbers of twins, their parents, siblings, spouses, and the adult children of twins and siblings. Data collection has started in 1991 when most twins were adolescents. Since then, a survey with data on health, lifestyle, and personality (including data on exercise behavior) has been sent out to the participants in 1993, 1995, 1997, 2000, 2002, 2004, and 2008 [26]. In total, leisure-time exercise behavior and general physical activity data have been collected in about 30,000 subjects. It has been shown that twins are comparable with non-twins and representative for the population at large with regard to their participation in regular leisure-time exercise [18].

Regular exercise in leisure time was measured in detail in each survey. First, the participants were asked whether they exercised regularly in their leisure time ("Yes" or "No"). If participants responded affirmative, they were asked to indicate in which types of exercise activities they engaged. For each activity reported, they noted down the number of months per year, weekly frequency, and average duration in minutes of the activity. Ainsworth's Compendium of Physical Activity [27] was used to assign a metabolic equivalent (MET) score to each exercise activity, reflecting its energy expenditure as a multiple of the basal energy expenditure (~1 kcal/kg/h) in an average subject engaged in that activity. For each participant, a total weekly MET score was computed across all exercise activities by summing the products of the number of hours spent weekly on each exercise activity and its MET score. Activities were only scored if that participant had engaged in them for at least 3 months during the past year. For adolescents, exercise during physical education classes at school was not included in the weekly MET score.

Subjects were classified as moderate to vigorous exercisers if they exercised at least 60 min/week with a MET score of 4 or more. They were classified as non regular exercisers otherwise. In addition, data were collected on the frequency of exercising to sweat during leisure time ("Sweat Index") and the frequency of being physically active during leisure time during at least 20 min in the past 6 months ("Twenty minutes active"). The five answering categories for the Sweat Index were "No," "Yes, once per week," "Yes, 2 times per week," "Yes, 3 times per week," and "Yes, more than 3 times per week." The Twenty minutes active variable had six answering categories, which were "Never," "Less than once per month," "About once per month," "About 2–3 times per month," "1–2 times per week," and "3 times per week or more." The Sweat Index and the Twenty minutes active variable were measured on all time points except 1991 and 2008.

Table 115.1 shows the prevalence of these three regular exercise behavior phenotypes in the Dutch twin family population. To achieve this, we constructed a maximal cross-sectional dataset by selecting the most recent measurement for each individual. This resulted in data from over 21,000 participants for the Sweat Index and Twenty minutes active variable and data from over 29,000 participants for regular exercise status based on the weekly MET score. As can be seen in the table, about 70% of the population exercises at least once per week to sweat or has been physically active during leisure time for at least 20 min at least once per week during the past 6 months. The percentage of the population exercising to sweat or exercising at least 20 min for three times a week or more is much lower and lies around 25%–40%. When taking into account the intensity of the exercise activities in METs, about half of the population engages in moderate to vigorous exercise activities (4 MET or more) for at least 60 min/week.

For the Sweat Index, there are clear sex differences, with men exercising on average more than women. Furthermore, the prevalence of regular moderate to vigorous exercise behavior for at least an hour a week generally declines with age. For example, 55% of the youth between 10 and 20 years old engage in regular moderate to vigorous exercise but this is only 28% in older adults between 60 and 80 years. Interestingly, no obvious sex difference or age-related decline is observed in the answer to the question whether they were physically active during leisure time for at least 20 min in the past 6 months. In contrast to the other two questions, intensity of the exercise activity may not play a role when subjects answer these questions.

Although it is clear that these three exercise phenotypes measure different aspects of leisure-time exercise behavior, they also measured an overlapping construct. A series of univariate ANOVA's showed that the Sweat Index, the Twenty minutes active variable, and Regular moderate to vigorous exercise were all significantly and positively associated with the total weekly MET hours based on the

TABLE 115.1
Prevalence of Different Exercise Phenotypes in the Netherlands Twin Register

	Sweat Index				Twenty Minutes Active				Regular Moderate to Vigorous Exercise		
	N	<1 Time/Week Sweating	≥1 Times/Week Sweating	≥3 Times/Week Sweating	*N*	<1 Times/Week 20 Minutes Active	≥1 Times/Week 20 Minutes Active	≥3 Times/Week 20 Minutes Active	*N*	No Regular Exercise	≥1 h/Week of Moderate to Vigorous Exercise (MET ≥ 4)
Total	21,818	31.0	69.0	23.6	21,896	26.6	73.4	38.1	29,526	56.4	43.6
Men	9,300	27.6	72.4	28.9	9,333	27.3	72.7	38.7	12,446	55.0	45.0
Women	12,518	33.4	66.6	19.5	12,563	26.1	73.9	37.7	17,080	57.4	42.6
Age 10–20 years	1,507	8.5	91.5	37.8	1,511	17.7	82.3	55.0	3,486	45.0	55.0
Age 20–40 years	11,004	26.7	73.3	24.7	11,022	28.8	71.2	34.0	12,480	51.5	48.5
Age 40–60 years	7,195	36.6	63.4	19.7	7,222	26.2	73.8	38.7	10,093	62.0	38.0
Age 60–80 years	2,112	42.6	57.4	20.3	2,141	23.2	76.8	45.5	3,107	71.3	28.7

N, number of participants with valid data on the phenotype.

TABLE 115.2
Association of Weekly MET Hours with the Categorical Sweat Index, Twenty Minutes Active, and Regular Moderate to Vigorous Exercise Variables

	Mean Weekly MET Hours (SD)	*F*-Test
Sweat index		
No	2.79 (8.41)	
Yes, once per week	7.47 (11.55)	
Yes, two times per week	11.99 (14.70)	
Yes, three times per week	18.31 (19.84)	
Yes, more than three times per week	19.93 (26.99)	$F(4.18563) = 743.9$; $p < 0.001$
Twenty minutes active		
Never	2.21 (8.82)	
Less than once per month	2.88 (9.41)	
About once per month	3.32 (8.33)	
About two to three times per month	4.84 (10.24)	
One to two times per week	8.59 (12.59)	
Three times per week or more	14.79 (21.07)	$F(5.18624) = 276.8$; $p < 0.001$
Regular moderate to vigorous exercise		
No	0.63 (4.37)	
Yes	22.19 (21.21)	$F(1.27012) = 14560.9$; $p < 0.001$

questions on type, frequency, and duration of reported exercise activities (Table 115.2).

The prevalence for leisure-time exercise behavior in the Dutch twin families is very consistent with the prevalence reported by five other large-scale studies [6,7,20–22]. Three of these studies were conducted in 10,000–20,000 university students aged 18–30 years from the European Union (EU) and elsewhere [6,20,21]. All three studies found comparable prevalence for leisure-time exercise: about 70% of the students exercised regularly, meaning they engaged at least one time per 2 weeks in exercise (e.g., sports activities and physically active pastime). About 30%–35% of the students were vigorous exercisers (i.e., had exercised on five or more occasions during the previous 2 weeks). The fourth study was a pan-European study of exercise participation in more than 15,000 adults aged 15 years up to more than 65 years old from 15 member states of the EU [7]. They found that 76% of the male and 71% of the female EU population participated in some kind of physical activity during leisure time, a result best comparable with our Twenty minutes active variable. In a fifth study, physical activity levels were assessed in 43,732 men and women from the United States, aged 18 years and older [22]. The average prevalence across adulthood for any form of exercise behavior (five or more times a week and 30 min or more per occasion of any activity, but no intensity specified) varied between 73% for women and 79% for men, a result again comparable with our Twenty minutes active variable.

Overall, a clear picture arises from the six studies described earlier in the text. Despite the well-documented benefits of exercise, a large group of adolescents and adults does not engage in exercise on a regular basis. Across Europe and the United States, the prevalence for sedentary behavior varies between 26% and 34% depending on the exact question used. What factors cause exercisers to exercise and, more importantly, what keeps non-exercisers from doing the same? The remainder of this chapter will review evidence from behavioral genetics for a significant genetic contribution to physical activity behaviors.

TWIN STUDIES ON EXERCISE BEHAVIOR

As with many other traits, exercise behavior appears to run in the family. The familial resemblance observed for exercise behavior can represent environmental influences that are shared within a family ("nurture") or they can represent genetic influences ("nature"). Twin studies can separate these two mechanisms by comparing the resemblance in exercise behavior between monozygotic (MZ) and dizygotic (DZ) twins. When twins are reared together, they share part of their environment, and this sharing of the family environment is the same for MZ and DZ twins. The important difference between MZ and DZ twins is that the former share (close to) all of their genotypes, whereas the latter share on average only half of the genotypes segregating in that family [28]. This distinction is the basis of the classical twin study. If the resemblance in physical activity within MZ pairs is larger than in DZ pairs, this suggests that genetic factors (A) influence physical activity. If the resemblance in physical activity is as large in DZ twins as it is in MZ twins, this points to shared environmental factors (C) as the cause of family resemblance [29].

The extent to which MZ and DZ twins do not resemble each other is ascribed to the unique (or non-shared) environmental factors (E). These include all unique experiences like differential jobs or lifestyle, accidents or other life events, and in childhood, differential treatment by the parents, and non-shared friends and peers. Shared environmental factors are defined as those environmental factors that are shared within a family, such as parenting style, family functioning, neighborhood, or socioeconomic status. Additive genetic factors represent the sum of all linear effects of the genetic loci that influence the trait of interest.

The effect of genetic and environmental factors on exercise behavior in a sample of MZ and DZ pairs can be graphically depicted in a path diagram (Figure 115.1). The heritability of exercise is defined as the relative proportion of the total variance explained by genetic factors. In terms of the parameter estimates obtained from fitting the twin model to the data (see Figure 115.1), the heritability can be expressed as $a^2/(a^2 + c^2 + e^2)$. The heritability can also be represented as a percentage by multiplying this ratio by a hundred. The proportions of variance ascribed to shared environmental and unique environmental factors can be computed in a similar manner and are given by, respectively, $c^2/(a^2 + c^2 + e^2)$ and $e^2/(a^2 + c^2 + e^2)$ [30].

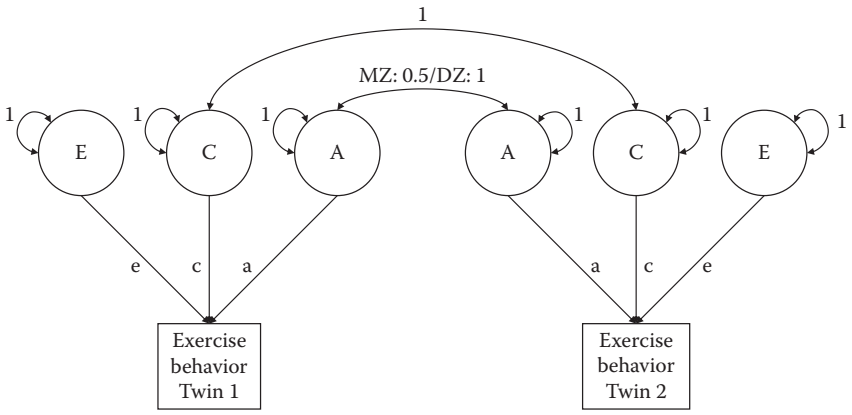


FIGURE 115.1 Path diagram depicting correlated latent additive genetic (A) and shared environmental (C) factors that can cause twin resemblance in exercise behavior, as well as unique environmental (E) factors that are uncorrelated in the twins. We set the correlation of the latent genetic factors for MZ twins to 1 and for DZ twins to 0.5. The correlation of shared environmental factors is set to 1 for both types of twins. The latent unique environmental factors are (per definition) uncorrelated. Unobserved latent variables have no scale: their variance is arbitrarily set to 1 (the double arrows that start and end in the latent factors). Path coefficients a, c, and e represent the factor loadings of exercise behavior on the latent factors.

An overview of twin studies on exercise behavior conducted in adolescents and adults is given in Table 115.3. These studies almost without exception converge on the finding that exercise behavior is heritable, both in adolescence and in adulthood, despite the different definitions of exercise behavior that were used (i.e., leisure-time exercise behavior, TPA, sports participation, or participation in specific high-intensity exercise activities). The heritability of regular exercise in the Netherlands Twin Register has been published in several studies for adolescents of different birth cohorts [17,24] and during adulthood (18–50 years) [31,32]. We extended these studies by estimating the heritability of regular exercise, the Sweat Index, and the Twenty minutes active variable in a sample of 5221 adult twin pairs of a broader age range (18–65 years) and by adding regular exercise data from the most recent survey (sent out in 2008/2009). All three variables were found to be heritable, with the highest heritability for regular exercise (60%; consistent with the previous studies in adults [31,32]). Somewhat lower heritabilities were found for the Sweat Index (38%) and the Twenty minutes active variable (36%). There was no evidence for quantitative or qualitative sex differences in heritabilities. In addition, we computed the phenotypic, genetic, and environmental correlations among the three phenotypes. The three phenotypes were strongly related at the phenotypic (polychoric correlations 0.51–0.67), genetic (0.69–0.78), and environmental level (0.38–0.59). These results confirm that the three phenotypes are not identical but show considerable overlap.

Twin studies in adolescence [17,24,33,34] show that variation in adolescent leisure-time exercise behavior is explained by a combination of genetic, shared environmental, and unique environmental factors. In a study of Dutch adolescent twins aged 13–20 years and born between 1971 and 1987 [34], it was observed that exercise behavior in young adolescents (up to 16 years) is largely determined by shared environmental factors. The influence of these factors rapidly waned when the adolescents became older. In a study of Dutch adolescent twins of the same age but from a later birth cohort (birth year ranged between 1986 and 1994) [17], it was shown that the shared environmental factors in young adolescence (13–14 years) were only present in girls but not in boys, whereas at age 15–19 years again genetic factors accounted for the largest proportion of the variances, and shared environmental factors did no longer play a role in explaining individual differences in boys and girls. Other twin studies confirm that family resemblance in adolescent leisure-time exercise behavior is explained by a combination of additive genetic and shared environmental factors and that shared environmental factors seem most important in young adolescent girls [33,34].

Studies conducted in adult twins aged between 19 and 68 years [31,34–39] show that variation in exercise behavior is almost entirely accounted for by genetic and non-shared environmental factors, with heritability estimates ranging between 35% and 83% of the variance in exercise. Most of these studies included twins of a wide age range, for example, 19–40 years [31] or 18–60 years [40]. A recent study [41] of seven different countries investigated whether the heritability of exercise behavior during adulthood (19–50 years) changes with age. In four of the seven countries (Denmark, Finland, Sweden, and the Netherlands), a significant decrease in heritability was observed with age (from 60%–90% at age 19 years to 0%–40% at age 50 years). In the other three countries (Australia, Norway, and the United Kingdom), the heritability of exercise was found to be stable during adulthood.

Taken together the results from adolescent and adult twin studies, it seems that heritable factors are present at all ages, but that the heritability of exercise behavior peaks during young adulthood [42]. This may also be the period in which the environmental influences on exercise behavior are lowest. For example, most young adults will have left their parent's house and started a more independent life, such that the influences of the home family environment have become less strong. Similarly, young adults may not yet experience some

TABLE 115.3
Twin Studies on Exercise Behavior

Study	Sample	Phenotype	Results
This chapter	2319 MZ and 2902 DZ Dutch twin pairs (18–65 years)	Frequency of engagement in leisure-time physical activities to the extent that it makes you sweat (Sweat index; <1 time/week, 1–2 times/week, ≥3 times/week) Frequency of engagement in leisure-time physical activities of at least 20 min during the last 6 months (Twenty minutes active; <1 time/week, 1–2 times/week, ≥3 times/week) Engage in leisure-time exercise activities with a minimal intensity of four METs for at least 60 min/week (Regular exercise; yes, no)	Sweat index: a^2 = 38%; c^2 = 0% Twenty minutes active: a^2 = 36%; c^2 = 0% Regular exercise: a^2 = 60%; c^2 = 0% Genetic correlations: Sweat index—Twenty minutes active: 0.78 Sweat index—Regular exercise: 0.75 Twenty minutes active—Regular exercise: 0.69
Van der Aa et al. [17]	8355 Dutch MZ and DZ twins (aged 13–14, 15–16, and 17–19 years)	Engage in leisure-time exercise activities with a minimal intensity of five MET hours weekly (moderate exercise) or 30 MET hours weekly (vigorous exercise)	a^2 = 85%; c^2 = 0% for 13–14-year-old boys a^2 = 38%; c^2 = 46% for 13–14-year-old girls a^2 = 80%; c^2 = 0% for 15–16-year-old twins a^2 = 72%; c^2 = 0% for 17–19-year-old twins
Aaltonen et al. [40]	4280 MZ and 9276 DZ twins on wave 1 (18–54 years) and 4383 MZ and 9439 DZ twins on wave 2	Leisure-time physical activity expressed in MET hours/day	Wave 1: a^2 = 44%; c^2 = 0% Wave 2: a^2 = 34%; c^2 = 0%
Duncan et al. [73]	1003 same-sex MZ and 386 DZ adult twin pairs (mean age 30 years)	Total minutes per week of moderate to vigorous activity (more than 60 or 150 min)	60 min criterion: a^2 = 27%; c^2 = 16% 150 min criterion: a^2 = 11%; c^2 = 18%
Nelson et al. [46]	5524 US adolescent twins and siblings on wave 1 (mean age 16.5 years) and 4368 young adult twins and siblings on wave 2 (mean age 22.4 years)	Engage in leisure-time exercise activities with a minimal intensity of 5 METs at least five bouts per week	Age 16.5 years (mean age at wave 1): a^2 = 59%; c^2 = 2% Age 22.4 years (mean age at wave 2): a^2 = 12%; c^2 = 50%
Eriksson et al. [36]	359 MZ and 232 DZ Swedish male twin pairs (19–25 years)	Total physical activity, occupational physical activity and leisure-time physical activity	TPA: a^2 = 49%; c^2 = 0% LTPA: a^2 = 55–56%; c^2 = 0% OPA: a^2 = 54–56%; c^2 = 0%
Carlsson et al. [34]	5334 MZ and 8028 DZ twin pairs (aged 14–46 years)	Frequency of engagement in leisure-time exercise activities in the past year	Age 14–28 years: a^2 = 64%; c^2 = 7% for males a^2 = 51%; c^2 = 15% for females Age 29–46 years: a^2 = 40%; c^2 = 0% for males a^2 = 41%; c^2 = 0% for females
Stubbe et al. [31]	13,676 MZ and 23,375 DZ pairs from seven different countries participating in the GenomEUtwin project (aged 19–40 years)[3]	Engage in leisure-time exercise activities with a minimal intensity of four METs for at least 60 min/week (yes/no)	a^2 = 27%–67%; c^2 = 0%–37% for males a^2 = 48%–71%; c^2 = 0% for females

TABLE 115.3 (continued)
Twin Studies on Exercise Behavior

Study	Sample	Phenotype	Results
Stubbe et al. [24]	2628 complete Dutch twin pairs (aged 13–14, 15–16, 17–18, and 19–20 years)	Engage in leisure-time exercise activities with a minimal intensity of four METs for at least 60 min/week (yes/no)	a^2 = 0%; c^2 = 84% for 13–14-year-old twins a^2 = 0%; c^2 = 78% for 15–16-year-old twins a^2 = 36%; c^2 = 47% for 17–18-year-old twins a^2 = 85%; c^2 = 0% for 19–20-year-old twins
Beunen et al. (2003)	92 male and 91 female Belgian twin pairs (aged 15 years)	Number of hours spent on sports each week	a^2 = 83%; c^2 = 0% for males a^2 = 44%; c^2 = 54% for females
De Geus et al. [42]	157 adolescent (aged 13–22 years) and 208 middle-aged Dutch twin pairs (aged 35–62 years)[3]	Average weekly METs spent on sports or other vigorous activities in leisure time in the past 3 months (≥4 METS)	a^2 = 79%; c^2 = 0% for adolescent twins a^2 = 41%; c^2 = 0% for middle-aged twins
Frederiksen and Christensen [39]	616 MZ and 642 same-sex DZ twin pairs (aged 45–68 years)	Engage in leisure time in any of 11 different exercise activities (jogging, gym, swim, tennis, badminton, football, handball, aerobics, rowing, table tennis, volleyball) (yes/no)	a^2 = 49%; c^2 = 0% for males and females
Kujala et al. [37]	Data on both members of 1772 MZ and 3551 dizygotic same-sex twin pairs (aged 24–60 years)	Participation in vigorous physical activity based on the question: "is your physical activity during leisure time about as strenuous, on average, as (1) walking, (2) alternatively walking and jogging, (3) jogging (light running), or (4) running?" Those who chose alternative 2, 3, or 4 were classified as participating in vigorous activity	a^2 = 56%; c^2 = 4% for vigorous activity
Maia et al. [33]	411 Portuguese twin pairs (aged12–25)	A composite sports participation index (SPI), that takes into account the energy expenditure for a given sport, number of hours practiced per week and number of months per year	a^2 = 68%; c^2 = 20% for males a^2 = 40%; c^2 = 26% for females
Lauderdale et al. [38]	3344 male twin pairs of the Vietnam Era Twin Registry (aged 33–51 years)	Five questions assessed regular participation in specific, intense athletic activities (running, bicycling, swimming, racquet, and other sports) (yes/no)	a^2 = 0%; d^2 = 53% for jogging a^2 = 48%; c^2 = 4% for racquet sports a^2 = 30%; c^2 = 17% for strenuous sports a^2 = 0%; d^2 = 58% for bicycling a^2 = 8%; c^2 = 31% for swimming
Koopmans et al. (1994)	1587 adolescent Dutch twin pairs (aged 13–22 years)	Do you participate in leisure-time exercise? (yes/no)	a^2 = 48%; c^2 = 38% for males and females
Heller et al. (1988)	200 twin pairs (aged 17–66 years)	Engaged in vigorous exercise in the past 2 weeks (yes/no)	a^2 = 39%

of the environmental barriers for exercise that are common in adult life, such as lack of time due to work or family responsibilities [43].

Recently, studies have appeared that not only investigate individual differences in exercise behavior but also focus on specific sedentary activities such as sitting behavior, watching television, time spent on the computer or the Internet, and gaming [e.g., 44,45]. Two studies investigated to what extent variation in these sedentary behaviors could be explained by genetic factors [46,47]. In a large sample of 5524 U.S. twins and siblings (mean age 16.5 years), the heritability of sedentary behavior, measured as hours per week engaged in TV/video watching and/or playing video/computer games, was 34%. Shared environmental effects accounted for 10% of the variance. At follow-up (mean age 22.4 years), the heritability of sedentary behavior was 28%, while the effects of shared environment had disappeared.

The second study in 5074 Dutch twins and siblings (mean age 15.9 years) found similar results [47]. The heritability of screen-viewing sedentary behaviors, measured as frequency of watching TV, gaming, and computer/Internet-use during leisure time, was 47% in boys and 30% in girls. The proportions of variance due to shared environment in boys and girls were 5% and 14%, respectively. They also investigated whether the heritability changed with age. They found that the effects of genetic factors became stronger in the age

period from 12 to 20 years. At age 12 years, heritability of sedentary behavior was 35% in boys and 19% in girls, while at age 20 years this was 48% in boys and 34% in girls. The effects of shared environmental factors diminished in this age period from 29%–48% at age 12 years to 0% at age 20 years. Although the genes affecting sedentary behavior need not to be the same as those for exercise behavior, it is striking that the heritability estimates and the observed age trends are very similar.

EXTENDED TWIN FAMILY STUDIES

The heritability estimates obtained from twin studies are only valid if the assumptions underlying the twin method hold. An important assumption is the equal environment assumption, which states that environmentally caused similarity in the trait or behavior of interest (i.e., exercise behavior) is the same in MZ and DZ twin pairs [48]. One twin study explicitly tested the equal environment assumption [36]. It was tested whether twin pairs with higher contact frequency were more similar in their total physical activity and physical activity at work or in leisure time separately and whether this effect depended on zygosity status. No evidence for violation of the equal environment assumption was found for any of the physical activity measures [36].

Other assumptions of the twin method include absence of assortative mating and the independence of genes and environment. If assortative mating is present, the genetic correlation in DZ twins or full siblings is underestimated in the twin model, which can cause underestimation of heritability and overestimation of the shared environmental effects. If assortative mating is present for exercise behavior, this could explain the finding for C in (young) adolescents. The previously mentioned assumptions can be tested by adding data from more types of relatives to the twin design, such as data from parents, grandparents, spouses, and siblings. Spouse correlations inform on the presence of assortative mating. Parent–offspring correlations enable to test for the effects of cultural transmission, i.e., the extent to which the shared environment found in adolescent twin studies on exercise behavior represents effects of the parent's exercise behavior on the exercise behavior of the children. Five studies employ extended family designs to report on the familial resemblance of exercise behavior among adolescent offspring (age range 13–20 years) and their parents, using different definitions such as TPA, leisure time exercise, and sports participation [16,23,49–51]. Two of these studies only included non-twin siblings and their parents [23,50]. One study included twins and their parents [16], while the other studies added to this data from either grandparents [49] or non-twin siblings and spouses of twins [51].

The spouse correlation for exercise behavior was significant in all these studies and ranged from 0.16 to 0.60 [16,23,49–51]. De Moor et al. [51] analyzed twin–spouse pairs to demonstrate that the significant spouse correlation for exercise was best explained by phenotypic assortment (i.e., that partners choose each other because they are similar in their exercise behavior) rather than by social homogamy (i.e., that partners similar in exercise behavior meet and marry because they come from similar social backgrounds) or social interaction processes (i.e., that partners resemble each other because they spend time together and mutually influence each other).

Parent–offspring correlations have ranged from 0.05 to 0.54 and are generally somewhat lower than the full sibling correlations [16,23,49–51]. De Moor et al. [51] estimated in a sample of 3525 adolescent twins and their siblings (13–18 years) and 3138 parents from 1736 families that variation in adolescent exercise behavior in boys could be explained for 42% by genetic factors and for 52% by shared environmental factors shared by family members of the same generation but not with the parents. In girls, 36% of the variance in exercise was explained by genetic factors and 41% by generation-specific environmental effects. Cultural transmission effects from parents to offspring were not significant. The effects of assortative mating on the heritability estimates were small. Thus, the results of extended twin family studies show that heritability estimates for exercise behavior obtained from studies using only twins are not overly biased.

GENE-FINDING STUDIES

The heritability of exercise behavior has been well established, but less is known about the genetic variants that are associated with this trait. So far, seven candidate gene association studies, three genome-wide linkage studies, and one genome-wide association (GWA) study have been conducted for exercise behavior or related physical activity phenotypes.

Seven studies tested for association of genetic variation in six candidate genes with exercise or physical activity phenotypes. In a study of adolescent girls [52], the calcium-sensing receptor (*CASR*) gene was associated ($p = 0.01$) with weekly hours spent on physical activities. In a study of Pima Indians [53], the leptin receptor (*LEPR*) gene was associated ($p = 0.007$) with 24 h energy expenditure and physical activity levels. In a study of 222 prepubertal boys [54], *LEPR* was also associated with physical activity energy expenditure ($p = 0.016$). In another study [55], the dopamine 2 receptor (*DRD2*) gene was associated ($p = 0.016$) with past year physical activity in women reporting European ancestry but not in subjects reporting African ancestry. In a sample of postmenopausal women [56], the aromatase (*CYP19*) gene was associated ($p = 0.04$) with physical activity. In a study of mild hypertensives [57], the angiotensin-converting enzyme (*ACE*) gene was associated ($p = 0.001$) with leisure-time physical activity. Finally, a study conducted in adults [58] showed that the melanocortin-4 receptor (*MC4R*) gene was associated ($p = 0.005$) with daily physical activity levels, independent of sex, age, and body mass index (BMI).

The first genome-wide linkage study for exercise behavior was conducted in 767 Caucasian adults from 207 families [59] (see also Table 115.4). Four physical activity phenotypes were measured, of which three reflected daily physical activity and one past year physical activity. For past year physical

TABLE 115.4
Genome-Wide Linkage and Association Studies on Exercise Behavior

	Sample	Phenotype	Categorization	Results[a]
Genome-wide linkage studies				
Simonen et al. [59]	767 Caucasian adults from 207 families	Daily physical activity Past year physical activity		Past year physical activity: 11p15 and 15q13.3 Daily physical activity: 2p22-p16, 4q28.2, 7p11.2, 9q31.1, 13q22-q31, and 20q13.1
Cai et al. [60]	1030 children from 319 Hispanic American families	Daily physical activity		18q12-q21
De Moor et al. [61]	1432 adult Dutch sibling pairs from 622 families	Exercise participation (yes/no; based on 4 MET hours/week)	Moderate plus vigorous activities	19p13.3
Genome-wide association studies				
De Moor et al. [25]	1644 unrelated Dutch and 978 unrelated American adults of European ancestry	Exercise participation (yes/no; based on 4MET hours/week)	Moderate plus vigorous activities	*PAPPS2*

[a] For linkage studies, chromosomal regions are reported for which suggestive or significant linkage was found. For the genome-wide association study, genes are reported for which genome-wide significant SNPs were found.

activity, suggestive linkage ($p < 0.01$) was found on chromosomes 11p15 and 15q13.3. For daily physical activity, a promising linkage ($p < 0.0023$) was found on chromosome 2p22-p16, and suggestive linkages were found for different loci on chromosomes 4q28.2, 7p11.2, 9q31.1, 13q22-q31, and 20q13.1. The second study consisted of 1030 children from 319 Hispanic American families [60]. Significant linkage was found on chromosome 18q12-q21 (logarithm of odds = 4.09) for daily physical activity. This region contains the *MC4R* gene, for which a significant association with adult physical activity had been found in a candidate gene study [58]. The third linkage study was conducted in 1432 adult Dutch sibling pairs from 622 families [61]. Suggestive linkage was found for regular exercise participation on chromosome 19p13.3 (LOD = 2.18).

The first GWA study tested 1,607,535 observed and imputed single nucleotide polymorphism (SNP) markers that passed stringent quality controls for their association with leisure-time exercise behavior in two independent samples comprising 1644 Dutch and 978 American subjects. Their most promising finding was in the *PAPSS2* gene (37 SNPs with pooled p values $< 1.0 \times 10^{-5}$) and in two intergenic regions on chromosomes 2q33.1 and 18p11.32. The *PAPSS2* gene encodes a protein that is involved in the sulfation of compounds such as lipids, carbohydrates, proteins, and exogenous drugs. The gene is widely expressed in skeletal and smooth muscles and the brain as well as in several other organs. The 10q23 region that harbors the *PAPSS2* gene has been linked to maximal exercise capacity in a genome-wide linkage study of 453 sib pairs [62]. This suggests that exercise ability may be an important determinant of leisure-time exercise behavior as has been suggested from a theoretical point of view [63].

There was no overlap in findings between this GWA study and previous candidate gene association and linkage studies, except for the suggestive evidence found for the *LEPR* gene (rs12405556: pooled p value 9.7×10^{-4}; American sample p value 9.8×10^{-5}) and in the *GABRG3* gene (rs8036270: pooled p value 4.6×10^{-5}) in the linkage region 15q12-13. The *LEPR* gene is expressed in the hypothalamus [64] and has frequently been linked to obesity and type 2 diabetes mellitus through its effect on positive energy balance and weight gain [64,65]. The genetic effects of SNPs in the *LEPR* gene found for exercise were independent of BMI [25]. This suggests that the *LEPR* gene may directly impact on the drive to exercise through the hypothalamic regulation of energy balance.

Replication of genes across the earlier summarized gene-finding studies for exercise behavior is modest. This is found to be a common problem for many of the complex traits we study in humans [66]. Clearly, more large-scale collaborative studies, combined with increased coverage of the genome using larger sets of genetic markers, refined phenotyping, and alternative methods are needed to solve part of this problem. This has already shown to be successful for other complex traits like height and BMI [67–69]. Nevertheless, the current findings for exercise already point to some (biological) pathways through which genetic variants may influence exercise behavior. These pathways may include genetic effects through exercise ability (i.e., the *CASR, PAPSS2*, and *ACE* genes), the hypothalamic drive to exercise and spend energy (i.e., *LEPR* and *MC4R*), and the rewarding or aversive experience of exercise (i.e., *DRD2* and *GABRG3*). These suggested pathways may also all to some extent explain the well-known phenotypic and genotypic links of exercise with other

lifestyle behaviors such as overeating and smoking, physical health problems like cardiovascular and metabolic disease [37,61,70], and mental health problems including depression [18,71]. Exercise training studies in twins (see, e.g., Bouchard et al. [72]) are needed to more fully understand the exact mechanisms though which genes, exercise, and different aspects of physical and mental health are related. Such studies have the great potential to inform on more "personalized" intervention programs.

CONCLUSIONS AND FUTURE RESEARCH

To summarize, it is shown that genetic influences play a role in exercise behavior at all ages. Although genetic influences are relatively stable across the life span, the heritability of exercise behavior seems largest in young adulthood. In (early) adolescence, shared environmental influences additionally explain family resemblance in exercise behavior. These influences appear to be largely generation specific and independent of the exercise behavior of the parents. The small number of GWA and linkage studies suggests that the heritability of regular exercise behavior may be explained by genes affecting exercise ability, the hypothalamic drive to spend energy, and the acute rewarding and aversive effects of exercise. An example is the independent involvement of the hypothalamus expressed *LEPR* gene in both exercise and obesity. Future progress is expected to come from the large-scale meta-analytic GWA studies that are being conducted for various exercise phenotypes.

ACKNOWLEDGMENTS

Marleen de Moor (VENI-016-115-035) is financially supported by the Netherlands Organization for Scientific Research (NWO).

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116 Influence of Physical Activity on Brain Aging and Cognition

The Role of Cognitive Reserve, Thresholds for Decline, Genetic Influence, and the Investment Hypothesis

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CONTENTS

Introduction and Organization of the Chapter 1379
Brief History of the Field 1380
Exercise and Aging: Normal versus Pathologic 1381
Neurobiological Benefits of Exercise on Brain and Cognition 1383
- Neurotransmitters 1383
- Neurotrophic Factors 1384
- Synaptogenesis 1384
- Neurogenesis 1385
- Angiogenesis 1385
- Mitochondrial Synthesis 1386
- Attenuation of Glucocorticoids 1386

How Does Physical Activity Counteract Normal and Pathological Cognitive Aging? 1387
- Cognitive Reserve: Epidemiological Evidence 1387
- Physical Activity and Brain Connectivity 1388
- Genetic Influence on Cognition and the Mediating Role of Physical Activity 1389
- Characteristic Differences in APOE ε4 Carriers 1389
- Physical Activity and Cognition in Relation to APOE Genotype 1389
- Benefits of Physical Activity in Children and Young Adults: An Investment Hypothesis 1390

Additional Considerations: Exercise Intensity and Modality versus Skillful Movement 1391
Challenges for Future Research 1391
References 1392

INTRODUCTION AND ORGANIZATION OF THE CHAPTER

The purpose of this chapter is to highlight how physical activity (i.e., gross bodily movement) and exercise (i.e., engagement in purposeful physical activity to improve physiological capacity) improve cognitive function in the areas of thinking and memory. Just as physical activity benefits cardiovascular and musculoskeletal function, it also exerts remarkable effects on the brain resulting in the enhancement of cognitive function through the lifespan and the delay of cognitive decline with aging. Positive effects have been observed in the brains of animals and humans with benefits accruing in processing speed, working memory, learning, attention, executive and inhibitory control, as well as mental flexibility. Exercise has been shown to increase oxygen delivery to the brain and to expand blood vessels and mitochondria, resulting in improved metabolic capacity. Exercise also improves uptake of neurotransmitters and increases levels of neurotrophic factors, enabling more efficient brain communication, better maintenance and repair of neurons, and improved dendritic strength and connectivity. Evidence has even been provided in animal studies for the generation of new neurons in an area of the brain susceptible to deterioration with age, the hippocampal region that mediates the formation of new memories. All of these neurobiological effects contribute to a better working brain that is more efficient and can withstand insult from injury, stress, or aging, with greater integrity, ability to focus, networking between brain regions, and improved ability to adapt to change.

The chapter is organized around a three-part conceptual framework in which the first component considered is that of central nervous system (CNS) decline as related to both normal aging and pathological conditions such as Alzheimer's disease. A reasonable assumption is that the alterations in the anatomy and physiology of the brain with age and disease translate or present as cognitive decline in the form of memory loss and executive dysfunction. The second component considered is that related to the evidence for the benefits of physical activity and exercise to the brain, which has been revealed in both animal and human studies. In essence, these neurobiological benefits serve as a non-pharmacological prescription that can counteract the neural degeneration that is incurred over time. The third component considered is the promotion of resilience to age-related and pathological degeneration by building *biological reserve of the brain*. In essence, participation in physical activity serves to "vaccinate" the brain such that it can tolerate insult, injury, or cognitive decline to a greater degree as compared to the sedentary lifestyle. *This model of exercise-induced tolerance to age and diseases of the CNS applies to the entire brain and is the central concept offered in this chapter.* The principle provides a reasonable explanation of the benefits of exercise to cognitive function in older men and women. In addition, the masking of degenerative processes may be achieved through active compensatory strategies by which alternative brain networks are activated to respond to a given cognitive challenge when typical brain responses fail to meet the challenge. Interestingly, the foundation for this benefit during older age may well be laid during childhood and young and middle adulthood, as the benefits accruing to the brain may not reveal until significant decline has occurred such as experienced with advanced age and the presence of pathology. In this manner, *a physically active lifestyle at a younger age could be conceived as an "investment"* that provides apparent benefits to cognition and emotion in older age. Furthermore, genetic influence on the brain may yield different magnitudes of benefit from physical activity such that those who are at greater risk of age-related decline or accelerated aging, like carriers of the apolipoprotein E (APOE) ε4 allele who appear less resilient to neuropathology, have an apparent benefit relative to those who practice a sedentary lifestyle, thus underscoring the notion that exercise is *essential medicine for some!*

BRIEF HISTORY OF THE FIELD

A number of individuals have made outstanding contributions to the study of physical activity and neurocognitive processes, with some providing truly pioneering investigations. Seminal research on physical activity and cognitive function appeared in the 1970s with animal and human investigations into the role of dopamine (DA) and reaction time, with comparisons of young and older subjects [1]. More specifically, Waneen Spirduso [1] reported faster reactivity (i.e., shortened reaction times) in older men and women who engaged in regular physical activity and sport activities while advancing the notion that reaction time was an index of general integrity of the CNS. As such, Spirduso believed that an active lifestyle promoted the health of the brain. She provided biological plausibility for such a benefit in humans by the employment of animal models (rats) with demonstration of maintenance of central DA levels and increased receptor binding affinity with exercise across the lifespan. The research evolved beyond the consideration of reactivity with assessment of exercise-induced effects on perceptual and basic decision-making abilities in the first reported randomized clinical trial (RCT) with older men and women [2]. This classic work, reported by Robert Dustman et al. in 1984, provides the initial causal evidence of the benefit of physical activity on neurocognitive function in light of the rigorous experimental design. Subsequently, identification of specific cognitive tasks that benefitted most from exercise participation were identified by Chodko-Zajko and Moore [3], who described the difference between crystallized (i.e., vocabulary and accumulated knowledge) and fluid intelligence (i.e., effortful analyses and reasoning), with the former revealing little benefit from physical activity while, conversely, the latter revealed significant positive influence. This was the first time that specificity of the effect of exercise was reported, and determination that tasks that were more attentionally demanding, or more novel, were the most likely to benefit from physical fitness [3]. Kramer et al. advanced this concept further with the publication of a landmark study that further supported cognitive specificity in the response to exercise such that executive function tasks were particularly improved by engagement in physical activity [4].

Early in the 1990s, the psychophysiological approach to study in this area was introduced to the field, with use of event-related potentials (ERPs) derived from electroencephalography to determine workings of the brain in both young and older men who were characterized by low and high levels of cardiovascular fitness. Specifically, Dustman et al. examined the latencies and amplitudes of ERPs to determine the speed and engagement, respectively, of cerebral cortical responses to various stimuli as well as assessment of cortico-cortical communication between brain regions. They reported that high-fit older individuals exhibited relatively efficient neural responses and integrative processing when compared to low-fit older men [5]. In fact, the high-fit older men were more similar to younger men than they were to their age-matched counterparts—in essence, it appeared that physical fitness had arrested the aging of the human brain! The neurobiological basis of such effects in the human brain were provided by the first mechanistic studies on the neurogenic and neurotrophic effects of exercise that were observed in animal studies conducted under the leadership of Gage and Cotman, respectively [6,7]. These studies offered a robust and profound mechanism for the impact on cognition of a physically active lifestyle in children and men and women of all ages if such effects also occurred in the human brain. The first neuroimaging study, using structural magnetic resonance imaging (MRI), was reported by Colcombe et al. [8] and revealed a positive

relationship in brain tissue density and the integrity of white matter tracts with cardiovascular fitness in older men and women. These structural differences in the brains of individuals characterized by high and low fitness, suggested that a physically active lifestyle positively impacted the scaffolding of the human brain. This notion is based on the finding that older adults who were characterized by cardiovascular fitness exhibited resistance to atrophy of the brain with aging [8]. Further evidence that exercise causally influenced the brain in a positive manner was provided by Colcombe et al. [9] who reported the results of a RCT of the effects of cardiovascular conditioning on cortical and subcortical activation during executive challenge. In effect, the exercise training promoted an enhanced hemodynamic response during challenge via assessment of functional MRI (fMRI) blood-oxygen level dependent (BOLD) response, suggesting improved concentration and focus as a result of training [9]. These studies were the first to employ a measure of high spatial resolution in their studies of exercise and the brain (i.e., MRI), thus increasing our understanding and confidence in the biological underpinnings of the impact of exercise on the human brain.

The consideration of individual differences through the role of genetics was brought into the picture in 2001 with a landmark study that showed particularly strong cognitive benefits of physical activity for carriers of the APOE ε4 genotype, which has been associated with a higher risk of Alzheimer's dementia (AD) [10]. More recently, a RCT with employment of MRI in middle-aged men and women was reported by Erikson et al. [11]. They specifically examined the impact of exercise on the hippocampal region, which is the brain region primarily attacked by the pathology (i.e., plaques and tangles) that is responsible for AD [11]. The work holds profound implications for the prophylactic effect of exercise as a prescription for this terrible affliction. Research has continued to evolve in the aging literature, with neuroimaging studies investigating possible reversal of cognitive aging processes through exercise intervention with mid life and older adults [9,11], and detailed looks at the connectivity, or networking, of the brain, which appears to be more efficient with physical activity [12–14]. Investigations of the effects of physical activity in children have recently appeared in the literature as well, with consensus in the findings that aerobic fitness promotes superior executive functioning, improved academic performance, and increased brain volume of specific areas [15–18]. Collectively, both prospective and retrospective epidemiological studies, as well as the experimental studies with animal and human subjects cited earlier, strongly support the lifelong effects of a physically active lifestyle with promising results for "cognitive reserve." This suggests that an investment of physical activity and other healthy lifestyle factors throughout life may promote resilience to cognitive decline in old age [19,20].

It is truly amazing to consider the remarkable advances in our understanding of the influence of physical activity and exercise on the brain and cognition in a period spanning just 35 years from the seminal work of Spirduso in the mid-seventies to the present time with sophisticated molecular biology and advanced neuroimaging studies. In essence, modern science is providing confirmatory evidence for the ancient notion of mens sana in corpore sano—that is, a "sound/healthy mind within a sound/healthy body."

EXERCISE AND AGING: NORMAL VERSUS PATHOLOGIC

The beneficial influence of exercise on brain processes and cognition is pronounced when the opportunity for benefit is significant. Such is the case in older men and women (i.e., typically over the age of 60 years) who are likely to incur age-related decline of the CNS, promoted by such processes as inflammation, oxidative stress, and apoptosis [21] thus allowing "room for improvement" from physical activity participation compared to those who are characterized by relative integrity of brain processes as would be the case with young men and women. As such, investigations with older adults have been in the forefront of exercise and cognition research because this population appears to show some of the strongest benefits for physical activity in terms of a protective effect against both normal cognitive decline with aging as well as dementia-related pathology and deterioration.

It is helpful to understand the differences between "normal" or "demented" aging in order to understand the effects of physical activity more clearly. Individuals change over a lifetime, and as one ages, change in the brain can occur either as a normal process or, alternatively, as pathological aging manifested as various forms of dementia such as AD. The effects of normal aging, currently understood as a reduced ability for synaptic plasticity as opposed to a significant loss of neurons [22], reveal in the cognitive-behavioral domain as slower processing speed, less efficient working and episodic memory, as well as difficulties with executive function—a set of behaviors typically described as organizing, goal direction, and inhibition [23]. The loss of executive function can present in several ways such as perseveration or persistence in cognitive set as opposed to adaptive set shifting. This kind of age-related behavioral change can be revealed with challenge such as presentation of the Wisconsin Card Sort Test to older individuals, which requires mental flexibility. Typically, such individuals exhibit difficulty in recognition and adoption of a new rule to guide behavior relative to younger men and women, and this is likely due to frontally mediated executive decline, where such processes are largely mediated [24]. Interestingly, knowledge and expertise tend to be maintained in normal aging [23] and it is likely due to the relative independence of such processes in relation to the frontal lobes.

The cognitive decline associated with age is typically accompanied by structural changes in the brain. There is a decrease in brain volume in normal aging that occurs by the seventh decade [24] with major decreases found primarily in caudate, cerebellum, frontal gray matter, and hippocampal regions [23,25,26]. There are also changes in the characteristics of white matter, which is composed of the axonal

projections and tracts in the brain with the greatest loss of integrity concentrated in the frontal area [23]. Since white matter is associated with loss of myelin, this change may be correlated with the "slowing" of perceptual, cognitive, and motor processes typically observed in older adults [23]. White matter hyperintensities, revealed as abnormal alterations of healthy structure in structural magnetic resonance images, increase with aging [27,28]. Loss of dendritic complexity, with reduction in synapses, is another structural change with normal aging [24], as is reduction of blood vessel density and blood flow [29], both of which contribute to the alterations in memory, focus, and mental flexibility.

One common feature of non-pathological aging is a tendency toward reduced levels of regional specialization in neural processes when negotiating a cognitive challenge as compared to the neural activity seen in younger individuals. This difference is exemplified by bilateral cerebral hemispheric activation during problem solving (i.e., heightened activation of the brain when compared to younger adults who exhibit specificity of hemispheric activation) [23]. Such bilateral activation of the prefrontal cortex has been observed consistently in older adults, and suggests an adaptive compensatory mechanism, allowing for the requisite recruitment of neural resources to accomplish a task. While this adaptation, known as hemispheric asymmetry reduction in older men and women [30], has traditionally been considered indicative of diminished cognitive ability, current research suggests that it may be a positive and dynamic adaptation to a normally aging (i.e., changing) brain. Accordingly, individuals who are able to adjust to such changes are likely to maintain performance for a longer period through the aging process. In support of this notion, compensation has been shown to be associated with higher intellectual and physical activity [12,31] and retention of performance in attention- and memory-related functions. As a general proposition, it appears that normal aging is associated with accelerated frontal decline, relative to other brain regions, and that compensatory activation patterns are engaged as a coping strategy, particularly in the frontal region, in order to maintain executive function. Failure to maintain such an adaptive strategy can then reveal as a loss, to some degree, of executive function (focus, working memory, etc.).

The characterization of demented aging is less clear than that of normal cognitive aging. In terms of development toward dementia, there are questions as to whether AD is simply an exaggerated form of natural aging or whether it is a distinct disease process. Although there is no definitive anatomic or physiological landmark available that allows for a clinical diagnosis, there are data from neuroimaging investigations that appear to show distinct patterns of brain processes progressing toward dementia. Differences in brain activation and structural atrophy have been employed to successfully identify pathological aging. In this manner, Head et al. [26] examined brain volume in young compared to older adults who were classified as cognitively healthy or who were diagnosed with dementia. They reported an overall loss in frontal volume for all older adults regardless of status when compared to younger adults. However, the hippocampal structure of those with dementia revealed significant atrophy.

In another series of investigations, Sperling [32] employed a face-name recognition task during fMRI to assess the BOLD response, in order to compare young and older adults, the latter who were cognitively healthy versus those diagnosed with AD and mild cognitive impairment (MCI). MCI is characterized by memory dysfunction for which the magnitude does not impair the ability to maintain activities of independent daily living. MCI does not always convert to AD but is considered by some as a prodromal stage. The AD patients exhibited a pattern of hypoactivation in the hippocampal region that was not present in older healthy adults. Sperling's investigation with MCI patients revealed a period of hyperactivation of the hippocampus in early MCI, which changed to hypoactivation with late MCI. This dynamic evolution of brain activation could indicate a threshold whereby compensation described in normal aging is no longer able to work as deterioration of brain structure goes beyond the ability to function normally, rendering adaptation no longer possible [32]. The failure to maintain compensation can then reveal as memory impairment (see Figure 116.1).

The critical physical change in the brain associated with pathologic aging is the significant development of neurotoxic extracellular amyloid plaques and neurofibrillary tangles. Plaques are formed from amyloid peptides that are released from the amyloid precursor protein (APP), which is cleaved by beta and gamma secretases. In the most destructive form, APP is cleaved to a longer B42 form that has a greater tendency to aggregate destructively [33]. In addition, neurofibrillary tangles are formed from intracellular hyperphosphorylated tau protein. Tau protein is important to the cell, aiding in scaffolding of microtubules, but when the pathologic process occurs, it becomes hyperphosphorylated, forming tangles that disturb cell structure and function. The amyloid cascade theory postulates that these two processes are responsible for the beginning of the disease process of dementia, and that the destruction that follows is due to the degenerative properties of the plaques and tangles [34].

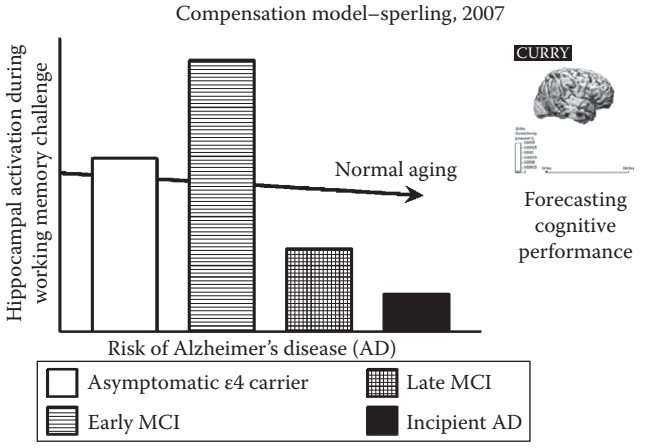


FIGURE 116.1 Compensation model. (From Sperling, R., *Ann. N. Y. Acad. Sci*., 1097, 146, 2007.)

As described in Figure 116.1, heightened activation of critical brain regions during challenge may provide for maintenance of cognitive function but may also serve as a "forecast" of cognitive decline to come. In the future, if the cost of such neuroimaging (e.g., fMRI) is reduced, routine examination of brain activation during medical exams over time may serve to predict forthcoming cognitive decline!

Although few studies have been conducted on the efficacy of exercise to influence neurocognitive processes in the elderly suffering from dementia, there is ample evidence of benefit in those who are normally aging, albeit somewhat more apparent for frontal regions and executive functions relative to other brain regions and nonexecutive tasks [35]. That is, cognition is maintained over time or even improved in several domains, but the magnitude of benefit is greatest with the frontally mediated executive tasks. A brief summary follows as to the biological plausibility of "exercise as good medicine for the mind."

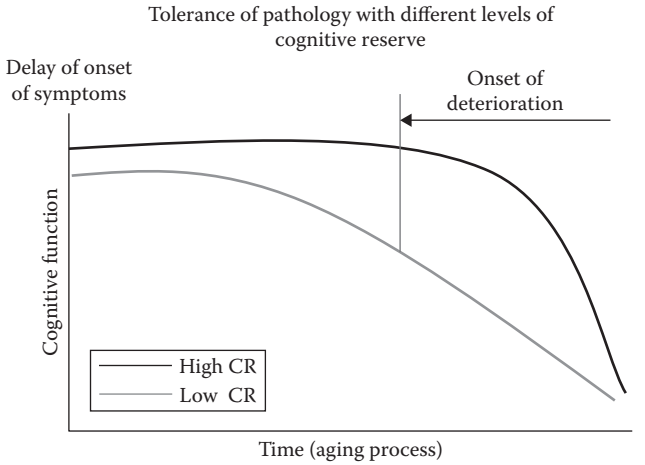


FIGURE 116.2 Tolerance of pathology with different levels of cognitive reserve. (Adapted from Hatfield and Kaplan, *NSCA's Essentials of Personal Training*, 2nd edition, 130, 2012.)

NEUROBIOLOGICAL BENEFITS OF EXERCISE ON BRAIN AND COGNITION

While there is robust evidence for the benefits of physical activity for cognition in humans, the mechanisms that determine these effects are not fully understood. However, animal studies have revealed several factors that appear to contribute positively to cognitive function. Examination of learning and memory in animals exposed to either an enriched environment (ladders, tubes, ropes, toys) or aerobic exercise regimens (running wheels or treadmill running) has consistently shown beneficial effects of exercise on cognitive function in young, adult, and aged animals.

In humans, it is challenging to determine specific effects of physical activity on brain function in light of ethical constraints, but noninvasive neuroimaging in tandem with cognitive-behavioral testing is informative of how exercise may impact the human brain. Overall, the use of animal studies to complement investigations involving human subjects suggests pathways and mechanisms for the beneficial effect of physical activity on the human brain. Neuroimaging studies, such as those described previously, have offered insight into brain mechanisms underlying cognition, such as compensatory activity, and these tools can be used to examine the effects of exercise on the brain. The benefits described later in this section are not likely to reverse any pathology (e.g., plaques and tangles in the brain), but they may help to build the reserve or resilience to both normal brain aging and pathology so that the individual may tolerate such degradation, be it largely concentrated in the frontal region as in normal aging or in the hippocampal region as in demented aging.

In this manner, we maintain that the primary role of physical activity and exercise on the human brain is to build reserve. Specifically, cognitive reserve is the hypothesized capacity of the mature adult brain to sustain the effects of disease or injury sufficient to cause clinical dementia in an individual possessing less cognitive reserve [21]. This important element of brain integrity can be classified as both active and passive reserve. The former refers to the efficiency and adaptability of neural circuits to respond to cognitive challenge exemplified by compensation, as described earlier, while the latter refers to brain tissue density, white matter integrity, and vascularity (see Figure 116.2). All of the neurobiological benefits of exercise likely contribute to a healthier cognitive reserve throughout life (note: most likely passive reserve) and are particularly beneficial in older adults to delay cognitive decline.

The following elements of the neurobiological response to exercise are likely contributors to cognitive reserve

Neurotransmitters

Physical activity elevates a number of neurotransmitters that enable communication between neurons underlying cognitive, motor, and affective processes. This is important as DA, for example, is reduced in the frontal regions of the brain with aging [36]. It exerts a significant effect on the quality of cognitive function, particularly on motor and executive processes in light of the relevant anatomical structures in these regions (i.e., basal ganglia and frontal lobes, respectively). Animal research has revealed that running can help reduce degeneration of DA both through the upregulation of brain-derived neurotrophic factor (BDNF), as observed in mice [37], as well as increased receptor binding affinity in aged rats [38]. In addition, acetylcholine (ACh), a neurotransmitter that is strongly associated with Alzheimer's disease (AD), with levels attenuated during the course of the disease [39], is affected by exercise. Importantly, long-term treadmill running in rats results in attenuation of the decline of muscarinic ACh receptor density that normally occurs with aging [40]. Based on another study using rats, Park et al. [41] reported that an enriched environment resulted in higher ACh synthesis in the cortex and hippocampus. The significance of such exercise-induced effects was revealed in a lesion study on cholinergic neural tracts in rats as the

lesions resulted in diminished neurogenesis in the dentate gyrus and increased cell death [42]. The importance of the finding rests on the fact that ACh is critical to memory and administration of ACh after its depletion results in reversal of memory deficits [43]. Serotonin (5HT) is also closely associated with BDNF and neurogenesis in the hippocampal region, which plays a key role in pathways related to memory and cognition. Of note, there is evidence that exercise results in increased 5HT levels in several areas of the brain, [44], and a study incorporating a $5HT_{1A}$ neurotoxin resulted in decreased cell proliferation in the dentate gyrus [45]. Collectively, these studies support a positive effect of exercise on neurotransmitter levels (i.e., DA, Ach, and 5HT) that mediate the critical neuronal communications that underlie executive, memory, and motor functions in the human brain thus contributing to cognitive reserve.

Neurotrophic Factors

Another way that physical activity likely benefits cognitive function in the human brain is through increased expression of neurotrophins. Neurotrophins are a family of growth factors that are responsible for the survival and maintenance of neurons and work toward growth and development of dendritic connections. The main neurotrophin that has shown a strong connection to exercise's role in cognitive function is BDNF, which supports neuronal maintenance and repair in many areas of the brain and is particularly active in the hippocampus and cerebral cortex [7]. It is associated with long-term potentiation (LTP) that is believed to underlie learning and memory [46] and facilitates synaptic plasticity. The blockage of BDNF uptake has been shown to reduce LTP and degrade learning and memory relative to animals not receiving BDNF blockade, which exhibit the typical exercise-induced improvements in cognition [44,47]. Conversely, increased brain BNDF levels are associated with dendritic complexity in the dentate gyrus, greater arborization, and increased dendritic length [48].

Studies reveal that BDNF upload is regulated both through activity such as exercise as well as an enriched environment [49,50]. Uptake of BDNF in the hippocampus has been shown to be greatly increased with physical activity in animals. In fact, BNDF mRNA has increased as high as 20% with running-wheel activity [7]. Tong et al. [51] showed, in a genetic study, that physical activity resulted in an elevation of numerous proteins related to BDNF and synaptogenesis, LTP, and synaptic plasticity, all providing additional support for findings of BDNF and downstream effects [51]. In addition, a recent clinical trial with human subjects examined memory performance on the Auditory Verbal Learning Test (AVLT) after a 6-month exercise period in older adults and revealed significant improvement in cognition as well as a positive effect for peripheral BDNF [52]. This finding reinforces the notion that the neurotrophic effects of exercise in animals likely occur in the human brain as well. There is a polymorphism of the BDNF gene ($val^{66}met$) that has been shown to have effects on cognitive function, with individuals having BDNF met revealing relatively impaired memory and hippocampal differences [53]. While there has been no published physical activity research to date in relation to cognition and this genetic relation, this may be important research in the future.

Other studies have revealed that different neurotrophic factors such as insulin-like growth factor-1 (IGF-1), a neurotrophin with structural similarities to insulin, may also be involved in the beneficial effects of exercise on cognition. Carro et al. observed that serum IGF-1 is upregulated from peripheral sources to several areas of the brain such as the cortex, hippocampus, striatum, cerebellum, thalamus, hypothalamus, and brain stem nuclei as a result of physical activity [54]. Ding et al. also reported that exercise elevated hippocampal IGF-1 and that blocking the uptake of IGF-1 reversed the exercise-induced elevation of hippocampal BDNF, eliminated the benefits of exercise on recall in the Morris Water Maze memory task, and abolished the effects of proteins downstream in the BDNF pathway related to synaptic function such as synapsin I [55]. IGF-1 is also known to promote both neurogenesis and angiogenesis in animals, with blockage of receptor uptake by IGF-1 completely eliminating exercise effects on neurogenesis [56] and blood vessel remodeling [57].

Vascular endothelial growth factor (VEGF) is a protein that also appears relevant to the benefit of exercise on cognition. VEGF is involved in angiogenesis and neurogenesis, suggesting an interaction between the two processes [58]. Experimental administration of VEGF has been shown to result in improvement in learning on a passive-avoidance task as well as memory processes during the performance of the Morris Water Maze in rats [58], while the blockade of peripheral VEGF results in elimination of exercise-related increased neurogenesis. Blockage also affects generation of new blood vessels in the brain, while not affecting the existing vasculature [59]. Overall, VEGF acts in concert with both IGF-1 and BDNF and appears to play an important modulatory role on the effects of physical activity on brain processes.

Synaptogenesis

There is evidence for synaptogenesis as a result of exposure to enriched environments, as animal studies have revealed that such exposure positively contributes to dendritic branching and synaptic density. Studies have demonstrated elevations in synapse number, with more synapses per neuron, as well as the strengthening of existing synaptic connections [60,61]. For example, synaptogenesis has been observed in mice exposed to complex obstacle courses requiring "acrobatic" activity, with specific adaptation in the motor and cerebellar cortices when compared to wheel running or sedentary controls [62]. The protein synapsin I, which acts to enhance neuronal communication through neurite outgrowth and synaptogenesis, is elevated with exercise and appears to be upregulated by the exercise-induced elevation of BDNF [63]. The relevance of this work to the exercise-cognition relationship in humans is

that engagement in exercise typically occurs in complex settings such as sport activities and outdoor settings that require navigation and memory of complex running routes. Thus, it seems reasonable that regular participation in physical activity would positively impact the vascular and neuronal architecture of the human brain, contributing to the resilience of active and fit individuals to age-related and disease-related degenerative processes.

Neurogenesis

Beyond the neurotrophic effects of exercise described earlier, neurogenesis, the growth of new neurons in the brain, as revealed in the dentate gyrus in animals, represents an exciting finding that holds great promise for medicine since the appearance of new neurons in the human hippocampus—the brain region most affected by AD dementia—would suggest resilience to the pathology (i.e., plaques and tangles) through participation in physical activity! In a classic study, van Praag et al. [6] reported that neurogenesis in adult mice occurred in response to wheel running activity. After controlling for the effects of environment, they determined that physical activity, alone, was responsible for the observed proliferation of neurons in the dentate gyrus [6]. In addition, van Praag et al. determined that the appearance of new hippocampal cells in adult mice housed with running wheels was associated with improved cognition, as shown in performance on the Morris Water Maze, and enhanced LTP, when compared to controls in standard housing [64]. Although neurogenesis is reduced in older adult animals [65], it has been shown that exercise can offer benefits for the creation of new neurons even during advanced age. van Praag et al. [66] extended the study of neurogenesis and enhanced learning in response to physical activity with aged mice who were sedentary until they were 19 months old. After a 1 month running-wheel intervention, they observed that aged mice exhibited improved water maze performance compared to age-matched controls, which coincided with a reversal of decline in neurogenic activity [66]. Comparison of the older exercisers to young adult mice revealed that the new neurons from enhanced neurogenesis in the older group were similar in quality to those of the younger mice. The investigators observed equivalent dendritic length and spine density, revealing that neurons in aged mice were functionally equivalent to those of younger animals. Such an effect in older humans would underscore the notion that it is never too late to accrue the benefits of a physically active lifestyle.

Neurogenesis cannot be determined directly in humans, although one study did confirm the process through postmortem examination [67]. However, a recent 12-month exercise intervention in older adults by Erikson et al. [11] revealed a specific increase in anterior hippocampal volume of 2% for an aerobic exercise group, while a decline in volume of 1.4% was seen over the course of the study in a comparison group that did stretching and toning activities. The change was accompanied by increases in circulating serum BDNF. Importantly, this increase in hippocampal volume was in the area where the dentate gyrus is located—the area where neurogenesis occurs. These researchers commented that normal hippocampal decline with aging averages 1%–2%/year, so this increase in volume in essence offered up to 2 years of reversal of deterioration for 1 year of exercise. While the study results cannot pinpoint that the hippocampal volume increases are indicative of neuronal cell proliferation and could alternatively be indicative of increases in dendritic branching or angiogenesis as well, the findings do show that the hippocampus is subject to positive change in aging individuals.

Angiogenesis

An additional manner by which physical activity may offer improvement in cognitive function in men and women is through improved vasculature and increased blood flow in the brain. Cerebral blood flow is normally decreased with age and in dementia [68,69], and exercise has been shown to improve both blood volume and the vasculature of the brain. Angiogenesis, the development of new blood vessels through sprouting of existing endothelial cells, results from an enriched environment and physical activity interventions in animals [62,70]. Angiogenesis takes place in several areas of the brain. Ding et al. observed increases in both angiogenesis and VEGF in the motor cortex and striatum of aged rats exercised on treadmills for 3 weeks [55]. These changes contributed to improved oxygen and nutrient delivery, as well as increased neurotrophin uptake, which provides for brain maintenance and repair [49,70].

More specific association of angiogenesis to improved cognitive function and interconnections with neurogenesis have been reported in several studies. Pereira et al. [71] investigated the relationship between angiogenesis and neurogenesis in the dentate gyrus in exercising mice and humans. A 2-week voluntary running-wheel intervention (compared to a non-exercising control group) was conducted with 7 week old mice. MRI was conducted at baseline, at cessation of the exercise period, and at 4 and 6 weeks after exercise to determine cerebral blood volume (CBV) in regions of the hippocampus. Thymidine analog BrdU marker was administered during the second week of exercise to examine for evidence of neurogenesis. The results revealed a selective increase in CBV in the dentate gyrus for the exercising group, and these findings also correlated with increased neurogenesis [71]. Pereira et al. also conducted a 3-month aerobic exercise intervention with men and women (mean age 33 years, range of 21–45 years), measuring CBV before and after training with MRI, changes in fitness via assessment of VO_2max, and memory function with the AVLT. As with the mice, there was increased CBV in the dentate gyrus post exercise, which correlated with increased VO_2max and improved learning in a short-term memory portion of the AVLT [71]. Additional animal studies support Pereira et al.'s findings. van De Borght et al. observed increases in blood vessel density after

3–10 days of wheel running in mice, which was correlated with cell proliferation in the dentate gyrus [72]. These findings were reversed upon cessation of the exercise regimen. Palmer et al. also observed that neurogenesis in mice was associated with clusters of capillaries and speculated that the angiogenic effects of exercise provide the critical adaptation that promotes neurogenesis [73].

The role of angiogenesis to improved cognitive function in older adults was revealed in a longitudinal study by Rogers et al. [74]. They examined the role of cerebral blood perfusion in cognitively healthy older adults. Lifestyle and work status were assessed, cerebrovascular function was obtained using positron emission tomography, and cognitive function was determined through a Cognitive Capacity Screening Examination annually over a period of 4 years. Rogers et al. observed that individuals who retired and lived sedentary lives exhibited reduced cerebral oxygen perfusion over time. This correlated with poorer cognitive function while older adults who continued to work or who retired, but maintained a physically active lifestyle, showed maintenance of cerebrovascular function and cognition [74]!

Mitochondrial Synthesis

Exercise training in mice also results in mitochondrial synthesis in many brain regions [75]. An enriched environment has been shown to improve mitochondrial function in the cerebral cortex and hippocampus in rats [76]. In addition, synaptogenesis may be dependent on mitochondrial adaptations in the hippocampus; a voluntary exercise intervention in mice that increased mitochondrial number was associated with increased synaptic density [77], and an in vitro experiment by Li et al. also revealed that mitochondria in the dendrites of hippocampal cells were associated with synaptic strengthening [78]. While there have not been direct findings in relation to mitochondria, exercise, and cognition, these findings illustrate additional links and interdependencies in the neurobiological effects that may contribute to improved cognitive function.

Attenuation of Glucocorticoids

Beyond the direct effects of exercise on the brain, exercise can mitigate the impact of chronic mental stress throughout life. Such stress contributes to cognitive dysfunction, possibly through degradative action on neurotrophins, such as BDNF, and through structural and functional deterioration in the hippocampus. Mental stress activates the hypothalamic-pituitary-adrenal axis, which results in elevation of corticosteroid hormones from the adrenal cortex. Elevated levels of adrenal steroid hormones in animals are known to decrease levels of BDNF [79], reduce neurogenesis [80], alter dendritic branching in the amygdala, hippocampus, and frontal cortex [81], and impair learning and memory tasks [82]. In fact, experiments with marmoset monkeys revealed decreased cell proliferation in the dentate gyrus after a single exposure to stress [83]. A study of 4-month-old rats found that social stress contributed to reduced reference and working memory [82]. Cameron and McKay observed that while a decline in neurogenesis in aged rats was associated with high corticosteroid levels, eliminating these steroid hormones through adrenalectomy returned dentate gyrus cell proliferation to that of younger animals [80].

Studies of older men and women have revealed a positive relationship between cortisol and hippocampal atrophy, memory deficits, and general cognitive decline. Lupien et al. reported that older adults with extended elevations of cortisol exhibited 14% lower hippocampal volumes than controls with normal cortisol levels, and that the reduced volumes correlated with diminished performance on hippocampal-dependent tasks of delayed memory recall and spatial memory (time to finding way through simple and complex maze) [84]. These relationships have been found to be of particular significance for individuals who are carriers of the APOE ε4 gene, which is a known risk factor for AD. In this manner, Lee et al. [85] tested midlife and older adults (ages 50–70 years) with or without the APOE ε4 genotype on several cognitive procedures and measured salivary cortisol levels. Poorer performance in all participants was correlated with elevated cortisol levels, and homozygous ε4 carriers who also exhibited high cortisol levels performed significantly worse than noncarriers in processing speed, executive function, and verbal memory [85]. As such, the impact of stress on some individuals is profound and it follows that exercise may be essential medicine for them.

Accordingly, exercise reverses some of the effects of elevated corticosterone in animals. Adlard and Cotman [86] studied four groups of adult mice—stressed or nonstressed, sedentary or exercising groups. After 3 weeks, during which half of the animals were given running wheels, restraint stress was applied to half of the sedentary and half of the exercising animals that were then sacrificed for testing. Sedentary stressed mice showed elevated corticosterone and decreased hippocampal BDNF compared to control groups. Exercised animals, on the other hand, exhibited increased corticosterone, but also showed increased hippocampal BDNF levels compared with controls, suggesting that exercise had countered the effect of stress exhibited in sedentary stressed mice. When animals were subjected to adrenalectomy in a second experiment, neither exercised or sedentary stressed mice showed a decrease in BDNF [79]. In related work, Nakajima et al. [87] examined cognitive function in mice subjected to restraint stress (12 h/day) for 8 weeks. An exercising group was allowed free running-wheel access during the hours not restrained. After 5 weeks of stress, the Morris water maze was administered, and the exercising group showed superior performance compared to control sedentary stressed group. This was accompanied by increased cell proliferation in dentate gyrus and increases in IGF-1 in the cerebral cortex [87]. Again, such findings, if also relevant to humans, suggest an additional mechanism by which exercise would build the reserve of the brain and the tolerance to stress, aging, and pathology.

HOW DOES PHYSICAL ACTIVITY COUNTERACT NORMAL AND PATHOLOGICAL COGNITIVE AGING?

It appears that building a biological reserve is one distinguishing effect of physical activity that appears to be a structural benefit, with evidence for a reduction in normal age-related atrophy and even reversal of structural decline. For example, MRI evaluation of older adults classified by cardiovascular fitness level found that higher fitness resulted in increased brain volume of white and gray matter [88]. Further investigations of physical activity interventions have confirmed that some structural deterioration may be reversed with exercise, with findings of significant increases in brain volume in both gray and white matter after a 6-month aerobic exercise intervention in older adults [89]. Another study revealed specific improvements in hippocampal volume after a 12-month intervention with an aerobic exercise intervention but not with a stretching and toning group [11].

The executive functions of inhibitory control, mental flexibility, and memory encoding have all shown benefit from physical activity. Aerobic exercise interventions with older adults have resulted in improvements in the frontally mediated executive functions of task switching and response inhibition [4,89]. Neuroimaging of older adult participants in a 6-month aerobic exercise intervention revealed greater post-intervention activation in prefrontal and parietal regions, with an accompanying decrease in activation of the anterior cingulate cortex (ACC), an area associated with conflict monitoring [9]. Collectively, the results of the study suggest improved function of the cortical attentional networks, thereby reducing the demand on the ACC. The finding is also significant in that the impact of exercise on the brain was regionally specific and not a generalized directional change—this illustrates the importance of examination of functional neural networks and not limited regions. Otherwise the results of various studies that examine different brain regions may appear contradictory in the effect of exercise!

Of essential importance to the basic theme of this chapter, it appears that physical activity may also delay the symptoms associated with dementia and the normal aging process. Importantly, the increase in hippocampal volume reported in the Erikson et al. study described earlier may offset the known hippocampal decline associated with progression to dementia [11]. More specifically, cardiovascular fitness in early-stage Alzheimer's patients was negatively related to brain atrophy and positively related to white matter [27]. In addition, biomarkers for amyloid plaque and tau protein tangles obtained through cerebrospinal fluid samples and amyloid imaging revealed that older adults engaging in higher levels of physical activity exhibited less accumulation of neurotoxic pathology [90].

In a recent study, Baker et al. [91] also observed a significant improvement in executive functioning as a result of a vigorous exercise intervention with individuals diagnosed with mild cognitive impairment (MCI), which is believed to be a prodromal stage for AD. Importantly, the observed improvement in cognitive function was more pronounced in women than in men. This gender-selective association was also related to improvement in insulin sensitivity and reduced cortisol levels in women [91]. The observed benefit to cognitive function in MCI patients suggests a reversal of neuropathological processes. However, the notion of a synchronous benefit (owing to neurobiological benefit of exercise that outweighs the presence of pathology) is equally tenable and even a more likely explanation as there is little evidence in humans of a reversal of brain pathology as a result of exercise participation. The notion of synchronous benefit is consistent with that of the building of cognitive reserve through regular participation in physical activity.

Cognitive Reserve: Epidemiological Evidence

The studies discussed earlier highlight some effects of physical activity interventions and provide a "window" on the state of brain and cognitive health through cross-sectional observation and intervention studies with humans as well as those with animals. Beyond such investigations, large-scale epidemiological studies offer a broader look at the exercise-cognition/brain health relationship across the lifespan and pose answers to the question of how choices made throughout life, including participation in physical activity, affect cognitive aging.

The theory of cognitive reserve suggests that an individual may be able to partially offset the effects of brain aging by nature of the resources he or she possesses or develops throughout life. It is believed that factors such as intellectual capacity, education, socioeconomic class, and intellectual, social, or physical lifestyle choices may affect how one is able to resist brain injury or insult. This theory is relevant, in particular, to the development of dementia, allowing one with superior reserve to operate cognitively at a more efficient level for many years of aging, or to function through use of alternative brain regions during early stages of pathology, possibly delaying decline into clinical dementia [31].

Cognitive reserve is classified as either passive or active. Passive reserve describes a model in which an individual is able to withstand disease by nature of superior brain "hardware"—such as greater brain volume, increased neural density, improved blood vessel organization, increased neurotransmitter uptake, or neurotrophin expression. These physical characteristics allow for the brain to sustain degenerative insult to a greater extent without revealing clinical symptoms, allowing for a greater threshold to be passed before exhibiting cognitive decline or dementia. An individual with passive reserve is also able to engage cognitive function with more efficiency. Alternatively, active cognitive reserve involves brain "software" and utilizes the concept of compensation, with which one who has compromised brain networks and processes may employ greater brain resources (neuronal recruitment) to solve a problem, using alternative brain networks for function when original regions or networks have been compromised through damage from aging

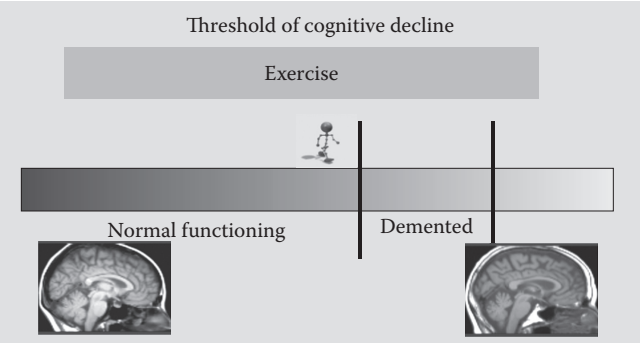


FIGURE 116.3 Threshold of cognitive decline, threshold moved to right-most vertical line.

or injury. Active reserve implies that deterioration in the brain can be tolerated, and that the symptoms of cognitive decline are not exhibiting clinically since the individual is able to compensate for the loss [31]. In this manner, the threshold for cognitive decline is elevated and the symptoms delayed (see Figure 116.3, threshold moved to right-most vertical line).

Cognitive reserve is examined most commonly through epidemiological investigations conducted prospectively or retrospectively to determine characteristics that may affect cognitive aging. Studies of early life factors have revealed that IQ or intellectual ability may correlate with later life cognitive ability. Researchers examining neuropathology postmortem in a study of Catholic nuns were able to correlate their dementia-related findings to the quality of writing exhibited by the young women upon entering the convent (i.e., at an early stage of life—approximately 20 years of age). Linguistic ability at a young age was positively associated with total brain volume and negatively related to clinical evidence of AD. Those with low idea density in early life showed significantly greater impairment in old age and pathology at postmortem [92]. Another study that examined IQ, educational level, and intellectual, social, and physical activities during early life found a strong positive correlation for IQ and education level to cognitive functioning in later life, but no long-lasting effects of social or physical activities [93]. Different researchers, however, have found a positive correlation for early life physical activity and processing speed in later life for men but not women [94]. These varied findings may indicate different mechanisms by which various reserve factors act, with some factors working from childhood and others being more responsive to adult manipulation. Limitations of retrospective studies may also affect outcomes for physical activity, since it is extremely difficult to obtain detailed and accurate information about lifestyle choices that occurred several decades in the past.

Examination of midlife activities has revealed more about the relation of physical activity to cognitive functioning in older adults. Scarmeas and Stern [19], in a review article examining midlife activities and education and their relation to later cognitive decline, revealed that there was a synergistic effect of high education and high levels of intellectual, social, and physical activities in helping older adults maintain cognitive function and resist cognitive decline or dementia. Physical activity performed in midlife has shown to be protective against dementia decades later [19]. Rovio et al. [20] examined 1449 survivors from a cohort study conducted with individuals at midlife (average interval to follow-up was 21 years). They discovered that those who engaged in leisure-time physical activity at least twice a week for 20–30 minutes that "made them breathless or caused them to sweat" exhibited 50% lower odds of developing dementia of any type, and were 60% less likely to experience AD, even after controlling for age, education, APOE genotype, vascular and other physical conditions, smoking, and alcohol [20]. Two other studies with follow-up times of 5 or 6 years showed similar findings [95,96]. While these findings do not indicate any "prevention" of AD and other forms of dementia, they do lead one to believe that physical activity can provide the means to delay onset of dementia by providing a reserve that enables a greater threshold to be passed before pathology is exhibited. The underlying basis of such an effect (i.e., building reserve) is likely due to the neurobiological mechanisms described in animals mentioned earlier.

Physical Activity and Brain Connectivity

Neuroimaging studies with humans provide more insight to the basis of cognitive reserve. Recent interventions examining connectivity between brain regions have allowed for investigation of how physical activity is related to both passive and active reserve, revealing that exercise can facilitate brain networks by working efficiently with elevated coherence between regions. This adaptation would likely promote resilience to aging or dementia, enabling one with good connectivity to achieve greater neuronal activation or strategically employ alternative networks as required by the age-related or pathology-related changes in the brain. Voss et al. [13] observed that 1 year of aerobic training resulted in greater functional connectivity in the brain's default mode network (DMN) and frontal executive networks. One year of stretching and toning (that involved learning of new routines) also resulted in greater connectivity, with increased DMN connectivity after 6 months and improved frontal-parietal network connectivity after 12 months. These neural changes were reflected in improved executive function in the participants and provide strong evidence of exercise-related brain plasticity in men and women [13]. Another study of networking by Burdette et al. [14] reported a comparison of brisk walking to a health education treatment and a "light stretching" control group (4 months duration for the interventions). The researchers observed that the ACC was better connected to the hippocampus in the walking group when compared to the sedentary control group and accompanied by improved cerebral blood flow [14]. These improvements show the power of physical activity to keep the brain operating efficiently and ready to meet cognitive challenges that could not be met if disconnectivity was occurring.

Genetic Influence on Cognition and the Mediating Role of Physical Activity

Although the study of genetic factors and cognition is in its infancy, there is evidence that genetics plays a role in the typical cognitive decline of older adults, both in terms of normal aging and in the development of AD. Autosomal dominant genes play a role in the small proportion of early-onset Alzheimer's (before age 65 years) accounting for about 5% of the disease [97,98]. The APOE gene is notable in its relation to development of late-onset AD, but it appears as a risk factor rather than showing direct causality. APOE is characterized by three variants or alleles—ε2, ε3, and ε4—with the ε4 allele present in about 15% of the population, but associated with about 40% of late-onset AD [33]. The risk for possession of one ε4 allele increases the risk of developing late-onset AD by three times, with two copies of the allele increasing risk to eight times compared to the general population [99]. However, about 50% of ε4 carriers at age 90 years will not have AD [100], so it is indeed a complex issue and raises the question about protective factors that enable cognitive reserve to occur in these genetically at-risk individuals, increasing the threshold to defend against dementia-related pathology.

The ε4 allele has a different orientation, with amino acid substitutions that contribute to a more unstable protein with higher likelihood of fragmentation of the protein [101]. As a result of these differences from ε2 or ε3, the ε4 genotype is associated with greater amyloid buildup, reduced amyloid clearance, increased neurofibrillary tangles, decreased glucose metabolism in some areas of the brain, reduced brain volume, lysosome leakage, translocation and damage to cytoskeleton, mitochondrial impairment, differences in brain activation, and cognitive impairment, particularly in regard to memory and executive function tasks in healthy adults [102]. In this manner, the ε4 carrier would garner greater neurobiological benefit from exercise owing to the lessened ability to maintain and repair aging and insult to the human brain!

Characteristic Differences in APOE ε4 Carriers

The characteristics of brain activity in ε4 carriers throughout life show some distinct differences from non-carriers. Hypometabolism at rest has been shown repeatedly to be a distinct aspect of ε4 carriers' brain function, even in healthy young adulthood, with reduced metabolism and lower oxygen delivery to the frontal, parietal, medial temporal lobes, and posterior cingulate cortex [103]. Differences in brain structure in APOE ε4 carriers compared to non-carriers also exist. For example, older adult ε4 carriers frequently show more brain atrophy compared to non-carriers even in cognitively healthy individuals [104], and this difference is pronounced in the hippocampal area [105]. With regard to brain activity, cognitively healthy APOE ε4 carriers show altered brain activation under memory challenge tasks [32,106]. Sperling reported that ε4 carriers displayed increased hippocampal activation that converted to hypoactivation as memory became more impaired, possibly forecasting a path toward dementia [32]. (Note: refer to Figure 1). Numerous studies have shown that older adults carrying the APOE ε4 allele exhibit lower cognitive function in areas of executive function, working memory, episodic memory, and perceptual processing and reveal cognitive deficits even in the absence of pathology [107–109]. Some recent findings in younger adults have shed some new light on possible effects of the ε4 allele. One study that examined postmortem gene transcripts from brain cortical samples of young adults who were either ε3 or ε4 revealed differences in mitochondrial function with ε4 carriers that was occurring before evidence of plaque or tangle formation [110]. Another study revealed mitochondrial damage postmortem in the posterior cingulate cortex in young adults, again found without plaque [111]. Both of these studies offer support for a theory of mitochondrial dysfunction mediating, at least in part, the role the APOE-ε4 allele in cognitive aging and development of AD. The mitochondrial synthetic effect of exercise reported earlier may mitigate this process.

Physical Activity and Cognition in Relation to APOE Genotype

With all of the findings showing differences in brain structure and function between APOE genotypes, as well as poorer cognitive performance in older adult ε4 carriers and a higher rate of development of AD, one may wonder about the benefit of physical activity for ε4 carriers in comparison to the general population. Few such studies are currently available, but findings from them suggest there may be particular benefit of physical activity for APOE ε4 carriers.

In light of the known risk of APOE genotype for AD, Schuit et al. [10] conducted a prospective study of the effects of physical activity participation on cognitive decline over a 3 year period in 347 older men aged 65–84 years. Participants were characterized for presence of APOE ε4, exercise behavior at baseline (less than or more than 1 h/day of walking, bicycling, gardening, odd jobs, and sport), and cognitive performance on the mini-Mental Status Exam (MMSE), both at study inception and follow-up. Incidence of cognitive decline, indicated by a drop of 3 or more points on the MMSE over the 3 year period, was related to activity level and genotype. Specifically, the risk of cognitive decline was 13.7 times higher in sedentary ε4 carriers relative to physically active non-carriers. Higher physical activity involvement was associated with remarkable attenuation of cognitive decline in the ε4 carriers [10].

Deeny et al. [112] investigated the effect of exercise on working memory in adults 50–70 years of age with regard to APOE genotype. Using both behavioral and magnetoencephalographic brain imaging evidence, these researchers examined cortical dynamics and cognitive performance on a behavioral Sternberg memory task, comparing carriers and non-carriers of the APOE ε4 allele. Highly active ε4 carriers showed faster reaction time in the memory task compared to

sedentary carriers. Seven sedentary ε4 carriers also showed a lower level of activation in the right medial temporal lobe compared to highly active ε4 carriers who were undifferentiated from non-carriers in activation [112]. This lower activation may be forecasting that a change to hypoactivation may be occurring even at midlife for sedentary ε4 carriers, while physical activity is providing cognitive protection. In addition, Etnier et al. [113] examined working and episodic memory in relation to aerobic capacity (VO_2max) in older women who were classified according to APOE e4 carrier or non-carrier groups. They reported that the cognitive-behavioral effects of ε4 showed evidence of a dose response, for sedentary ε4 carriers, with ε4 homozygotes of lower aerobic fitness exhibiting poorer response to a delayed memory task compared to ε4 heterozygotes or non-carriers [113].

Furthermore, Kayes et al. [114] examined the relation of both physical activity and cardiovascular fitness to cognitive function across a continuum of cognitive challenges consisting of inhibitory control, working memory, and mental flexibility (set shifting) in older adults considered with regard to APOE genotype. They reported that an inhibitory task (Erikson Flanker) revealed a benefit for cardiovascular fitness without regard to genotype, such that fitness was inversely related to interference (i.e., higher fitness was associated with reduced interference/distraction). However, when the cognitive challenge was more complex, as in the case of working memory or a combination of working memory and set shifting, the cognitive benefit from physical activity was observed only for ε4 carriers [114]. In essence, a pattern in the findings revealed that sedentary e4 carriers showed inferior performance to non-carriers, while participation in physical activity resulted in progressive improvement such that sufficiently active ε4 carriers exhibited similar cognitive performance to non-carriers.

In terms of the neurobiological mechanisms provided through physical activity, it appears reasonable why exercise would be particularly beneficial to carriers of the APOE ε4 allele. As previously described, physical activity increases angiogenesis in the brain and improves mitochondrial function, which could provide a direct benefit for the hypometabolism or mitochondrial dysfunction exhibited by ε4 carriers. The fact that physical activity increases uptake of BDNF may indicate possible repair to damage caused by the unstable conformation of ε4, and neurogenesis as reported in animal studies (and implied in at least one human study that showed improved hippocampal volume after an exercise intervention) could delay the destruction toward AD caused by this genotype if hippocampal regions show reversal of damage with aging due to the effects of physical activity. It should be noted that APOE-ε4 carriers are subject both to normal cognitive decline and pathological dementia-related decline, so there is a double insult to these individuals. Studies have revealed that even cognitively healthy ε4 carriers experience lower cognitive function in areas of working and episodic memory, processing speed, and executive function, and they may benefit from exercise in ways to improve frontal as well as hippocampal function [107–109]. Overall, exercise may offer benefits to APOE-ε4 carriers to extend cognitive reserve, preserving brain structure and function, offering ability to repair damage, and improving resilience to effects of aging and dementia pathology.

Benefits of Physical Activity in Children and Young Adults: An Investment Hypothesis

The notion that lifestyle choices in youth or young adulthood could affect cognitive aging decades later is intriguing, and studies in children have shown that physical activity may improve cognitive function. Some studies are revealing distinct effects of increased brain volume and improved executive function or working memory in children as young as 9 years of age. Greater relational memory in high-fit 9- and 10-year-olds compared to lower-fit children has been reported in one study, with the difference mediated by increases in hippocampal volume [17]. Another study revealed superior performance on an inhibitory control measure (Eriksen Flanker) in high-fit children compared to lower-fit children, with greater activation of the dorsal striatum that was positively related to inhibitory control [16]. Davis et al. [115] conducted a 3-month exercise intervention with 7- to 11-year-old children with two exercise groups (one 20-min three times per week; one 40-min) and observed improvement in executive function based on the Cognitive Assessment System and significant improvements in mathematics scores on the Woodcock-Johnson Test of Achievement. Both of these improvements showed a dose-response effect with the 40-min exercise group achieving significantly better than the 20-min exercise group. In addition, the exercise groups (combined) showed increased bilateral activation in the prefrontal cortex and decreased activation in bilateral posterior parietal cortex when compared to non-exercising controls [115]. Hillman further reported improved P300 amplitude and reduced latency in children who are "high fit," indicating that they exhibit enhanced attention resource allocation when challenged [15].

There is less research with young adults, but there are interesting results that add credence to the investment reserve theory. Woo et al. employed an oddball and go/no-go executive task in college-aged men with consideration of cardiovascular fitness and APOE genotype, and reported that fitness proved to be especially beneficial for APOE-ε4 carriers [116]. Further, a retrospective study of military records of young Swedish males born between 1950–1976, including comparisons in monozygotic twin pairs, found that cardiovascular fitness in adolescent years predicted intelligence in several areas (global, verbal, visuospatial, logical, and technical) [117]. A cohort study of adults revealed that physical activity at age 36 years was associated with verbal memory performance at age 43 years and was protective against memory decline from ages 43–53 years. This study reflects that effects of cognitive aging begin at surprisingly young ages for sedentary individuals and underscores the importance of physical activity in preserving memory [118]. The work

of Woo et al. suggests that the preservative effects of fitness on cognition in later life may be particularly important for APOE e4 carriers [116]. Even the prenatal environment may contribute to lifelong cognitive development. A study of guinea pigs in which nutrient and blood supply was reduced in utero showed a strong effect on hippocampal development, with lower volume and suboptimal dendritic outgrowth [119]. On a positive note, other studies have shown that when the mother is physically active during pregnancy, there is improved brain development [120]. While there is synaptic remodeling throughout life and evidence that enriched environment may offset prenatal insufficiencies, these findings do lead to questions about lifelong influences of cognitive reserve. This is an area in which additional research would be welcome!

ADDITIONAL CONSIDERATIONS: EXERCISE INTENSITY AND MODALITY VERSUS SKILLFUL MOVEMENT

One common question concerning the role of exercise in cognition is that of exercise prescription. Unfortunately, there is no definitive answer as to what type, intensity, frequency, or duration of physical activity extends the greatest benefit to cognitive function, but there are hints that can be gleaned from animal and human investigations that may provide a basis for future research in this area. Most of the research has involved aerobic exercise, and studies have consistently revealed associations between vigorous physical activity and improved executive function. However, animal research has shown that there are also important effects from enriched environment—i.e., social housing, tubes, toys, ladders, nesting material, and running wheel—that involves more learning or spatial activity when compared to running-wheel activity, alone. For example, Olsen et al. reported that elements of enriched environments offered more specific effects in memory improvement or in increasing synaptic strength [121]. In terms of neurogenesis, it appears that high-intensity running in animals is important for proliferation of progenitor cells in the dentate gyrus, but that an enriched environment is more related to survival of new cells [49,122]. A study that investigated running and enriched environment in tandem revealed that 10 days of wheel running followed by 35 days of enriched environment resulted in a 30% increase in neurogenesis compared to either alone. These authors suggested that aerobic exercise provides a "priming" mechanism for learning, with more complex physical activity from an enriched environment leading to more long-lasting benefits [123]. A study conducted with older rats revealed that an enriched environment preserved memory and synaptic plasticity in aging compared to sedentary controls [124]. Interestingly, a study that controlled for the social effects of enriched environment did not reveal the benefits for the socially enriched group that were shown when complex motor activities were present [49].

Translating to human research, several epidemiological studies have revealed that a variety of activities provides the most impressive cognitive benefit in older adults. Chan et al. reported on a cross-sectional study that mind-body exercises involving more cognitive processing (i.e., tai chi) and cardiovascular exercise performed together resulted in significantly improved memory scores for participants [125]. Another study revealed that overall physical activity, including leisure, household, and occupational activities, as measured by actigraphy predicted improved global cognition in older adults, whereas a self-report of physical activity that was more limited to exercise type activities did not [126]. Interestingly, these improvements were associated with increases in peripheral IGF-1. Even intervention studies that revealed impressive effects of aerobic exercise on improved hippocampal volume or improved networking also revealed positive effects on cognition from moderate physical activity relative to control groups whose intervention involved learning routines. Overall, it appears that both high-intensity aerobic activity and more moderate activity that involves cognitive challenge may be important for different aspects of cognition.

The issue of aerobic fitness versus motor fitness areas of strength, balance, or flexibility in humans is also of interest, and several studies of strength training have shown that these programs alone can provide cognitive effects. A moderate 6-month resistance and balance intervention predicted individual improvement in memory in older adults when compared to a wait-list control [127]. A 24-week intervention revealed that both moderate and high-intensity resistance training improved cognitive performance in older adults in attention and memory compared to a stretching control [128]. A recent fMRI study by Voelcker-Rehage et al. [129] examined motor fitness (strength, balance, flexibility, and fine motor control) as well as aerobic fitness and found distinct areas where each type of fitness was optimal for cognitive improvement. These researchers reported that inhibitory executive function accrued a selective benefit for aerobic fitness. Visuospatial tasks that required more attentional control were found to be more related to motor fitness [129]. These findings underscore that at this point in time, understanding of effects of different modalities and duration of exercise is in its infancy—the puzzle has only begun to be solved. Future kinesiology/cognitive neuroscience research with both animal and human research may be productive as it tries to elucidate the subtleties of movement and or aerobic fitness to find more specialized answers.

CHALLENGES FOR FUTURE RESEARCH

It appears that a reasonable role for physical activity participation and exercise is the building of cognitive reserve, both through active and passive mechanisms. In this manner the neurobiological benefits of exercise observed in animals, if also present in the human brain, would result in tolerance to age-related decline and pathology such as AD. The work on neurotrophic influence in animals and the observed benefit of exercise on hippocampal volume in humans suggest a powerful remediation effect that could reasonably delay the aging

and the symptoms associated with the pathology of dementia. In this manner the threshold for cognitive decline would be increased with a physically active lifestyle. In addition, it may be that physical activity early in life and during midlife exerts a profound benefit to cognitive function in later life. This type of an investment would underscore the importance of a physically active lifestyle throughout the entire developmental sequence. Finally, it appears that there are individual differences in genotype that may underscore a higher need for exercise in some individuals relative to others such as e4 carriers and non-carriers. In this manner, exercise may be essential medicine for some! The insight that has been accrued over the past 35 years in this area is remarkable and lends strong scientific support for the ancient notion of a sound mind with a sound body (mens sana in acorpore sano).

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117 Physical Activity and Anxiety

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CONTENTS

Anxiety: Definitions and Diagnoses 1397
Treatment: How Can Anxiety Disorders Be Treated? 1398
Psychotherapeutical Treatment of Anxiety Disorders 1398
Pharmacological Treatment of Anxiety Disorders 1399
Is a Combination of Pharmacotherapy and Psychotherapy Even Better? 1399
Complementary Treatment Methods 1399
What Links Anxiety (Disorders) and Physical Activity? 1400
Physical Activity, Exercise, and the Prevalence and Incidence of Anxiety Disorders 1400
Evidence of Therapeutical Impact of Physical Activity on Anxiety 1401
Anxiolytic Effect in the Healthy 1401
One-Time Physical Activity and Anxiety 1401
Endurance Training and Anxiety 1401
Mechanisms of the Activity of Exercise 1402
Psychological Mechanisms 1402
Biological Mechanisms 1402
Conclusion and Recommendations 1404
References 1405

ANXIETY: DEFINITIONS AND DIAGNOSES

Anxiety generally is a normal and even essential human emotion as it secures survival. In preparing the organism for a fight or flight reaction, it signals (assumed) danger and may so protect the organism. It activates physiological changes (e.g., sweating, faster heartbeat), and, consequently, also has cognitive (e.g., dashing thoughts) and behavioral correlates (e.g., leaving the situation). Panic is differentiated from anxiety in the even faster changes and a very quick onset. So a panic reaction is a fast defensive reaction, which allows the organism to leave a possibly dangerous situation as fast as possible.

Anxiety will be considered as pathological if it emerges in situations not objectively dangerous, if it is excessively strong, and if anticipatory anxiety constrains life of the affected [1,2]. In this regard, anxiety disorders can be differentiated from "normal" and subclinical anxiety.

According to the International Classification of Diseases (ICD) of the World Health Organization (WHO), anxiety disorders are grouped within the neurotic, stress-related, and somatoform disorders (F4).

We will focus here on diagnoses relevant for the following chapter, i.e., anxiety disorders that have been studied in association with physical activity. For any other and for detailed diagnostic criteria, we recommit to ICD-10 [2].

Generally, the specific diagnoses can be classified by the nature of anxiety. In phobic anxiety disorders, anxiety is evoked only, or predominantly, by well-defined situations, which are not currently dangerous. As a result, these situations are avoided whenever possible or endured with dread. Furthermore, contemplating entering the phobic situation generates anticipatory anxiety.

Agoraphobia

- Anxiety in at least two of the following situations: public places, crowds, traveling far away from home, or traveling alone. Agoraphobia is further specified by existence of a history of panic disorder (PD).

Social anxiety disorders

- Are centered around the fear of scrutiny by other people.

Specific (isolated) phobias

- Anxiety is restricted to highly specific situations such as proximity to particular animals, heights, and thunder, and the phobic stimulus is avoided whenever possible.

In contrast, in the so labeled "other anxiety disorders," manifestation of anxiety is the major symptom and is not restricted to any particular situation or object.

Panic disorder

- Core feature are recurrent attacks of severe anxiety (panic). These are discrete periods of intensive fear accompanied by somatic or cognitive symptoms like sweating, trembling, breathlessness, dizziness, fear to lose control, or even mortal fear. Panic attacks are unpredictable as they are not restricted to any particular situation or circumstances. Although anticipatory anxiety (fear of further panic attacks) is common, people experience intervals without anxiety in between the attacks.

Generalized anxiety disorder

- Essential feature is anxiety, which is free-floating, i.e., which is generalized and persistent but, again, not restricted to any particular situations or circumstances.
- Furthermore, patients present worries (e.g., themselves or a relative will become ill), muscular tensions, vegetative hyper-irritability, and other physical symptoms.

Obsessive-compulsive disorder

Essential features are recurrent obsessional thoughts or compulsive acts, which are distressing, and the patient often tries to resist them. The acts are done to prevent objectively unlikely events, which the patient fears might otherwise occur. Anxiety is almost invariably present and gets worse if compulsive acts are resisted.

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) differs from the others as to the existence of causative influences. It occurs as a response to a stressful event or situation of an exceptionally threatening or catastrophic nature, which is likely to cause distress in almost anyone. Typical features include episodes of reliving the trauma and feelings of emotional "numbness", detachment from other people, unresponsiveness to surroundings, anhedonia, and avoidance of activities or situations remembering the trauma. Usually, autonomic arousal with hypervigilance, an enhanced startle reaction, and insomnia are also present.

Anxiety disorders: incidence and impact

Within all mental disorders, anxiety disorders are among the most common and their prevalence and course are reasonably well documented. The overall prevalence of anxiety disorders is shown to be quite high. Kessler et al. [3,4] report a lifetime (12 month) prevalence of 28.8% (18.1%) for any anxiety disorder in the United States. There are considerable variations from the most (specific phobias, 12.5% [8.7%]) to the least prevalent (agoraphobia without a history of PD, 1.4% [0.8%]) disorders [3–5]. Statistics from six European countries reveal lower lifetime (and 12-month) prevalences (any anxiety disorder: 13.6% [6.4%], [6]) in these countries. The relative frequency is similar across countries [7].

Age of onset typically is in childhood or adolescence, course is often chronic-recurrent, and anxiety disorders are highly comorbid with each other and with other mental disorders [5]. Furthermore, women, with being twice as likely to suffer from anxiety disorders, are at a significantly higher risk [3,6,8].

The individual and social impact of anxiety disorders has been pointed out repeatedly. Among people with psychiatric disorders, those with anxiety disorders are high care utilizers who present to general practitioners more frequently than to psychiatric professionals [9], which places a high burden on the health care system. Their economic costs include psychiatric and nonpsychiatric care, emergency care, hospitalization, drug prescription, reduced productivity, absenteeism from work, and suicide [9].

TREATMENT: HOW CAN ANXIETY DISORDERS BE TREATED?

Psychotherapeutical Treatment of Anxiety Disorders

Cognitive behavioral therapy (CBT) is long known to be the gold standard in psychotherapy of anxiety disorders. Its positive effect is one of the best assured results in psychotherapy research in general. Numerous clinical trials have supported the efficacy of CBT for anxiety disorders. Several meta-analytic results of treatment outcome studies have supported this finding, showing strong effects of CBT for PD and agoraphobia, social phobia, obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), and PTSD [10]. Cognitive therapy and exposure therapy alone, in combination or combined with relaxation training, could be shown to be effective across different anxiety disorders, with no differential efficacy for any treatment components for any specific diagnoses [10]. The authors reported that their meta-analytic findings showed superior effects for CBT in GAD and PTSD than for social anxiety disorders (SAD) as the only difference on the diagnostic level. In line with these earlier findings also is a more recent review of meta-analytic findings for the efficacy of CBT for the treatment of anxiety disorders by Olatunji et al. [11]. The authors reviewed contemporary meta-analytic studies and support the finding that CBT procedures and particularly exposure-based treatment approaches are highly efficacious. They could resume that CBT, in general, outperforms wait-list as well as placebo controls and achieves incremental efficacy above and beyond nonspecific factors. There now also are references that CBT is more efficacious than other psychosocial treatment modalities for some anxiety disorders [11]. While the efficacy of CBT for the treatment of anxiety disorders is one of the best empirically proven result in the field of research on psychotherapy, there are also relatively new sectors in the field to be looked at, e.g., the associated neuroanatomical changes coming along with the cognitive behavioral modification of psychotherapy. A recent systematic review [12] reported that CBT modified the neural

circuits involved in the regulation of negative emotions and fear extinction in treatment responders, which speaks in favor of CBT being able to change dysfunctions of the underlying neural basis. Neuroimaging also is considered to hold the opportunity to identify predictors of response to therapy, which will be one of the future challenges in the research of treatment efficacy. Until now, there is only evidence regarding OCD, where higher pretreatment regional metabolic activity in the left orbitofrontal cortex was associated with better outcome [12].

Recently, self-help efforts have also been taken into a closer look, playing a role as an initial minimal treatment in stepped-care models of treatment or as a strategy to prevent a disorder developing. Furthermore, it might be promising meeting the lack of professionals providing evidence-based therapy and the demand for treatment with minimal cost to health services. For a review on the outcomes of self-help efforts, see Morgan and Jorm [13].

Pharmacological Treatment of Anxiety Disorders

The pharmacological treatment of anxiety disorders has made great progress over the past few decades and has been intensively studied. Clinical trials showing the effectiveness of selective serotonin reuptake inhibitors (SSRIs) have been well replicated, while the effectiveness of other medication classes needs to be further validated [14]. When looking at PD, SAD, GAD, PTSD, and OCD, findings suggest that both SSRIs and serotonin-norepinephrine reuptake inhibitors are the first-line medications for most of the previously mentioned disorders [14,15]. Other antidepressants (tricyclic antidepressants or monoamino oxidase inhibitors) should rather be seen as second- and third-line choices, due to their tolerability issues. Other agents as anticonvulsants may have an adjunctive role. On the level of different diagnoses, azapirones have been used effectively for GAD, while in PD and GAD, there is empirical evidence for the use of benzodiazepines [14]. Benzodiazepines are very effective due to their rapid onset of action and ability to be used on an as-needed basis, although their long-term use is limited by the potential for abuse and dependence and their lack of antidepressant properties [16]. For detailed reviews of randomized, placebo-controlled trials and meta-analyses investigating the effects of different psychotropic medications used in the treatment of particular anxiety disorders, see Ravindran and Stein [14], Plag et al. [15], or Hoffman and Mathew [16].

In conclusion, though, when it comes to the pharmacological treatment of anxiety disorders, antidepressant treatment is the clinical standard for all types of anxiety disorders (excluding specific phobias) [15,17,18].

Is a Combination of Pharmacotherapy and Psychotherapy Even Better?

In order to increase the efficacy of either psychotherapy or pharmacological treatment, the combination of both has been discussed as an option toward faster and more sustained treatment. Although this approach may seem obvious, confirming empiric findings are not.

For patients with PD, Barlow et al. [19] could show that combining pharmacotherapy (Imipramine) and CBT was more effective than either therapy alone. In line, Blanco et al. [20] found combined therapy as being superior to either treatment alone and to placebo in patients with SAD.

Pull [21] resumed little benefit for a combination of psychotherapy and pharmacotherapy for the treatment of anxiety disorders versus monotherapies when taking randomized controlled trials, meta-analysis, and reviews into account. Zwanzger et al. [22] review that there might be some evidence for the superiority of combination therapy under some conditions, although the authors do not see evidence for beneficial effects of combined treatment for long-term outcome. Consistently, Hofmann et al. [23] report in their meta-analysis that pharmacotherapy may be a useful strategy for enhancing acute-phase CBT outcomes, while they do not see evidence for a benefit of combination therapy in the long-term CBT outcomes. Interestingly, the authors also report a significant publication bias in terms of smaller effects in more recent studies, which might be due to more rigorous assessment methods.

Following Bandelow et al. [17], the missing evidence for the combination of both strategies might, in part, be due to the number and quality of existing studies. Nevertheless, combined pharmacotherapy and psychotherapy is current clinical guideline for treating PD and agoraphobia, while for treatment of GAD, SAD, OCD, and PTSD, the benefit of a combined therapy up to date can neither be clearly supported nor rejected [17].

Complementary Treatment Methods

Psychotherapy and pharmacotherapy are the treatments of choice and recommended as the current treatment guidelines [17], although other complementary approaches might partly be useful in the amelioration of therapy. Although for most of them until now, only poor evidence base has been generated [24], complementary and alternative interventions used to treat anxiety are highly popular.

Due to methodological limitations of the underlying trials available up to date, empirically based recommendation cannot be given for the use of herbal and dietary supplements [17,25], homeopathy [26], acupuncture [27], therapeutic touch [28], tai chi, and qigong [29] in the treatment of anxiety. Conflicting results exist for meditation [29,30], while yoga has shown to be effective in a recent review [29]. All those approaches have to be further investigated.

Meta-analytic investigations could not support the effectiveness for repetitive transcranial magnetic stimulation [31], while the anxiolytic potential of relaxation trainings (e.g., applied relaxation, autogenic training, Jacobson's progressive relaxation) has been meta-analytically proven [30].

Exercise has been considered a promising therapeutical option for anxiety disorders, as in a wide range of research, it has been shown to have positive effects on major

depression [32]. A detailed illustration of evidence-based results for the link between anxiety disorders and physical activity will be given in the following passages.

WHAT LINKS ANXIETY (DISORDERS) AND PHYSICAL ACTIVITY?

Physical activity has been defined as bodily movements produced by skeletal muscles that result in energy expenditure [33]. It therefore includes either leisure activity (like jogging, cycling), which increases fitness such as labor, gardening, housework, or walking. Exercise is seen as a subset of physical activity, as it is defined as planned, structured, and repetitive physical activity that has improvement or maintenance of physical fitness as a final or intermediate goal [33]. Most research has focused on exercise [34], although in the last decade, there has been a shift in the public health recommendations, now also regarding everyday physical activity as beneficial [35]. In literature, though, both terms are not always differentiated. In the following, we will use physical activity, exercise (training), and sports equivalently.

Physical Activity, Exercise, and the Prevalence and Incidence of Anxiety Disorders

Physical activity is known to be associated with a range of health benefits and the absence can have harmful effects on health and well-being as it increases the risk for coronary heart disease, diabetes, certain cancers, obesity, hypertension, and all-cause mortality [36].

Compared with a wide range of research on the positive effects of physical activity in depression, anxiety disorders have been less frequently studied. Additionally, the diversity of anxiety disorders does not allow to generalize from studies in one specific anxiety disorder to other disorders. Furthermore, changes in the diagnostic criteria complicate the interpretation of early studies.

Cross-sectionally, the link between physical activity and anxiety has been intensively studied, and high self-reported levels of physical activity have mainly been found to be associated with better mental health.

When controlling for social class and status, e.g., Steptoe and Butler [37] could show that vigorous exercise participation was related to lower emotional distress in a large cohort (n = 5061). In line, Stephens [38] found in samples from the United States and Canada that self-reported levels of recreational physical activity were correlated with better mental health, which included fewer symptoms of anxiety as well. His results held after controlling for confounding variables such as sex, age, sociodemographic status, and physical illness, which speaks in favor of the robustness of the found relation.

The link between physical activity and (mental) health in the European Union was intensively studied by Abu-Omar et al. They were able to replicate earlier findings of associations between physical activity in everyday life with self-rated health in general [39] and also with self-rated mental health [40]. They used the relatively new developed International Physical Activity Questionnaire [41], which allows calculating of metabolic equivalents during the last week. This instrument had been developed following a shift in public health recommendations to allow standardized assessment of physical activity independent of the context.

Concerning different diagnoses in the field of anxiety disorders, Goodwin [42] analyzed the data of the U.S. National Comorbidity Survey and found significant associations of regular physical activity and a lower prevalence of specific phobia, social phobia, and agoraphobia in a representative sample of adults in the United States. These findings as well persisted after controlling for sociodemographic characteristics, self-reported physical disorders, and comorbid mental disorders.

Furthermore, a representative, cross-sectional study in Japan [43] including 4000 persons could show a positive relation between dislike of physical activity and higher odds ratios for panic attacks and PD, which was found to be especially true for women.

On the other hand, studies can be found, which do not underline the association between physical inactivity and symptoms of anxiety. For example, Thorsen et al. [44] could not replicate a positive association between (self-reported) physical activity and lower prevalence of anxiety in their study with long-time cancer survivors and in men of similar age from the general population after adjusting for background variables. In line with those findings is Backmand et al. [45], who could not find physical activity being associated with less symptoms of anxiety when examining former athletes.

Despite numerous studies on the topic, there are certain problems when it comes to their comparability as measurement of anxiety as well as measurement of physical activity has not been consistent. Furthermore, in most studies, fitness was not directly assessed, and measuring exercise habits and anxiety disorders in cross-sectional surveys generally is ambiguous about cause and effect. That is why prospective longitudinal studies are needed to further investigate the association of physical activity and mental disorders. Until now, these studies are very rare when it comes to anxiety disorders. At least, in part, though, prospective longitudinal studies support positive results driven from cross-sectional studies. In a sample of 2548 adolescents and young adults, Ströhle et al. [46] combined a cross-sectional and a prospective longitudinal design within their study. The cross-sectional results showed that regular physical activity was associated with decreased prevalence of any and comorbid mental disorder due to lower rates of substance use disorders, anxiety disorders, and dysthymia. Physical activity was assessed with four questions as part of the diagnostic interview, answers were grouped into three categories: regular (daily and several times a week), non-regular (one to four times a month), and no (less than once a month or no exercise at all) physical activity. Findings comparing people exercising non-regularly versus people with no physical activity were similar.

The prospective results showed that regular as well as non-regular physical activity was associated with a substantially reduced risk compared with people not exercising to experience any incident disorder and to develop comorbid conditions. These effects hold for control of educational status and body mass index, other mental disorders, and impairment days due to physical problems. Taking anxiety disorders into a closer focus, 5 year incidence of any anxiety disorder was lower for people exercising regularly and non-regularly compared to the group labeled as no physical activity at baseline. Comparing regularly exercising people with people not exercising, on the specific disorders level, the effect could only be shown for agoraphobia and specific phobia. Comparing non-regularly exercising people with people not exercising revealed an effect for agoraphobia as well as for PTSD.

Overall, the authors suggest a substantial protective effect of physical activity, especially if participating in sports daily or more frequent. The association of regular activity and mental health, however, is different by age, gender, and type of disorder. Regarding anxiety disorders, significant associations were found for agoraphobia, specific phobia, and PTSD. All revealed lower rates among those who exercised regularly, and the effects were less impressive for non-regular activity levels.

Limitations of the study, though, include the lack of objective indicators of physical activity and fitness.

Recently, Jonsdottir et al. [47] conducted a prospective study in 3114 Swedish health care workers and social insurance officers. On a cross-sectional approach, they could show that individuals reporting light or moderate-to-vigorous activity were less likely to report high levels of anxiety (as measured with the Hospital Anxiety and Depression scale (HAD) [48], while an activity level of at least moderate was needed to reduce the risk of symptoms of anxiety at follow-up 2 years later.

Although there are diverse and inconsistent results and cross-sectional trials are often difficult to compare due to diverse acquisition of both anxiety and physical activity, generally there is an association between physical activity and less symptoms of anxiety. Nevertheless, more consistently designed studies and, particularly, prospective trials are needed to further investigate the association and to learn more about the nature of effect of physical activity on anxiety. Furthermore, it is still unclear whether there really is a causal relationship between physical activity and (less) anxiety, as often is implicitly assumed in population-based studies. It is also conceivable that common genetic factors both influence exercise behavior and anxious symptoms, a possibility a recent Dutch study [49] showed some proof for.

Evidence of Therapeutical Impact of Physical Activity on Anxiety

Physical inactivity is, according to the WHO, one of the risk factors that most often contribute to an early death and is comparable in its harmfulness to cigarette smoke [50].

The positive influence of exercise on psychological well-being and mental health has been demonstrated several times.

Endurance training reduces anxiety, enhances mood, increases self-confidence, and improves stress management capacity in healthy people [51–54].

At the same time, a twin study demonstrated a relationship between physical activity and reduced mortality [55].

Anxiolytic Effect in the Healthy

The anxiolytic effect of aerobic physical exercise in healthy subjects has been investigated in numerous studies. Several meta-analyses suggest a fear-reducing effect in healthy people [56–58]. A training period of at least 10 weeks and a workout in the aerobic power range seem to be critical for the anxiolytic effect [58].

One-Time Physical Activity and Anxiety

The anxiolytic effect of a one-time physical activity was examined by Orwin [59]. Other case reports describe the anxiolytic effect of a one-time physical activity in patients with specific phobia [60,61]. Physical symptoms of anxiety in healthy patients, in which anxiety symptoms were experimentally induced by caffeine intake, cholecystokinin tetrapeptide (CCK-4), and CO_2 transfer, decreased after a single session of physical exercise on the bicycle ergometer or on treadmill [62–64].

Before a CO_2 challenge, 18 PD patients practiced either moderate exercise or very light exercise. Panic reactions were smaller in patients who performed moderate exercise compared with patients in the control condition (very-light exercise) [65].

In a crossover design, healthy subjects and patients with PD were studied by Ströhle et al. [66]. The effects of rest and 30 min aerobic treadmill exercise were compared with each other after CCK-4-induced panic attacks. It could be shown that panic attacks were less frequent in the exercise condition and that 30 min of physical activity caused an acute antipanic and anxiolytic activity.

Endurance Training and Anxiety

The effect of physical training in patients with manifest anxiety disorder has so far received little systematic study. Dratcu [67] could show an effect of aerobic endurance training for the treatment of patients with PD in his case series.

In a study of patients with anxiety neurosis, a 2 month endurance training led to a significant decline in anxiety scores [68]. Here, a 2 month training course was compared in terms of anxiolytic effect with 2 months of walking training (three to four times a week, 30 min). Both forms of training showed a significant effect in terms of anxiety reduction regardless of training status of subjects. In the follow-up after 6 months, however, the improvement of training correlated with the reduction of anxiety symptoms. Interestingly, patients who had completed the walking training increased their training frequency by their own initiative after the 2 month period. This suggests that walking exercise is sufficient to achieve an anxiolytic effect, which should also lead to higher compliance in the patients compared to running [68].

In a placebo-controlled study of Broocks et al. [69], the effect of a 10 week endurance training (5 km jogging three to four times a week) was compared to a proven drug therapy in patients with PD. Both endurance training and pharmacotherapy was superior to placebo for reduction of anxiety symptoms. However, the drug therapy was a bit faster and better. The delayed effect of endurance training can be attributed to some of the patients only being able to run the entire distance of 5 km after several weeks. Under treatment with the endurance training, there were no side effects in contrast to the pharmacotherapy [69]. In a more recent trial, Wedekind et al. [70] did not find exercise training to be superior to relaxation in patients with PD. However, the authors state that their similar results for exercise and relaxation were not due to in efficacy of exercise but to the large unspecific effects of the control group. Taking these two studies together, Wedekind et al. [70] resume that exercise seems to have an effect that exceeds pure placebo effect but seems to be less effective than drug treatment.

More recently, a meta-analysis by Wipfli et al. [71] concludes that exercise can reduce anxiety significantly better than other methods of anxiety reduction. Since that analysis is based on 49 randomized and controlled studies, the authors believe they can recommend the treatment of anxiety disorders through sport with high evidence (Level 1, Grade A). In general, it is found that sport and exercise can relieve so-called state anxiety by even a single exercise session. However, a significant improvement of "trait anxiety" requires more intensive and longer training.

A meta-analysis of Petruzzello et al. [58] came to the conclusion that a single training session needs to take at least 21 min and the overall treatment needs to last at least 10 weeks to establish significant effects on "trait anxiety."

There also exists evidence that patients with PTSD may benefit from exercise training [72,73], although adequately sized randomized controlled clinical trials are still needed to conclude that exercise training is effective. This is comparable to the situation up to date when it comes to patients with agoraphobia, social phobia, specific phobia, and GAD.

Also for OCD, promising but preliminary effects of exercise for acute symptom reduction have lately been reported [74].

In summary, it can be stated provisionally: next to a doubt-free "acute" anxiety-dissolving effect, physical exercise appears to have longer-term anxiety reduction effects when used in appropriate clinical pictures as an additional measure. To what extent exercise can also be used as the main intervention for anxiety disorders is still an unsettled question. Particularly, suitable sports cannot be named yet. It is, however, certain that athletes are consistently less anxious and depressed than physically inactive people [75]. On the other hand, it is not clear whether sport really sustains mental health or whether mental health is the basis for engaging in sports and being able to do so.

Mechanisms of the Activity of Exercise

Psychological Mechanisms

From a psychological point of view, there is some empirical evidence that the effect of exercise is based, in part, on the improvement of perceived coping skills and increased self-efficacy [76]. Anxiety disorders often go hand in hand with the most stressful experience of sitting in a trap, seeing no solution, and therefore helplessly being at the mercy of the symptoms. In such situations, the possibility to gain relief through exercise and sport opens a way out. Once a person sees a way out of a seemingly hopeless situation, and feels being able to exercise control over the events, the stress levels reduce and the associated symptoms improve. The awareness to have the means to self-regulate improves self-confidence and thereby promotes health [77].

Bahrke and Morgan [78] believe that the effect of physical activity lies in the deflection of negative thought content. If physical exercise is carried out in a group, social interaction could also contribute to the relieving of anxiety.

The anxiolytic effect of endurance training in patients with PD can also be explained by aspects of behavioral therapy. Panic patients often experience normal bodily sensations such as increased heart rate or a fast pulse as life threatening. If these sensations occur during a panic attack, they are inexplicable and uncontrollable for the patient. If these sensations, however, occur during exercise, they become natural for the patient. They are perceived as natural and not life-threatening reactions to the exercise. Physical exercise could be considered in this sense as a form of systematic desensitization [79].

Biological Mechanisms

Serotonin Metabolism

Animal experiments showed that acute physical stress leads to an increased turnover of serotonin, especially in the medial basal hypothalamus [80]. Endurance training appears to have the same effect. Broocks et al. [81,82] showed that endurance training leads to a normalization of serotonin receptors, which play a role in patients with PD. It is likely that endurance training leads to increased serotonin levels, as is also observed when serotonergic agents are administered (SSRIs). This belief is supported by a study of Dey et al. [83]. After a 4 week physical training, an increased serotonin synthesis and increased serotonin turnover was found in the cerebral cortex of rats.

Stress Hormone System

Among the physiological "stress systems," the so-called hypothalamic-pituitary-adrenal axis (HPA; see Figure 117.1) has a special position. The other subsystem is the autonomic nervous system, which consists of the sympathetic and parasympathetic nervous system. The HPA is a tripartite hormone axis, which consists of the hypothalamic peptide hormone corticotropin-releasing hormone (CRH), the pituitary peptide hormone adrenocorticotropic hormone (ACTH), and the adrenal steroid cortisol. The three hormones form several negative feedback loops to ensure optimal regulation of production and secretion of these messengers at all three levels. A dysfunction of the HPA axis is causally implicated in the development or pathogenesis of various diseases such as anxiety, depression, cancer, or eczema.

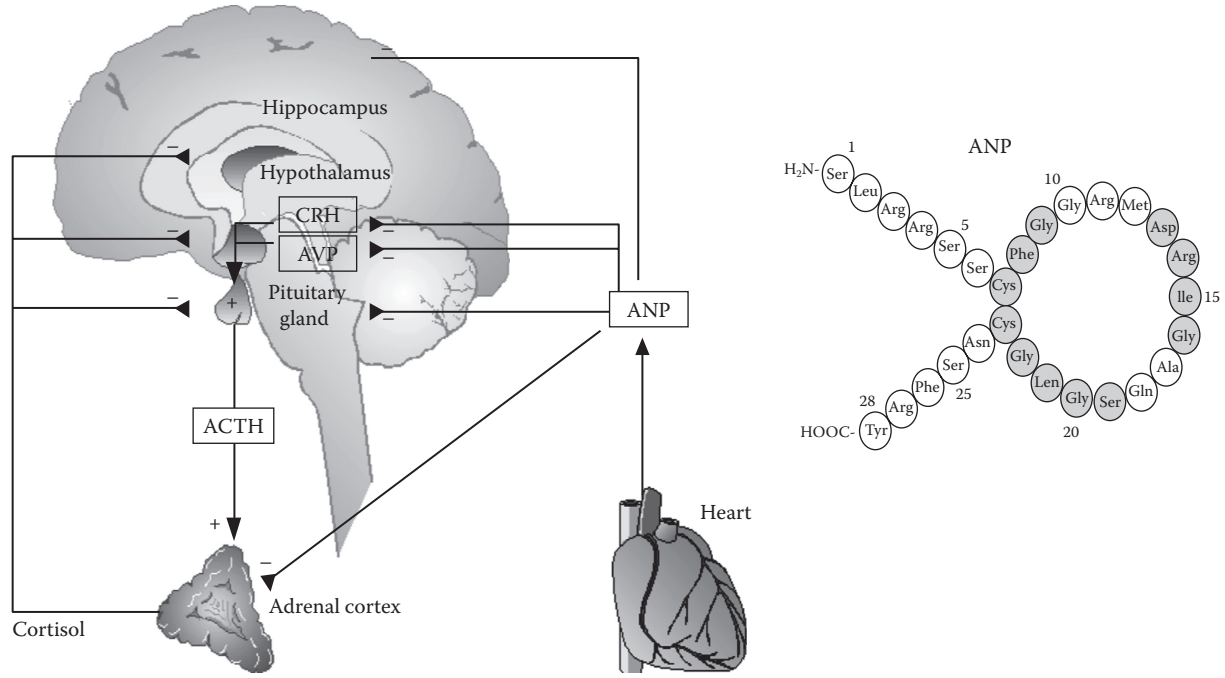


FIGURE 117.1 Inhibition of the HPA system by ANP. (From Ströhle, A., *Pharmacopsychiatry*, 36(3), 207, 2003.)

The end product of the HPA axis, cortisol, exerts lasting effects on nearly all organs of the body. In patients with anxiety disorders, an altered activity of the HPA system might be present [84]. The overactivity of the stress system in anxiety disorders is often associated with a permanently increased release of cortisol in the body. As the body immediately releases noradrenaline from the adrenal medulla in response to a threat, the release of cortisol represents a delayed onset of "supply response." A permanent increase in cortisol levels has many adverse consequences such as the loss of nerve cells in the hippocampus or the weakening of immune reactions [85,86]. Physical activity seems to be able to reduce cortisol levels in the body or prevent increases in cortisol [87].

In a study by Abelson and Curtis [88], the cortisol levels correlated with the severity of PD.

Ströhle et al. were able to show that induced panic attacks associated in patients with PD correlate with a strong activation of ACTH secretion without a simultaneous increase in cortisol secretion [89]. CRH stimulates the release of ACTH and appears to play an important role in the modulation of anxiety [90].

Various studies show that endurance training leads to decrease in cortisol concentration [91,92].

In a Swiss study, trained and untrained men were exposed to a stress test [93] in which various parameters such as cortisol response, heart rate, and psychological responses (mood, anxiety, and calmness) were measured before and after the test. In response to the stressor, cortisol levels and heart rate were significantly increased in both groups. However, trained men exhibited significantly lower cortisol and heart responses compared with untrained men. Furthermore, trained men showed better mood and lower state anxiety.

Through physical activity, the body learns to distribute less stress hormones under stress, to assimilate them better and to build protective factors against stress.

Persistent, regular physical training strengthens not only the physiological defenses but also the psychological resistance factors.

Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP; see Figure 117.1) is a powerful vasodilator and a protein (polypeptide) hormone secreted by heart muscle cells. It is involved in the homeostatic control of body water, sodium, potassium, and fat. It is released by muscle cells in the upper chambers of the heart, in response to high blood pressure. ANP acts to reduce the water, sodium, and adipose loads on the circulatory system, thereby reducing blood pressure. ANP was first described by de Bold et al. [94].

ANP is produced, stored, and released by cardiac myocytes of the atria of the heart. It is released in response to atrial stretch and a variety of other signals induced by hypervolemia, caloric restriction, or exercise. The hormone is constitutively expressed in the ventricle in response to stress induced by increased afterload (e.g., increased ventricular pressure from aortic stenosis) or injury (e.g., myocardial infarction) [95].

Acute physical exercise leads to an increase in ANP secretion, wherein the level of activity and quantity of the secreted ANP are proportional to each other [96,97]. This correlation, however, seems to affect only untrained persons. In a study by Rogers et al., they conducted a one-time maximum load in nine untrained volunteers to an increase in ANP concentration; at 10 trained subjects there was no change in plasma ANP levels to observe [98].

ANP and ANP-specific receptors were also detected in different brain regions, including the hypothalamus, the locus coeruleus, and central amygdala [99]. ANP inhibits the stress hormone system at several levels. Both the release of ACTH and CRH is reduced by ANP and thus inhibits the cortisol response induced by ACTH and CRH [100,101].

The effect of ANP on the stress hormone system and the impact on avoidance behavior in animals [102] points to a role of ANP in the modulation of anxiety. Ströhle et al. [103] showed that administration of ANP in the amygdala in rats showed an anxiolytic activity.

It has now been demonstrated that administration of ANP in humans shows anxiolytic effects. Pretreatment with ANP reduced the number of induced panic attacks and the severity of the symptoms compared to a placebo [104].

ANP appears to play an important role in the modulation of fear and panic and could be responsible for psychological adaptation processes during exercise. Moreover, it is possible that ANP is involved in the process of anxiolytic effects of chronic physical activity [105].

Endorphins

The influence of exercise on endorphins is another hypothesis to explain the anxiolytic activity of exercise.

Specially bred mice with a deficiency of endogenous opiates (enkephalins and endorphins) showed a significant increase in anxiety and solidified in even slightly threatening situations. They also only briefly tolerated to stay in the middle of a big box and preferred to hide themselves on to the edges of the box. Under light, these mice even avoided any activity and barely moved. A control population of normal mice behaved much more relaxed in these tests [106]. The body's own opiates, which also exist in humans, could therefore have the function to eliminate anxiety and fear.

Goldfarb and Jamurtas [107] showed in a study that physical activity with appropriate duration and intensity results in an increase of beta-endorphin plasma concentration. Furthermore, regular exercise leads to a potentiated release of beta-endorphins [108].

For a long time, the endorphin hypothesis was based entirely on findings of enhanced endorphin levels in the peripheral blood. Boecker et al. [109] were able to disclose the central mechanism and to identify a relationship to perceived euphoria during exercise by using a positron emission tomography study. The level of euphoria was significantly increased after running and was inversely correlated with opioid binding in several brain areas, such as the anterior cingulate cortex as well as temporoparietal regions. These findings indicate region-specific effects in frontolimbic brain areas that are involved in the processing of mood and affective states, such as anxiety. This has also been referred to as "runner's high."

Other Possible Mechanisms

In his case study, Dratcu [67] assumes that regular physical activity leads to a reduction of chronic hyperventilation in patients with PD, which may explain the antipanic effect.

A vegetative hyperarousal in patients with PD was demonstrated by Hoehn-Saric et al. [110]. These patients showed increased heart rates and elevated blood pressure even at rest. Endurance training may lead to compensation of the autonomic hyperarousal [110].

Physical activity is proven to lead to better sleep. Certain antidepressants are also based on a normalization of the sleep cycle [111]. Healthy sleep thus also appears to have anxiolytic effects.

Recent studies have shown that the body, under physical activity, releases a higher measure of so-called growth factors, which may lead to the formation of new nerve cells and a better "networking" (formation of synapses), particularly in the brain. At the center of the research and interest is brain-derived neurotrophic factor (BDNF) followed by insulin-like growth factor (IGF-1) [112,113]. BDNF can cause nerve regeneration particularly in the hippocampus, which is reduced in stress-affected patients. Since antidepressants produce the same effect, it is hypothesized that the antidepressant and anxiolytic effects of physical activity are mediated by an increased release of BDNF. It is based on neuroplasticity, the brain's ability to reorganize itself by forming new neural connections. Neuroplasticity allows the neurons (nerve cells) in the brain to compensate for disease and to adjust their activities in response to new situations or to changes in their environment. Physical activity can lead to a rapid transient increase of BDNF in the blood and the brain [114].

Another hypothesis is the hyperthermic model, which states that exercise leads to a rise in body temperature resulting in a relaxation of the muscles, an effect which has been compared to having a hot bath [115]. Relaxation and anxiety cannot simultaneously exist in the brain.

The most likely explanation is a multifactorial, psychobiological model, which combines several hypotheses.

CONCLUSION AND RECOMMENDATIONS

Although there are many studies underlining the association between (more) physical activity and (less) anxiety, many questions still remain. This especially concerns the empirical evidence of the causal mechanism underlying this association, as well as the further investigation of the therapeutic impact of physical activity. Further, methodically well-designed studies are needed in these fields.

Nevertheless, clear recommendations to integrate physical activity in our everyday life and to engage in exercise training can be given. Concerning the amount of physical activity people should engage in to achieve health benefits, the guidelines of the WHO and the Centers for Disease Control and Prevention of the U.S. Department of Health and Human Services can be followed (unless specific medical conditions indicate to the contrary): adults aged 18–64 years should at least do 150 min of moderate-intensity aerobic activity (e.g., brisk walking, general gardening) or 75 min of vigorous-intensity aerobic activity (e.g., jogging) or an equivalent mix of moderate- and vigorous-intensity aerobic activity each week, all performed in bouts of at least

10 min [116,117]. Additionally, strengthening exercises of all major muscle groups should be performed on at least 2 days a week, with exercises repeated 8–12 times a set [116,117]. Adapted recommendations are given for older adults and for children and adolescents.

At the end, it should especially be pointed out that, as referred, many trials have shown beneficial effects of physical activity in people not fulfilling any anxiety disorder diagnosis, so it should be considered if physical activity should not only be therapeutically used to treat anxiety disorders, but should be considered by healthy people as well as a way to encounter any states and conditions of (subclinical) anxiety.

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118 Physical Activity and Depression

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CONTENTS

Prevalence and Burden of Depression 1409
Cross-Sectional and Longitudinal Studies of Exercise 1409
Randomized Controlled Trials of Exercise 1410
Efficacy of Aerobic Exercise in Reducing Depressive Symptoms 1410
Efficacy of Resistance Training Exercise in Reducing Depressive Symptoms 1410
Meta-Analyses Examining the Efficacy of Exercise in Reducing Depressive Symptoms 1410
Exercise versus Established Treatments 1412
Exercise as an Adjunctive/Augmentative Therapy 1412
Exercise Prescription 1412
Session Frequency and Duration 1412
Exercise Intensity 1413
Intervention Duration 1413
Exercise Modality 1413
Adherence to Exercise Interventions 1413
Reduction of Depressive Symptoms in Diseased Populations 1414
Cardiovascular Disease 1414
Other Diseases 1414
Mechanisms of the Antidepressant Action of Exercise 1414
Serotonin 1414
Brain-Derived Neurotrophic Factor 1414
Hypothalamic-Pituitary-Adrenal Axis 1414
Endocannabinoids 1415
Psychosocial Factors 1415
Future Directions 1415
References 1416

PREVALENCE AND BURDEN OF DEPRESSION

Depressive disorders annually affect approximately 10% of the population in the United States with a lifetime prevalence of 10% in men and 15% in women. Along with the high prevalence, costs associated with depressive disorders have also grown, as the annual economic burden of depressive disorders is estimated at $83 billion [1]. Furthermore, even in individuals who do not meet diagnostic criteria for major depressive disorder (MDD), depressive symptoms have negative influences on health. Elevated depressive symptoms are associated with an increased risk of MDD [2], functional impairment [3–5], higher rates of disability [6], and increased social dysfunction [3,7].

Further increasing the burden of depressive disorders is the limited accessibility and effectiveness of treatments. Only 55% of people afflicted with a depressive disorder are receiving treatment, while alleviation of depressive symptoms is seen in only 32% of those receiving treatment [8]. Randomized controlled trials (RCTs) have shown the efficacy of three classes of treatment to be effective in reducing depressive symptoms: antidepressants, psychotherapy, and neurostimulation (electroconvulsive therapy [ECT], repetitive transmagnetic stimulation [rTMS]) [9]. Despite the empirical evidence demonstrating the efficacy of these treatments, response rates for antidepressants [10,11], psychotherapy [12], rTMS [13], and ECT [14] indicate that a significant portion of individuals do not respond to these treatments. These statistics indicate the need for more cost-effective, accessible, and alternative treatments for depressive disorders. Exercise is one potential treatment that has been supported through research.

Cross-Sectional and Longitudinal Studies of Exercise

The relationship between physical activity and depressive disorders was first identified in epidemiological work. Farmer et al. [15] examined the associations between depressive symptoms and physical activity in the National Health and Nutrition Examination Study I. In this nationally

representative sample, there were significant correlations with lower physical activity levels associated with higher levels of depressive symptoms. Additionally, low levels of physical activity in this sample were also associated with twofold increased risk of MDD at follow-up 8 years later. Similar results have been reported in other epidemiological studies. Results from the Harvard Alumni Study indicate that higher levels of physical activity were associated with lower incidence of MDD during a 5 year follow-up [16]. Using the Alameda County Study Data, Camacho et al. [17] found that individuals who reported low levels of physical activity were at greater risk for developing MDD at the 9 year follow-up. This study also included a second follow-up period that allowed for the examination of the relationship between changes in physical activity and future MDD. Participants who reported decreased physical activity from baseline to follow-up were at greater risk for MDD at a second follow-up 18 years after baseline, while participants who increased activity were not at a higher risk for MDD at the 18 year follow-up compared to those who remained physically active. Finally, Galper et al. [18] examined the relationship between physical fitness (assessed by maximal exercise test) and depressive symptoms in the Aerobics Center Longitudinal Study. Results of this analysis indicate a significant inverse relationship between physical fitness and depressive symptoms.

Randomized Controlled Trials of Exercise

Efficacy of Aerobic Exercise in Reducing Depressive Symptoms

Building on the findings from epidemiological studies, a number of RCTs have examined the treatment effects of aerobic exercise on depressive symptoms in individuals with MDD (Table 118.1). Dunn et al. [19] randomized 80 adults, aged 20–45 years, to either high dose aerobic exercise (17.5 kilocalories per kilogram of weight (KKW) at a self-selected intensity), low dose aerobic exercise (7 KKW at a self-selected intensity), or an exercise placebo group (i.e., stretching). In this sample, participants in the high dose group demonstrated significantly greater reductions in depressive symptoms following 12 weeks compared to both the low dose and placebo groups. The mean Hamilton Rating Scale for Depression (HRSD) score was reduced by 47% in the high exercise group, which was significantly greater than the reductions in HRSD score observed in the low dose exercise (30%) and placebo groups (29%). The individuals in the high dose exercise group were also more likely than those in the control group to elicit a treatment response (defined as a 50% reduction in HRSD score) and achieve remission (defined as an HRSD score of 7 or lower).

Similarly, Blumenthal et al. [20] randomized adults, aged 40 years and older, with MDD to one of four treatment groups: home-based aerobic exercise, supervised aerobic exercise, selective serotonin reuptake inhibitor (SSRI) (sertraline), or placebo pill. Following 16 weeks of treatment, greater remission rates were observed in the home-based (45%) and supervised exercise (40%) compared to a placebo pill (31%). The remission rates for the supervised exercise group and home-based exercise group were similar to those observed by Dunn et al. [19]. In another trial, Nabkasorn et al. [21] randomized females, aged 18–20 years, with MDD to either aerobic exercise or a wait-list control. They report greater decreases in depressive symptoms, measured by the Center for Epidemiologic Studies Depression scale, in the exercise group compared to a wait-list control.

Efficacy of Resistance Training Exercise in Reducing Depressive Symptoms

Another group of studies have examined the effect of resistance training exercise on depressive symptoms. One study examined the effects of a 10 week supervised resistance training program with an attentional-control group in 32 adults, aged 60 years and older. Following the intervention, the resistance training group had significantly reduced depressive symptoms compared to the attentional-control group. Furthermore, 59% of the resistance training group had achieved a clinically meaningful response (defined as 50% reduction in HRSD score) compared to only 26% in the control group [22]. After the 10 week assessments, participants in the resistance training group were instructed to continue engaging in twice-weekly, unsupervised resistance training sessions for another 10 weeks. Depressive symptoms, measured by the Beck Depression Inventory (BDI), remained significantly lower in the resistance training group after this phase, and the percentage of participants classified as "nondepressed" (defined as a BDI score of less than 9) was 73% compared to 36% in the control group. The difference in depressive symptoms between the groups remained at a 26 month follow-up [23].

In another trial of older adults, participants were randomized to one of three conditions: high dose resistance training, low dose resistance training, or standard care. At the end of 8 weeks, the high dose resistance training group had significantly greater reductions in depressive symptoms compared to the other two groups, and there was no significant difference between the low dose and standard care groups. Participants in the high dose group were also more likely to achieve a clinical response (defined as a 50% reduction in HRSD), as 61% of the high dose participants achieved a clinical response compared to 29% of the low dose group and 21% of the standard care group [24].

Meta-Analyses Examining the Efficacy of Exercise in Reducing Depressive Symptoms

In addition to the studies referenced earlier, several other trials have examined the effect of exercise interventions in patients with depressive disorders. The results of these studies have been summarized in a number of meta-analyses [25–28]. These meta-analyses report significant effect sizes for the reduction of depressive symptoms following an exercise intervention. The effect sizes reported in these meta-analyses range from 0.83 to 1.39, indicating a large treatment effect [29].

TABLE 118.1
Trials Examining Efficacy of Exercise in the Treatment of MDD

Study	Comparison Group(s)	*N*	Intervention Length (Weeks)	Exercise Frequency (per Week)	Bout Duration (min)	Intensity	Outcome
Blumenthal et al. [30]	1. Aerobic exercise 2. SSRI 3. SSRI + aerobic exercise	156	16	3	30	70%–85% HRmax	No significant differences in depressive symptoms among the three groups following treatment
Blumenthal et al. [20]	1. Home-based aerobic exercise 2. Supervised aerobic exercise 3. SSRI 4. Placebo pill	202	16	3	30	70%–85% HRmax	Remission rates were greater for three active treatment groups compared to placebo pill
Dunn et al. [19]	1. High dose aerobic exercise 2. Low dose aerobic exercise 3. Exercise placebo	80	12	3	NA	NA	Reduction in HRSD score and remission rates were significantly greater in the HD exercise group compared to the LD exercise and placebo groups
Martinsen et al. [117]	1. Aerobic exercise 2. Control (occupational therapy)	43	9	3	60	50–70% HRmax	Reduction in depressive symptoms was greater in exercise group
Martinsen et al. [37]	1. Aerobic exercise 2. Resistance training	99					
Mather [34]	1. Aerobic exercise 2. Control (health education)	86	10	2	45	NA	Exercise group had a significantly higher response rate compared to the health education group
McCann and Holmes [118]	1. Aerobic exercise 2. Exercise placebo (Stretching) 3. No-treatment control	43	10	2	60	NA	Greater reductions in depressive symptoms were observed in the exercise group
McNeil et al. [119]	1. Aerobic exercise 2. Social contact control 3. Wait-list control	30	6	3	40	NA	Exercise and social contact groups had significant decreases in depressive symptoms. Only exercise resulted in decreased somatic symptoms
Nabkasorn et al. [21]	1. Aerobic exercise 2. No-treatment control	49	8	5	50	<50% HRR	Decreases in depressive symptoms were greater in the exercise group compared to a wait-list control
Pinchasov et al. [120]	1. Aerobic exercise 2. Bright light 3. No-treatment control	63	1 week	7	60	75% HRmax	Exercise and bright light groups demonstrated significant reductions in depressive symptoms
Singh et al. [22]	1. Resistance training 2. Control (health education)	32	10	3	45	80% 1-RM	Exercise group had significantly reduced depressive symptoms and higher rates of treatment response compared to the control group
Singh et al. [23]	1. Resistance training 2. Control (health education)	32	20	3	45	80% 1-RM	Depressive symptoms were significantly lower in the resistance training group. The difference in depressive symptoms between the groups remained at a 26 month follow-up
Singh et al. [24]	1. High dose resistance training 2. Low dose resistance training	60	8	3	60	80% 1-RM	HD resistance training group had significantly greater reductions in depressive symptoms compared to the other two groups. No significant difference between the low dose and standard care groups. Participants in the high dose group were also more likely to achieve a clinical response

(*continued*)

TABLE 118.1 (continued)
Trials Examining Efficacy of Exercise in the Treatment of MDD

Study	Comparison Group(s)	*N*	Intervention Length (Weeks)	Exercise Frequency (per Week)	Bout Duration (min)	Intensity	Outcome
Trivedi et al. [35]	1. High dose aerobic exercise 2. Low dose aerobic exercise	126	16	NA	NA	NA	No significant difference in remission rates between HD and LD exercise
Veale et al. [121]	1. Aerobic exercise 2. No-treatment control	83	12	3	NA	NA	Augmenting treatment with exercise did not result in significantly greater reductions in depressive symptoms

Exercise versus Established Treatments

The studies described earlier compare exercise to some version of control group. Further studies have been conducted comparing exercise to established treatments for MDD. Blumenthal et al. [30] conducted an RCT in which participants were randomized to one of three conditions: aerobic exercise, an SSRI (sertraline), or a combination of exercise and medication. There were no significant differences in depressive symptoms among the three groups following 16 weeks of treatments. However, the SSRI group showed a more rapid response compared to the exercise and combination groups. At a 6 month follow-up, the exercise group demonstrated lower rates of MDD and engaging in exercise significantly predicted presence of MDD, while continued use of SSRI did not significantly predict presence of MDD [31].

Blumenthal et al. [20] randomized participants to one of four groups: two supervised aerobic exercise, home-based aerobic exercise, SSRI (sertraline), and placebo. The three active treatments resulted in higher remission rates compared to the placebo group, yet there were no differences in remission rates among the three active treatment groups. Similarly, one published trial has compared an exercise intervention to psychotherapy. Klein [32] found no significant difference in changes in depressive symptoms between exercise and group psychotherapy. These findings are further supported by the Rethorst et al. [27] meta-analysis, which also included the results of unpublished studies and reported no difference in effect size in studies comparing exercise to SSRI or psychotherapy.

Exercise as an Adjunctive/Augmentative Therapy

In addition to trials that have examined the efficacy of exercise as a monotherapy, trials have also examined the efficacy of exercise as an adjunctive or augmentative therapy. As previously mentioned, Blumenthal et al. [30] examined exercise as an adjunctive treatment by including a group that received both SSRI and aerobic exercise. While this group demonstrated significant reductions in depressive symptoms, this decline in depressive symptoms was not significantly different from those who received only SSRIs or aerobic exercise.

In an open label trial, augmentation with an aerobic exercise intervention resulted in reductions in depressive symptoms [33]. Additionally, two RCTs to date have examined exercise as an augmentative treatment for non-remitted MDD. Mather [34] randomized older adults who had received at least 6 weeks of antidepressant medications without a sustained response to either aerobic exercise or health education classes. Following a 10 week intervention, the exercise group had a significantly higher response rate (defined as a decrease of 30% or more on the Hamilton Ratings Scale for Depression) compared to the health education group. Trivedi et al. [35] compared the efficacy of two doses of aerobic exercise as augmentation for non-remitted MDD. In this study, non-remission was defined as residual depressive symptomatology following 2–6 months of SSRI treatment. Following the 12 week intervention, both groups had significant increases in remission rates, and there was a trend toward higher remission rates in the high dose exercise group, though the difference between the two groups was not significant.

Exercise Prescription

While there is substantial evidence supporting the use of exercise in the treatment of MDD, research has not provided a clear indication of the proper dose of exercise needed to elicit an antidepressant effect. Complicating the matter is the fact that several aspects of the exercise intervention could potentially influence the efficacy of the intervention including session frequency, session duration, exercise intensity, intervention duration, and exercise modality (Table 118.2).

Session Frequency and Duration

Exercise intervention trials in participants with MDD have varied in frequency of exercise sessions (i.e., the number of sessions per week). While most interventions have consisted of three exercise sessions per week, others have included session frequencies ranging from two sessions per week to five sessions per week. Dunn et al. [19] found no difference in effect between groups exercising three times per week versus five times per week. This finding is supported by meta-analytic results demonstrating no difference in effect sizes across trials with different session frequency [27].

Typically, exercise has been prescribed in terms of session duration, in which participants exercise for a set amount during each session. The session duration used in trials for

TABLE 118.2
Summary of Exercise Dosing Recommendations for Patients with MDD

Exercise modality
- Aerobic exercise or resistance training

Exercise session frequency
- 3–5 sessions per week. No evidence to support differential efficacy within that range

Exercise session duration
- 30–60 min. Meta-analytic support for sessions lasting 45–60 min
- Session duration can also be determined by energy expenditure. Weekly doses of 12–16 KKW can be equally divided over the weekly sessions

Exercise intensity
- Aerobic exercise: 50%–85% of HRmax. No evidence to support differential efficacy within that range
- Resistance training: 80% 1-RM results in greater reductions in depressive symptoms than 20% 1-RM
- Intervention duration
- At least 10 weeks. Greater reductions in depressive symptoms are observed in intervention lasting 10 weeks or more

MDD has usually ranged between 30 and 60 min. To date, no trial has directly compared interventions of differing session duration. However, examination of moderating variables in the Rethorst et al. [27] meta-analysis suggest that sessions lasting 45–59 min are most effective.

Another approach to prescribing exercise has been through calculation of caloric expenditure. For example, Trivedi et al. [35] and Dunn et al. [19] prescribed exercise dose based on KKW. Dunn et al. compared low dose (7 KKW) to high dose (17.5 KKW). In this trial, the high dose exercise resulted in greater reductions in depressive symptoms, suggesting that there is a minimum dose of exercise needed to elicit an antidepressant response. The Dunn et al. [19] trial suggests that the total amount of exercise completed may be more important in determining the optimal exercise dose than session frequency or session duration.

Exercise Intensity

Exercise intensity for aerobic exercise is typically quantified as a percentage of an individual's maximum heart rate (HRmax). One shortcoming in previous research in this area is the lack of adequate monitoring of exercise intensity. Some trials have not monitored exercise intensity or have allowed participants to "self-select" exercise intensity. Among those trials that did monitor exercise intensity, the prescribed exercise intensity ranged from 50% to 85% of HRmax. No trial has compared the efficacy of various exercise intensities in reducing depressive symptoms, though the Rethorst et al. meta-analysis found no difference in effect size across trials based on exercise intensity.

Exercise intensity for resistance training is typically quantified by percent of one-repetition maximum (1-RM; i.e., the maximum weight that can be lifted one time). Both trials conducted by Singh et al. [22,24] prescribed resistance training at 80% of 1-RM, though Singh et al. [24] compared this intensity of resistance training to a group of lower intensity resistance training at 20% of 1-RM. The results of this trial suggest a dose-response relationship between resistance training intensity and changes in depressive symptoms as the high dose group (80% 1-RM) had significantly greater reductions in depressive symptoms, while the low dose group (20% 1-RM) did not differ significantly from a usual care control group.

Intervention Duration

Transient reductions in depressive symptoms are observed immediately following an acute bout of aerobic exercise [36]. However, sustained reductions in depressive symptoms require intervention durations of several weeks or months. Previous trials have reported significant reductions in depressive symptoms in as little as 4 weeks, though most trials have treatment periods of several months. Meta-analytical results suggest that longer intervention durations may be more efficacious in reducing depressive symptoms in patients with MDD. Rethorst et al. [27] report larger effect sizes in trials of 10 weeks or longer compared to those trials with intervention durations of 4–9 weeks.

Exercise Modality

The majority of trials examining the antidepressant effects of exercise have used aerobic exercise activities (i.e., walking, running, cycling, or a combination of these activities). Though as previously noted, other trials have shown the efficacy of resistance training in reducing depressive symptoms [22,24]. However, there are no indications currently that one modality of exercise is more efficacious in treating MDD. One trial has directly compared differing modalities, finding no difference between an aerobic exercise group and a resistance training group [37], while meta-analytic results have revealed no difference in effect size between the two modalities [27].

Adherence to Exercise Interventions

Ultimately, the aim of prescription of exercise as a treatment for MDD is to individualize treatments to optimize patient outcomes. This requires identification of factors that may influence response to treatment. One of the largest influences on treatment efficacy is treatment adherence. It has been postulated that exercise may be unsuccessful as a treatment for MDD due to the belief that patients with MDD will not adhere to an exercise program. However, in studies that have compared exercise interventions to SSRIs, there are no statistical differences in treatment adherence between the two treatments [20,30]. Furthermore, the Rethorst et al. [27] meta-analysis calculated the adherence rates of trials included and found a dropout rate of 14.6%. This rate is comparable to dropout rates observed in groups receiving SSRIs and psychotherapy [38,39].

Additional strategies can be used in conjunction with an exercise intervention to improve adherence. First, the

intervention itself can be modified to improve adherence. For example, Blumenthal et al. [20] found better adherence to a home-based exercise compared to laboratory-based exercise. In another study, Dunn et al. [19] found altering session frequency (3/week vs. 5/week) resulted in no difference in adherence. Additionally, psychosocial strategies may be effective in increasing adherence to an exercise intervention. While there is strong evidence for the use of psychosocial interventions to increase physical activity [40–42], none have examined this in a depressed population. However, Trivedi et al. [35] did implement a web-based approach to monitor adherence and provide psychosocial support.

Reduction of Depressive Symptoms in Diseased Populations

In addition to trials examining the effect of exercise in individuals with MDD, another group of trials have examined the effect of exercise on depressive symptoms in diseased populations. Comorbid depressive disorders are commonly observed among individuals with chronic diseases. In addition to the burden associated with a MDD, the comorbidity of MDD is often associated with poorer disease outcomes due to a reduction in treatment adherence associated with the presence of a depressive disorder.

Cardiovascular Disease

Given the role of exercise in the prevention and treatment of cardiovascular disease, there have been several trials that have examined the effects of an exercise program on depressive symptoms in cardiovascular disease patients. Blumenthal et al. [43] found that participants with ischemic heart disease randomized to a 16 week aerobic exercise intervention had significantly lower BDI scores compared to participants receiving usual care. In another trial, participants with chronic heart failure randomized to an aerobic exercise intervention had significantly lower BDI scores compared to the treatment as usual (TAU) group [44]. Similarly, Kulcu et al. [45] found a significant decrease in BDI scores following 8 weeks of aerobic exercise in patients with congestive heart failure compared to TAU.

Other Diseases

While the number of trials in other diseased populations is not as large as in cardiovascular disease, research has examined the effects of exercise on depressive symptoms in patient populations with fibromyalgia, cancer, and chronic obstructive pulmonary disease (COPD). Patients with fibromyalgia display lower levels of depressive symptoms following exercise interventions [46,47]. Similarly, patients with COPD have reductions in depressive symptoms following an exercise intervention [48,49]. In patients with cancer, trials have examined the effects of exercise both during and following treatment. The outcomes of these trials are not always focused on depressive symptoms, and the results of those trials that did assess depressive symptoms are equivocal [50]. However, there are clear psychological benefits from exercise in cancer patients including decreased fatigue, increases in positive mood, and improved quality of life [44,51].

Mechanisms of the Antidepressant Action of Exercise

Several mechanisms have been proposed to explain the antidepressant action of exercise. These mechanisms typically fall into one of two categories: neurobiological markers and psychosocial factors.

Serotonin

Serotonin is the neurobiological marker most commonly associated with MDD. Low levels of plasma serotonin have been widely observed in patients with MDD [52]. Furthermore, SSRI medications target the release and reuptake of serotonin. SSRIs act on the serotonergic system by inhibiting 5-HTT and thus decreasing the reuptake of 5-HT from the synaptic cleft [53]. SSRI treatment has been associated with decreases in platelet, plasma, serum, and whole-blood serotonin levels [54–58].

Exercise has been found to alter function of the serotonergic system. Similar to SSRIs, exercise results in a decrease in serum 5-HT [59] and decreases in 5-HT_{2A} receptor densities [60,61]. Exercise also results in increases in tryptophan hydroxylase [62], which is necessary for serotonin synthesis. Furthermore, results of animal studies indicate that physical activity can increase the neural discharge of serotonin [52,62], increases in tryptophan levels in the raphe nucleus [63–65] and hippocampus [62], and increased serotonin metabolism [66–68].

Brain-Derived Neurotrophic Factor

Research indicates that brain-derived neurotrophic factor (BDNF) is thought to play a role in the development and treatment of MDD. Serum BDNF is lower in untreated MDD patients and inversely correlated with symptom severity [69]. In response to treatment, BDNF levels are increased following treatment with antidepressant medication [70] and ECT [71]. Similarly, an acute bout of aerobic exercise results in an increase in serum BDNF in patients with MDD [72,73]. In healthy subjects, chronic aerobic exercise results in an increased release of BDNF [74].

Hypothalamic-Pituitary-Adrenal Axis

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been associated with MDD. Patients with MDD demonstrate elevated levels of cortisol in plasma and urine [75–77], increased corticotropin-releasing factor (CRF) in cerebral spinal fluid [78,79], and increased size and activity of the pituitary and adrenal glands [80]. Patients with MDD also demonstrate increased HPA reactivity to psychological stress [81] and dexamethasone (DEX) [82]. Finally, there are indications that normalizing regulation of the HPA-axis indicates treatment response for MDD, as normalized response to DEX following SSRI treatment initiation can predict future remission [83,84].

Evidence also suggests alterations in the HPA-axis in response to exercise. Bouts of acute aerobic exercise result in

increased cortisol excretion, while chronic aerobic exercise is associated with reduced cortisol excretion [21]. Furthermore, physical fitness is associated with reduced cortisol response to stress in the form of exercise [85] and psychological stress [86]. These findings are supported by a wealth of animal research demonstrating altered HPA-axis response to stressors following chronic exercise training [87–89].

Endocannabinoids

Recent research has implicated endocannabinoids in the etiology and treatment of MDD [90]. Patients with MDD demonstrate lower levels of endocannabinoid ligands serum 2-arachidonylglycerol (2-AG) and anandamide [91,92], while the level of 2-AG is negatively correlated with the duration of the current depressive episode [92]. Studies in rats indicate that endocannabinoid receptor CB_1 antagonists produce antidepressant effects [93,94], while administration of fluoxetine results in a decrease in CB_1 gene expression [95].

A single bout of aerobic exercise in humans results in an increase in anandamide, suggesting that exercise activates the endocannabinoid system [96]. In an animal model, CB_1 gene expression is reduced with chronic aerobic exercise [97], mirroring the effect of fluoxetine of CB_1 gene expression. Exercise also alters CB_1 receptor sensitivity [98]. Furthermore, this altered sensitivity following exercise associated with a protective effect against exposure to stress [98]. Chronic exercise also increases CB_1 receptor density, resulting in increased proliferation of progenitor cells in the hippocampus. This increase in progenitor cell proliferation was attenuated through administration of a CB_1 receptor antagonist, thus highlighting the role of the endocannabinoid system in exercise-induced neurogenesis [99].

Psychosocial Factors

In addition to the neurobiological mechanisms described earlier, psychosocial factors may also play a role in the antidepressant effects of exercise. Low self-efficacy is often associated with depressive symptoms [100]. It has been proposed that self-efficacy can be improved through physical activity [101,102]. Trials in patients with MDD consistently report an increase in self-efficacy following chronic exercise [103–105], and these increases in self-efficacy are associated with a decrease in depressive symptoms [104]. Another construct proposed as a mechanism for the antidepressant action of exercise is distraction. It has been postulated that exercise can serve as a distraction from stress and therefore reduce depressive symptoms [106,107]. However, Craft [104] found no significant difference in distraction following an aerobic exercise intervention in women with MDD.

Future Directions

Research to date supports the efficacy of exercise interventions in the treatment of MDD. However, the quality of some of this research has been scrutinized [25,108]. These criticisms include the absence of clinical interviews to confirm MDD diagnosis, the lack of proper treatment allocation concealment, and a paucity of studies using intent-to-treat analysis. Therefore, it is vital that future research in the area adheres to strict scientific methodology.

In addition, several other areas for research will further clarify and define the role of exercise in the treatment of MDD. First, while there is evidence for a dose-response relationship, the combination of time, frequency, and intensity of exercise required for the optimal reduction of depressive symptoms has not been identified. Not only will this maximize the treatment effect, but identifying the appropriate dose of exercise is also important to allow physicians to provide a clear exercise prescription to patients. In addition, further work should continue to explore the role of exercise as an adjunctive or augmentation treatment. Integrating exercise with established treatments has the potential to maximize treatment in a population that typically has modest response to treatment. Results from previous trials suggest that exercise may be especially effective in maintaining treatment effects [23,31] and as a treatment for individuals who do not fully respond to initial SSRI treatment [34,35]. Finally, despite epidemiological evidence suggesting the protective effect of physical activity on future MDD, no trial has prospectively examined the preventive effects of exercise.

Considering the relatively low rates of treatment response in MDD, recent research has focused on identifying moderators of treatment efficacy. Identified moderators of antidepressant treatments range from demographic and psychosocial factors to candidate genes. In the STAR*D study, gender, race, employment status, income, and comorbid psychiatric disorders all moderated treatment efficacy [11]. Additionally, candidate genes such as the serotonin transporter gene, 5-HTTLPR, have been proposed to have a role in the etiology and treatment of depression [109–111]. Several studies have shown the *s* allele of 5-HTTLPR to be associated with lower remission rates following SSRI treatment as well as higher negative side effects associated with SSRI treatment [112].

Similarly, these factors are likely to moderate the changes in depressive symptoms following exercise. Trivedi et al. [35] report gender and family history of depression to moderate response to exercise in patients with non-remitted MDD. In this study, men and women with a family history of MDD had higher remission rates to high dose exercise, while women without a family history of MDD had higher remission rates with low dose exercise. There is also evidence for genetic moderation of treatment response to exercise. Given the potential role of the serotonergic system and BDNF in the antidepressant effects of exercise, it is plausible that these two candidate genes impact the treatment effect of exercise on MDD. In fact, one trial examined the moderating effect of 5-HTTLPR in a healthy sample, finding that the *s* allele was associated with a blunted antidepressant response to exercise [113]. Further evidence for genetic moderation of the antidepressant effect of exercise is seen in cross-sectional data. Mata et al. [114] report that the relationship between physical activity and depressive symptoms in a sample of adolescent

females is moderated by the BDNF gene. In this sample, physical activity was associated with lower levels of depressive symptoms in individuals with at least one *met* allele of the BDNF gene, while there was no association between physical activity and depressive symptoms in individuals with the *val/val* BDNF genotype.

Finally, the role of exercise in the treatment of MDD will ultimately depend on treatment professionals being willing and properly educated to prescribe exercise to their patients. Recent data indicate that only 5% of general practitioners include exercise as one of their most recommended treatments for MDD, compared to 92% for antidepressant medications. This disparity is likely due to the fact that only 41% of general practitioners believe exercise to be "very effective" or "quite effective" in treating MDD [115]. However, in the American Psychiatric Association's updated Guidelines for Treatment of MDD [116], exercise is now included as a treatment recommendation. Along with the growing evidence supporting the antidepressant effects of exercise, this recognition by an influential professional association will hopefully encourage more treatment professionals to consider the use of exercise in the treatment of MDD.

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119 Redrawing the Model of the Exercising Human in Exercise Prescriptions

From Headless Manikin to a Creature with Feelings

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CONTENTS

Spectacular Triumphs....1421
Epic Failures....1423
Exercise Is Medicine but What Should Be in the Prescription?....1424
Exercise Prescriptions as a Motivational (and Demotivational) Force....1425
If the Product Is So Good, Why Are We Still Failing in Marketing It?....1425
Pleasure as the Missing Essential Ingredient....1428
An Illustrative Example: The Boom–Bust Hypothesis of Exercise Behavior in Obesity....1430
References....1431

Please answer this simple pop-quiz question. Exercise and physical activity should be (a) effective in promoting health, (b) as safe as possible, (c) pleasant and enjoyable, (d) a and b, or (e) a, b, and c. If you answered (e), you might be surprised to learn that, according to the logic behind most of the contemporary exercise prescription guidelines and physical activity recommendations, your answer would be incorrect; the "correct" answer is (d). At least in the United States, such guidelines and recommendations have traditionally been developed based on a biomedical model, focusing strictly on effectiveness and safety and incorporating little or no evidence from psychology, behavioral economics, marketing, or the behavioral sciences in general.

The history of exercise science over the second half of the twentieth century is filled with spectacular triumphs but also some epic failures. The successes consist in discovering a wealth of scientific evidence supporting the beneficial effects of physical activity on health and raising the awareness not only of the medical community but also of the public at large. The failures are the result of the inability to raise the rates of physical activity participation, which remain discouragingly low in most industrialized countries. This chapter will specifically focus on the possible role played by exercise prescription guidelines and physical activity recommendations in these failures. These documents are criticized for lacking an overarching philosophy, containing numerous inconsistencies and conflicting messages, and having persistently neglected the importance of how exercise is experienced. Finally, a proposal is put forth for considering pleasure as a fundamental criterion when exercise is prescribed or physical activity is recommended. Ensuring that exercise and physical activity are not just effective and safe but also pleasurable can increase the chances that these behaviors will become lifelong habits. In turn, this may help the field of exercise science succeed in its central mission of promoting human health by increasing the number of people who have permanently integrated exercise and physical activity into their lives.

SPECTACULAR TRIUMPHS

A perusal of the medical literature over the past 60 years offers some perspective on the colossal attitudinal shift that has occurred in the biomedical community with respect to the public health value of exercise. The first substantial scientific evidence supporting a role of physical activity in health came from a series of studies conducted by the epidemiologist Jeremy Morris with British civil servants. Perhaps cognizant that they were addressing a skeptical readership, Morris et al.[1] were extremely circumspect in their analyses and interpretations, emphasizing that "we are dealing with what is still hypothesis rather than established fact" (p. 1120). They showed that "bus conductors (on double-decker vehicles) were found to have less coronary heart-disease than bus drivers, and postmen less than telephonists, executive officers, and clerks"; and on the basis of these findings, they proposed that "men in physically active jobs have a lower incidence of coronary heart disease in middle age than have men in physically inactive jobs" (p. 1120). In the following years, despite additional data, the hypothesis that physical activity may have a cardioprotective effect was viewed as a marginal and odd idea. Its impact on research was minimal and, on medical practice, practically nonexistent. Following another

publication by Morris' group in the early 1970s, the famous mile-runner and neurologist Roger Bannister[2] wrote a letter to *The Lancet* expressing his frustration: "Perhaps instead of reaching for the prescription pad we should help to swing our patients over to a more positive view of health so that they change their life style to include sufficient exercise" (p. 613).

In the United States, a landmark report published in 1970 by the Inter-Society Commission for Heart Disease Resources, entitled *Primary Prevention of the Atherosclerotic Diseases*,[3] included "sedentary living" among a list of possible secondary risk factors but stressed that the evidence linking it to coronary heart disease was "not entirely consistent" and that "the apparent impact… observed in some studies is less than that for the major risk factors" (p. A-71). Along the same lines, an additional statement that "exercise … may have a role to play in the prevention of atherosclerotic diseases" was immediately juxtaposed with the warning that "exercise is not free of danger both to the musculoskeletal and the cardiovascular systems" (p. A-89). This view remained prominent during the 1970s. Discussing data from the Framingham study, for example, Kannel and Sorlie[4] commented: "It has not yet been convincingly or consistently established that physical activity is an important determinant of the degree to which the major risk factors exist in the general population. Nor has it been conclusively shown that the protective role of physical activity found by some is the result of a favorable influence on the established major cardiovascular risk factors" (p. 860). Furthermore: "It does not seem likely that exercise programs can make as great an impact on incidence of cardiovascular disease as can control of blood pressure, the cigarette habit, obesity, or hyperlipemia" (p. 860). Echoing an argument that was commonly expressed at the time, Kannel and Sorlie[4] alerted physicians to the fact that "data from eastern Finland, where physical activity levels are high, record an incidence of ischemic heart disease that is the highest observed anywhere" (p. 860).

Reading these passages today, one cannot but be amazed by how parochial or even shortsighted they seem. In 1992, a committee of the American Heart Association[5] first declared that "inactivity is recognized as a risk factor for coronary artery disease" (p. 340). This was followed in 1995 by the first physical activity recommendations specifically developed for health promotion, published jointly by the Centers for Disease Control and Prevention and the American College of Sports Medicine (ACSM).[6] In 1996, the U.S. Department of Health and Human Services published a landmark Surgeon General's report[7] on the relationship between physical activity and health. Conducted by a panel of internationally recognized experts, this thorough analysis of the epidemiologic and experimental evidence led to the conclusion that "physical activity of the type that improves cardiorespiratory endurance reduces the risk of developing or dying from cardiovascular disease (coronary heart disease in particular), hypertension, colon cancer, and non-insulin-dependent diabetes mellitus and improves mental health" (p. 149). Furthermore, according to the report, the "findings are highly suggestive that endurance-type physical activity may reduce the risk of developing obesity, osteoporosis, and depression and may improve psychological well-being and quality of life" (p. 149).

In 2003, a report[8] developed by a committee of the American Health Association, entitled *Exercise and Physical Activity in the Prevention and Treatment of Atherosclerotic Cardiovascular Disease*, stated, in no uncertain terms, that habitual physical activity "prevents the development of coronary artery disease (CAD) and reduces symptoms in patients with established cardiovascular disease. There is also evidence that exercise reduces the risk of other chronic diseases, including type 2 diabetes, osteoporosis, obesity, depression, and cancer of the breast and colon" (p. 3109). Referring specifically to atherosclerosis, the committee declared:

> The data satisfy the criteria required to infer a causal relationship from epidemiological evidence. The results are strong, with the most physically active subjects generally demonstrating CAD rates half those of the most sedentary group. The data demonstrate a graded relationship of decreasing CAD rates with increasing levels of activity… Physical activity both prevents and helps treat many established atherosclerotic risk factors, including elevated blood pressure, insulin resistance and glucose intolerance, elevated triglyceride concentrations, low high-density lipoprotein cholesterol concentrations, and obesity (p. 3110).

Interestingly, the committee also encouraged physicians to "personally engage in an active lifestyle to… set a positive example for patients and the public" and recommended that information about the importance of physical activity for health "be incorporated into the education of physicians and other medical professionals" (p. 3114). In 2007, for the first time, the American Heart Association published physical activity guidelines[9] jointly with the ACSM, emphasizing that "frequent physical activity is an important behavior for individual and population health" (p. 1431). The culmination of more than five decades of research came with the publication of the first *Physical Activity Guidelines for Americans* by the U.S. Department of Health and Human Services in 2008.[10]

Besides these undeniable triumphs on the scientific front, there have also been some notable advances in communicating the message about the healthful effects of physical activity to the public. Of the 2002 U.S. adults surveyed by Morrow et al.,[11] representing the 48 contiguous states and the District of Columbia, 84% knew that physical inactivity was related to the development of heart disease. Furthermore, 97% identified physical inactivity as a health risk factor, with 52% rating it as "very important," 37% as "important," and 8% as "somewhat important."[12] Analyses of media coverage of stories about the effects of physical activity on health in western countries have shown that the topic receives some prominence, even if the journalistic quality of the articles is less than optimal[13] or if physical activity is allotted less space than other lifestyle factors, such as obesity or smoking.[14]

EPIC FAILURES

One might have expected that the staggering accumulation of scientific evidence over the past 60 years and the heightened awareness of the health benefits of physical activity among health care providers and the public would have begun to influence the rates of participation in physical activity. Unfortunately, this has not happened. Discovering and disseminating information, which is an intervention strategy credited with success in promoting other health behaviors (e.g., greatly reducing the rates of cigarette smoking or containing the HIV/AIDS epidemic), appears to have been largely ineffective in the case of physical activity.

A few years ago, an analysis of data from the Behavioral Risk Factor Surveillance System (BRFSS), which is a nationwide survey conducted by telephone, gave the impression that there might be some cause for optimism, showing that "from 2001 to 2005, the prevalence of regular physical activity increased by 8.6% (from 43.0% to 46.7%) among women overall and by 3.5% (from 48.0% to 49.7%) among men" (p. 1210).[15] The exuberance, however, was short lived. The final progress review of the Healthy People 2010 program,[16] which was based on data from the National Health Interview Survey (NHIS), collected from in-home (face-to-face) interviews, stated that "individual physical activity behaviors for adolescents and adults are essentially unchanged since baselines were established" (p. 2). Specifically, the percentage of adults who reported no participation in any leisure-time physical activity was 40% in 1997 and 39% in 2006.

As sobering as these statistics might seem, the problem of physical inactivity in the United States was shown to be significantly more severe when data from the 2003–2004 National Health and Nutritional Examination Survey (NHANES), in which physical activity was measured objectively by accelerometry ($N = 6329$), were analyzed.[17] Among adults between the ages of 20 and 59 years, only 3.5% (3.8% of men, 3.2% of women) participated in bouts of at least moderate-intensity physical activity totaling at least 30 min/day on at least 5 days/week. For those over the age of 60 years, the percentage was even lower, at 2.4% (2.5% of men, 2.3% of women). A latent class analysis[18] of the same data set showed that, when every minute of activity was considered, 78.7% of the population was included in two least active classes (33.6% averaging 5.3 min and 45.1% averaging 21.0 min of moderate-to-vigorous physical activity per day). When only activity performed in bouts of at least 10 min was considered (during which at least 70% of the counts were above the threshold for moderate-to-vigorous activity), 93.5% of the population was included in the two least active classes (56.1% averaging nearly zero and 37.4% averaging 10.3 min of moderate-to-vigorous physical activity per day). The data for vigorous activity were even more disconcerting. In 91.1% of all days, participants accumulated less than 1 min of vigorous physical activity. Of 3462 participants who provided valid data for at least 3 days, only 23 registered 20 min of vigorous physical activity on at least 3 days/week.

Although there is still no systematic study of objectively assessed rates of physical activity within special populations, data derived from self-reports suggest that individuals who face physical or psychological challenges tend to be even less active than the general population. A case in point is obesity, a condition for which regular physical activity would be of great benefit. According to data[19] from the 2000 BRFSS, 59.9% of overweight women and 35.9% of overweight men (i.e., with a body mass index (BMI) ≥ 25 kg/m^2) as well as 70.0% of obese women and 62.8% of obese men (i.e., with a BMI ≥ 30 kg/m^2) reported trying to lose weight. Approximately two-thirds of them reported using physical activity as part of their weight-loss efforts. However, only 19.8% of the overweight women and 22.8% of the overweight men reported combining a reduction in caloric intake and at least 150 min/week of physical activity (approximately five 30 min sessions/week). The numbers were even lower for obese individuals, with 15.9% of women and 21.3% of men reaching at least 150 min/week. Similarly, according to data[20] from the 1999–2002 NHANES, 44.7% of the overweight respondents and 61.8% of those who were obese reported trying to lose weight. However, only 30.0% of those who were overweight and 21.6% of those who were obese reported that their physical activity participation reached 600 min and 20 sessions/month or approximately five 30 min sessions/week.

Importantly, however, current recommendations for weight management set the minimum duration of daily physical activity at 60 min, twice the duration recommended for health promotion in the general population. According to data[19] from the 2000 BRFSS, only 4.1% of overweight women, 3.0% of obese women, 6.9% of overweight men, and 6.4% of obese men trying to lose weight reported reaching 420 min of activity weekly (or 60 min daily) besides restricting their caloric intake. Even in a study[21] in which participants knew that their activity was being monitored since they volunteered to wear accelerometers for 7 days, only 13% of the overweight or obese individuals accumulated 60 min of daily activity.

It is crucial to point out that the problem of physical inactivity is not merely the result of people's unwillingness to become physically active. To a large extent, it is also the result of discontinuation or "dropout." The exact magnitude of this problem is unknown. A statistic frequently reported in the literature is that 50% of those who start an activity program drop out within the first 6 months.[22] However, this number is somewhat deceptive for two reasons. First, this estimate is derived from published clinical trials, most of which include some intervention component designed to improve adherence and retention (e.g., anything from one-on-one counseling, goal-setting, social support, or efficacy-building approaches to provision of monetary incentives, free transportation, or childcare). Clearly, such benefits are absent outside the context of well-funded clinical trials. Second, the 50% figure is merely an average, which conceals the great variation that exists between studies. Dropout rates from individual published studies have ranged from a low of 9% to a high of 87%.[23]

It could be argued that the problem of dropout represents an even greater failure for exercise science and practice compared to the low rates of initial engagement. Although the responsibility for disseminating the message of physical activity is arguably shared among many stakeholders (including the media, national and state health agencies, health educators, and health care providers), the responsibility of designing and delivering exercise or activity programs that people want to incorporate into their lives on a permanent basis is primarily the responsibility of exercise scientists and practitioners.

Overall, the physical activity participation data paint a very disconcerting picture, one that stands in stark contrast to the remarkable successes on the scientific front. Exercise science has managed to uncover a wealth of evidence supporting the beneficial effects of exercise on human health and has, to a large extent, succeeded in publicizing, and even popularizing, these discoveries. On the other hand, no progress has been made in capitalizing on these remarkable scientific findings by changing behavior at the population level. For the most part, this is not due to an unwillingness to undertake policy initiatives or a lack of funds channeled into research and community outreach programs (although most researchers and practitioners would probably argue that more funds would be desirable). The culprit for the massive failure should probably be sought in an unsuccessful communication strategy and an inability to adequately prepare practitioners for their challenging mission. Addressing the problem of physical inactivity represents one of the greatest challenges in public health. Based on substantial epidemiologic evidence from the Aerobics Center Longitudinal Study that low cardiorespiratory fitness is a stronger predictor of mortality than "traditional" risk factors like hypertension, cholesterol, obesity, or smoking, Blair[24] proclaimed that physical inactivity should be recognized as "the biggest public health problem of the 21st century" (p. 1).

EXERCISE IS MEDICINE BUT WHAT SHOULD BE IN THE PRESCRIPTION?

Exercise prescription guidelines were first developed by the ACSM in the 1970s. From the beginning, the development of guidelines was driven by two main considerations: (a) maximizing the training effect, defined primarily as an increase in cardiorespiratory fitness (VO_2max) and (b) reducing the risk of adverse cardiac, skeletal, or muscular events, especially among individuals exercising in clinical or rehabilitation settings (e.g., pre- or postinfarct cardiac patients). Issue (a) pertains to cardiac, respiratory, and muscular (energy-system) adaptations and, thus, falls within the area of expertise of exercise physiologists, many of whom have backgrounds in sport and human performance. Issue (b) pertains to pathology and is, thus, within the purview of physicians. Four decades after the development of the first guidelines, the panel of experts convened by the ACSM to update the guidelines reportedly took into account the same two considerations: (a) "the dose that induces the greatest health benefit" and (b) "the potential risk in a particular population" (p. 133).[25]

As the aforementioned participation and dropout data illustrate, however, a program that is effective and safe may not necessarily be one that people want to follow. This brings up the crucial, yet seldom discussed, issue of the philosophy undergirding exercise prescriptions and physical activity recommendations. What should be the prime objective of such prescriptions or recommendations? What the public or each individual client is advised might differ, perhaps considerably so, if the prime objective, for example, is to stimulate the largest possible gain in cardiorespiratory fitness (or any other beneficial physiological adaptation) in the shortest amount of time compared to instilling a lifelong habit of physical activity. In the former case, developing a prescription based on the traditional bipartite rationale of effectiveness and safety could be sufficient. However, in the latter case, incorporating some additional considerations, beyond just effectiveness and safety, would probably be necessary. Although it is becoming increasingly clear that views on this subject within the field of exercise science diverge, an open debate has yet to take place.

The absence of a consistent guiding philosophy is evident in the guidelines issued by most scientific and professional organizations. It is interesting, for example, that a statement favoring behavior change as the prime objective of exercise prescriptions in the seventh edition of the ACSM guidelines[25] ("the most appropriate exercise prescription … is the one that is most helpful in achieving… behavioral change" [p. 136]) was edited out in the eighth edition.[26] Although a clear statement of philosophy is also missing from the guidelines[27] issued by the British Association of Sport and Exercise Sciences, it is reassuring to note that this document at least acknowledges some of the challenges faced by beginner exercisers, including the fact that the exercise may be too "demanding" (p. 585). Along the same lines, it is striking that, although activity guidelines for overweight and obese participants calling for at least 60–90 min of daily activity had been criticized as "too daunting" (p. 769)[28] and "too ambitious" (p. 2264),[21] the latest ACSM[29] and European College of Sport Science[30] position stands contain no mention of this challenge or the shockingly low participation rates among overweight and obese individuals. Likewise, several scientific groups have concluded that "adherence is lower with higher-intensity exercise programs" (p. 142)[25] and that "moderate-intensity physical activities are more likely to be continued than are high-intensity activities" (p. 243).[31] Nevertheless, in recent years, several authors have advocated higher intensities for cardiac adaptations,[32] weight management,[33] and health in general,[34,35] without addressing the implications of their suggestions for long-term motivation and adherence.

Presumably, guideline documents are revised following extensive debate among experts. So, an inspection of historical trends may be a good basis for deciphering the changing conceptual and philosophical undercurrents in this field. An analysis of the eighth edition of the ACSM guidelines[26] would suggest a resistance to the idea that exercise prescriptions may have to involve creative combinations of art and science. Furthermore, the notion that the ultimate goal of the

guidelines is to facilitate the instillation of a lifelong activity habit, a goal that necessitates input from psychology, is apparently viewed with ambivalence. It would be wonderful if the maximization of effectiveness, the ascertainment of safety, and the promotion of lifelong activity could all be accomplished within the same prescription. However, in many cases, this might not be feasible. This is why a clear philosophical stance on what the prime objective should be is of such fundamental importance. If we cannot accomplish all three objectives simultaneously, then having a crystalized consensus on a prime, overarching objective is the only way to develop a workable solution. Dishman[36] recognized this challenge approximately 30 years ago, when he wrote that "although exercise prescriptions based strictly on objective thresholds of energy demand or heart rate may optimize physiological adaptations, they may also minimize the chances that certain individuals will adhere to that prescription" (p. 174). He urged exercise scientists and practitioners to seek "some compromise between the ideal physiological prescription and a manageable behavioral prescription … to allow adherence to be sufficient for desired biological changes to occur" (p. 248).[37] Decades later, very limited progress appears to have been made on this front.

EXERCISE PRESCRIPTIONS AS A MOTIVATIONAL (AND DEMOTIVATIONAL) FORCE

In an exceptionally insightful review of the history of exercise prescriptions and physical activity recommendations in the United States, Blair et al.[38] offer a rare glimpse into the "battle of paradigms" that has taken place within the field. They identify the early 1990s as a turning point, at which the first realization was made that guidelines, besides serving as a technical aid to practitioners worldwide, also function as a communication and marketing apparatus whose echoes can influence public behavior. By specifying the minimum recommended dose of activity, the guidelines let the public make important judgments that have direct impact on behavioral decision making. These include, for example, whether the recommended dose is attainable or unrealistic, or whether exercising for a given amount of time or up to a given intensity is "worth doing."

According to Blair et al.,[38] a sense began to develop that the ACSM guidelines "led to somewhat regimented thinking about how much exercise should be recommended, … [causing] most persons to think that exercise not meeting these specific criteria would be of limited or no value" (p. 915S). In particular, exercise intensity emerged as a possible culprit, responsible for intimidating large segments of the sedentary public. This was first expressed in the 1990 ACSM position stand[39] on *The Recommended Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory and Muscular Fitness in Healthy Adults*, which stated that the "ACSM recognizes the potential health benefits of regular exercise performed more frequently and for a longer duration, but *at lower intensities* than prescribed in this position statement" (p. 266, emphasis added).

Along similar lines, the fifth edition of the ACSM guidelines[40] was prefaced with the statement: "It is increasingly clear that less regimented approaches are needed in community health and activity promotion efforts. The vast majority of physically active adults are not involved in structured, formal exercise programs, nor do they need to be" (p. 3). The 1995 physical activity recommendations[6] by the Centers for Disease Control and Prevention and the ACSM, the first that introduced the idea that "moderate-intensity," ordinary lifestyle activities like fishing, home care, or lawn mowing can be beneficial for health, were explicitly aimed "to encourage increased participation in physical activity" (p. 402). The preface to the seventh edition of the ACSM guidelines[25] included the following acknowledgment: "Because Americans are highly sedentary … persuading sedentary individuals to become physically active is more likely to be successful when the target level of physical activity is moderate, rather than the traditional higher-intensity level" (pp. 5–6). These statements illustrate that, over time, the leaders in the field of exercise science became sensitized to the fact that exercise prescription guidelines and physical activity recommendations were not just that; they also played a central role in the ongoing social marketing campaign to promote physical activity to larger segments of the public. In the mid-1990s, with the advent of the simpler and less intimidating message[6] of "30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week," most exercise professionals were anticipating a significant shift in physical activity behavior. However, more than a decade and a half later, it is clear that, contrary to expectations, the new approach has not been any more successful than the previous approaches in increasing the number of people who are active enough to benefit their health.

IF THE PRODUCT IS SO GOOD, WHY ARE WE STILL FAILING IN MARKETING IT?

It seems that, more than 35 years after the first exercise prescription guidelines and with no visible improvement in the rates of physical activity participation in industrialized countries, it is time for reflection and a reconsideration of the operational plan. Clearly, there are failures in the system that must be identified and corrected. The list of systemic failures is probably long and impossible to cover in a comprehensive manner. So, emphasis here is placed on just one: confusion. There is hardly a greater impediment to the success of a marketing campaign than message confusion, and there is hardly a more potent cause of confusion than inconsistency. On this issue, the failure is pervasive, persistent, and absolute. One would be hard pressed to find another health behavior for which more sets of guidelines and recommendations have been issued, by a larger array of scientific and professional bodies, or with so many revisions and updates. Marketing experts warn that social marketing campaigns have reduced chances of success if they are subject to "contradictory counter-marketing" or the concurrent exposure

of the target market to conflicting or inconsistent messages. The social marketing of exercise and physical activity faces contradictory counter-marketing from both external and internal sources.

Examples of contradictory counter-marketing messages from sources outside of exercise science abound. Following the recommendations by the ACSM and the Centers for Disease Control and Prevention,[6] as well as the Surgeon General's report[7] extolling the virtues of moderate-intensity physical activity, a best-selling book[41] by a well-known trainer to the stars asserted that people should exercise "at the highest intensity that is safe" (p. 108). According to the same source, the appropriate intensity is one that induces "a definite feeling of fatigue" (p. 113) and takes people "past [their] level of comfort" (p. 115). Presumably, this book was read by a much larger number of people than those who turned to credible scientific sources.

One illustrative example of a contradictory message from within the domain of public health was the call by the Institute of Medicine[42] in 2002 for 60, as opposed to 30, min of daily physical activity. In a draft report that received extensive media attention, the Institute of Medicine noted that "30 minutes per day of regular activity is insufficient to maintain body weight … and achieve all the identified health benefits fully." Thus, the institute recommended that "to prevent weight gain as well as to accrue additional, weight-independent health benefits of physical activity, 60 minutes of daily moderate intensity physical activity" should be performed. In the days that followed the release of the report, news articles were as critical of the 60 min figure, which was portrayed as exorbitant, as they were of the inconsistency. A search of the news archives for September 2002 shows that, in several of the articles, the focus was not on the contents of the report as much as it was on the fact that researchers cannot agree ("How much time does it take to stay healthy? Even the experts don't agree" read one headline). An article in a major newspaper on September 30 opened with the sentence "Millions of Americans are thrown into a tizzy of confusion" and proceeded with statements from an exerciser who said that the report was "confusing" and she was "unclear about what constituted 'moderately intense' exercise." In another major newspaper, on October 7, a journalist wrote that "the recent call for 60 minutes of daily exercise has sparked plenty of confusion among consumers and heated debate among fitness experts." In an interview, a member of the public said that she "[did] not know what to think anymore… It's confusing because you hear different schools of thought all the time … You don't know what to believe."

In August 2007, the joint recommendation[9] by the ACSM and the American Heart Association specified that each American adult should "perform moderate-intensity aerobic (endurance) physical activity for a minimum of 30 min on five days each week or vigorous-intensity aerobic activity for a minimum of 20 min on three days each week" (p. 1431). Thus the minimum recommended duration per week amounted to 150 min of moderate or 60 min of vigorous activity. Only 14 months later, in early October 2008, the Department of Health and Human Services published the first *Physical Activity Guidelines for Americans*.[10] Although the minimum recommended duration of moderate activity per week was also 150 min (2 h and 30 min), the minimum recommended duration for vigorous activity was not 60 but 75 min/week (1 h and 15 min).

Confusion can even be generated within the same document, by statements that do not appear to be entirely consistent. For example, in the physical activity recommendations[10] for adults issued by the ACSM and the American Heart Association, the purpose of which reportedly was to clarify some of the inconsistencies and confusing aspects of previous recommendations, some points seem hard to reconcile. On the one hand, the document advises the public that "individuals should start at the lower end of this range when beginning an activity program" (p. 1428) and warns that, by exceeding the minimal recommendations, the "musculoskeletal health risks are increased as well, possibly negating some of the added benefit" (p. 1430). On the other hand, the public is also advised that adults who "wish to improve their personal fitness or further reduce their risk for premature chronic health conditions and mortality related to physical inactivity *should* exceed the minimum recommended amounts of physical activity" (p. 1426, emphasis added). It is also noteworthy that issues of adherence and dropout are not addressed anywhere in this document, which is strictly based on a consideration of effectiveness and risk.

Moreover, confusion can be generated by a lack of specificity. For example, in exercise prescription guidelines, the standard approach since the 1970s has been to recommend a broad range of frequencies, durations, and intensities. These ranges are reportedly "intentionally broad" (p. 141)[25] in order to accommodate the widest possible array of individual capabilities and preferences. However, finding the level that is appropriate for each individual is left on the individual and his or her advisors (health care provider, exercise leader, or rehabilitation specialist). The guidelines do not (and perhaps could not) provide specific guidance. So, an interesting question to ponder is whether recommending such broad ranges ultimately serves to exacerbate the confusion and uncertainty that the guidelines were developed to alleviate in the first place. The current ACSM guidelines,[26] for instance, specify that the range of effective and safe intensity extends from a low of 40% of oxygen uptake reserve or heart rate reserve (or 64% of maximal heart rate) to a high of 85% of oxygen uptake reserve or heart rate reserve (or 94% of maximal heart rate). For most individuals, these intensities encompass a very broad range of activity modalities, from a slow to moderately paced walk to a fairly hard run. Similarly, the descriptors "moderate" (i.e., 3–6 metabolic equivalent units or 10.5–21.0 $mL \cdot kg^{-1} \cdot min^{-1}$) and "vigorous" (i.e., more than 6 metabolic equivalent units or 21.0 $mL \cdot kg^{-1} \cdot min^{-1}$), which are used in current physical activity recommendations,[10] are also essentially all-encompassing. According to a widely used compendium, examples of activities that correspond to 3.0 metabolic equivalent units include putting away household items, washing the car or windows, fishing while

standing, and dressing a child. On the other hand, activities that correspond to 9.0 metabolic equivalent units include cross-country running or skiing, playing football competitively, and climbing hills with a 42+ pound load. For adults returning to physical activity after decades of sedentary living, with no experience of how a severely deconditioned body responds to physical challenges, this array of options, all sanctioned as effective and safe, may be bewildering. It is also important to point out that, within these recommended ranges, there are intensities that will leave some individuals unchallenged or bored, as well as intensities that may cause overexertion, discomfort, exhaustion, pain, and even fear or embarrassment. All of these intensities might have been judged by experts to be effective and safe, but whether they are truly appropriate for a given individual is not always easy for a novice to decide.

Confusion can also be the unintended consequence of a seemingly mundane process, such as the periodic update and revision of guidelines. For example, the ACSM has revised the recommended ranges of intensity and duration for the development and maintenance of cardiorespiratory fitness several times since 1975 and has also varied these ranges for special populations, such as people with heart disease, hypertension, diabetes, or obesity (see Figure 119.1). Experts in physiology or medicine might argue that frequent updates are a necessity and a direct consequence of a rapidly evolving literature. On the other hand, a marketing or communications expert would probably claim that, if one considers the promotion of physical activity as a prime objective, then maintaining a consistent message should be seen as of overriding importance. From this point of view, a 5% upward or downward adjustment in the guidelines probably does more harm than good. One reason is that, in the eyes of the public and even of professionals in a wide range of health care-related fields, constant changes are more likely to be interpreted as a sign of an immature and unreliable knowledge base than a sign of a field striving to bring the latest scientific information to the forefront. Furthermore, the changes are so many that, outside of a dedicated core of specialists, keeping up with the new sets of numbers becomes a nearly impossible task. The challenge becomes even more difficult due to the fact that, in some cases, the changes may have more to do with transient trends than a clearly identifiable scientific rationale. As one example, the term "moderate intensity" was defined as extending from 60% to 79% of maximal heart rate in the fifth edition of the ACSM guidelines, from 55% to 69% in the sixth edition, and from 64% to 76% in the seventh and eighth editions.

The result of this stream of inconsistent messages over many years, not surprisingly, has been widespread confusion, not only among the public but also among health care providers, as documented in a growing number of studies. One of the goals set in the precursor to the Healthy People program in 1980 was that, by 1990, the proportion of adults who would be able to accurately identify the dose of exercise thought to promote cardiovascular fitness most effectively would be higher than 70%. At that time, this "most effective"

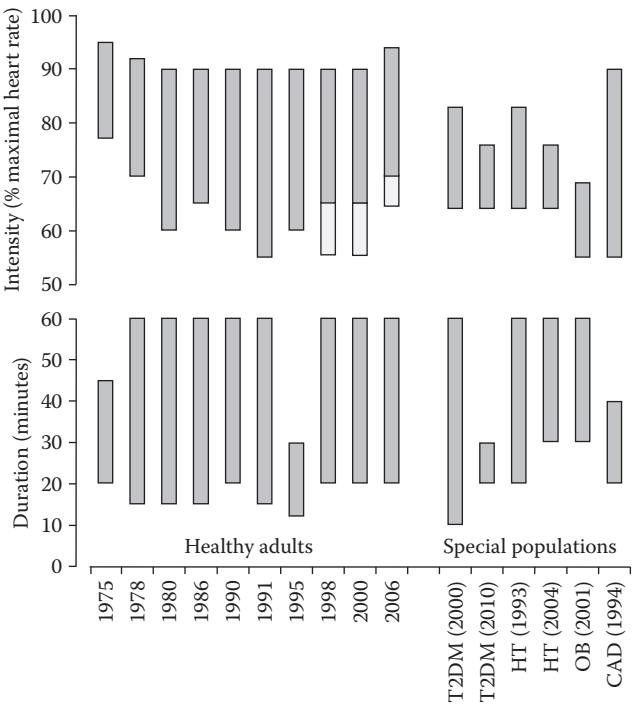


FIGURE 119.1 Changes in the lower and upper limits of the recommended range of exercise intensity (top panel) and daily duration (bottom panel), according to the American College of Sports Medicine. The figures for healthy adults are drawn from *ACSM's Guidelines for Exercise Testing and Prescription* and Position Stands on the *Recommended Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory and Muscular Fitness in Healthy Adults*. The lighter gray part of the bars refers to recommendations in which the lower limit of intensity was specified as a range, as opposed to a single level (e.g., 64%–70% of maximal heart rate). T2DM, type 2 diabetes mellitus; HT, hypertension; OB, obesity; CAD, coronary artery disease.

dose was believed to be at least 20 min, on ≥3 days/week, and an intensity of at least 60% of an individual's cardiorespiratory capacity. Caspersen et al.[43] analyzed the responses of more than 170,000 adults from the 1985 NHIS. They reported that 37.9% of respondents could not choose the correct answer from a list of options for any of the three questions (pertaining to frequency, duration, and intensity, respectively). Another 33.6% selected one correct answer and 23.5% selected two. However, only 5.1% of respondents selected all three answers correctly. Even when more relaxed criteria were used (considering any answer above the minimum recommended threshold as correct), the percentage of respondents answering all three questions "correctly" was 63.7%.

Morrow et al.[44] surveyed a random nationwide sample of 2002 individuals. Most respondents answered correctly that it is "true" that "Everyone should get 30 minutes of moderate physical activity most days of the week" (87.7%), that it is "false" that "Moderate levels physical activity do NOT provide any health benefits" (86.7%), and that it is "false" that "Vigorous levels of physical activity are necessary to provide a health benefit" (64.2%). On the other hand, more than

half (57.1%) of the respondents answered (incorrectly) that it is "false" that "Ten minutes physical activity three times per day provide the same health benefits as a single session of 30 minutes." Similarly, when asked in an open-ended fashion to specify "What is the minimum length of time (in minutes) one needs to be physically active throughout a typical day in order to achieve a health benefit," more than half (52.9%) gave answers other than "30 minutes."

Bennett et al.[45] analyzed data from 2381 participants in the 2005 Health Information National Trends Survey. When asked in an open-ended fashion, most participants responded correctly that the frequency of physical activity should be at least 5 days/week (57%) and the duration should be at least 30 min (86%), although any number over 5 days and 30 min was considered correct. However, only 33% of respondents gave correct answers to both questions. Importantly, 74.5% of respondents agreed (either "somewhat" or "strongly") that "there are so many different recommendations about physical activity or exercise that it's hard to know which ones to follow."

One might argue that the uncertainty and confusion reflected in public surveys might be due not to the flaws of the marketing message itself (i.e., inconsistencies and contradictions) but rather due to deficiencies in the preparation of the public to process the subtleties of the message (e.g., lack of specialized training and exposure to original research, lack of comprehension of important distinctions, such as between "exercise" and "physical activity"). The data, however, indicate that the confusion also extends to physicians and other health care professionals, to whom these limitations presumably do not apply.

Petrella et al.[46] surveyed 27,980 primary care physicians in Canada. Only 15.8% of them reported providing their patients with written exercise prescriptions, a finding that the authors attributed to "inadequate knowledge, skills, and tools needed to write exercise prescriptions" (p. 1779).

Allen et al.[47] surveyed 175 family physicians and 31 cardiologists in Canada. On a scale ranging from 1 (no knowledge) to 5 (strong knowledge), the family physicians rated their knowledge for prescribing exercise for two hypothetical cases (a patient with stable angina and a patient 2 weeks after discharge for an uncomplicated myocardial infarction) as 2.5 on average, with the cardiologists scoring just one point higher. To put these figures in perspective, the family physicians rated the knowledge needed in order to provide appropriate exercise prescriptions as 1.7 points higher than their perceived current level of knowledge. For family physicians, inadequate knowledge of safe levels of exercise was by far the most frequently reported barrier to prescribing exercise. In focus groups, physicians indicated that, although they are capable of providing general advice (i.e., that one should undertake physical activity), they did not know how to provide specific advice (i.e., cite specific figures for frequency, duration, intensity, and progression).

Essentially, the same finding was reported by Bull et al.[48] based on survey data from 789 family practitioners in Australia. Although nearly all (91.3%) physicians reported that they felt capable of providing general advice on physical activity, fewer than half felt capable of providing specific advice (45.5%; 51.4% of men, 31.7% of women).

Douglas et al.[49] studied 757 general practitioners, nurses, and health visitors in Scotland. The majority reported that they felt they had "sufficient knowledge to advise patients about physical activity" (66% of general practitioners, 71% of nurses, and 80% of health visitors either "agreed" or "strongly agreed"). However, when asked, only 13% of general practitioners, 7% of nurses, and 9% of health visitors correctly described the current recommendations (i.e., accumulation of at least 30 min of moderate activity, 5 days/week). The numbers of those who thought that the current recommendations call for 20 min, three times per week were larger (18% of general practitioners, 10% of nurses, and 12% of health visitors).

Daley et al.[50] surveyed 138 general practitioners in England. Almost two-thirds (64.5%) knew the "minimum amount of moderate-intensity physical activity that adults should aim to achieve each day for health benefits." On the other hand, only about a third (32.6%) knew the recommended minimum number of days per week and one-tenth (10.9%) knew how many minutes of moderate physical activity is recommended for the prevention of obesity.

One factor that may explain the relatively low level of knowledge of physicians and other health care professionals regarding exercise prescriptions is that such information is typically not offered as part of their formal education. According to a questionnaire survey[51] of 72 deans of medical schools and directors of medical education from the United States, even though almost half of them (47.2%) felt that being able to design an exercise prescription is "highly important," only 10.0% believed that students graduating from their programs were "highly competent" in doing so. Therefore, it seems that physicians, like the rest of the public, have to track down, read, and decode this information on their own. The fact that many, if not most, fail to do so effectively, despite their background, is an indication of the difficulty of this task.

PLEASURE AS THE MISSING ESSENTIAL INGREDIENT

At present, an exercise prescription or physical activity recommendation is considered successful if, within a relatively short period of time (i.e., usually that employed in experimental studies, such as 2–4 months), the exercise or physical activity is shown to produce statistically significant beneficial changes in the outcome variables without causing adverse events. This, however, is a dubious criterion of success since all short-term exercise- or activity-induced adaptations are reversible once the exercise or activity is discontinued. Therefore, although effectiveness and safety are obviously essential considerations, they may become meaningless unless participation is continued over the long haul, ideally for a lifetime. This fundamental principle implies that, ultimately, the prime objective of exercise prescriptions and

physical activity recommendations must be the instillation of a sustainable activity habit. If this principle is endorsed by exercise scientists and practitioners, it has the potential to act as a catalyst in reshaping the entire field. The development of instructions about what one *should* do without taking into account what one *can* do or *is willing* to do must become a thing of the past. Furthermore, shifting the focus to long-term maintenance as the prime objective could potentially unburden guidelines and recommendations from the massive confusion and marketing failures that have plagued them over the past four decades.

Certainly, instilling a lifelong activity habit is more easily said than done. The contributing variables are probably numerous, they may interact in complex ways, they are likely to vary from one individual to the next, and they remain mostly beyond the reach of our current understanding. Thus, the development of a comprehensive model that can serve as the basis of interventions that can be delivered by practitioners in the field is still a long way from becoming a reality. So, the position advanced here focuses specifically on one variable, namely pleasure.

This variable is selected for the following important reasons. First, the strong link between pleasure and human motivation for action has been known since antiquity. An emerging literature now suggests that the pleasure experienced during bouts of physical activity predicts subsequent physical activity participation. For example, Williams et al.,[52] using a single-item rating scale, measured pleasure at a "moderate" level of intensity (64% of age-predicted maximal heart rate) from a sample of formerly sedentary adults. These ratings were found to be significantly correlated with self-reported levels of physical activity 6 and 12 months later. Each one-unit increase on the 11-point rating scale of pleasure that was used was associated with 38 additional minutes of at least moderate-intensity physical activity per week at 6 months and 41 min/week at 12 months. Similarly, Schneider et al.[53] collected pleasure ratings from 124 adolescents as they cycled on an ergometer for 30 min at a moderate intensity (80% of the workload corresponding to their ventilatory threshold). After controlling for aerobic capacity and gender, each one-unit increase on the 11-point rating scale of pleasure was associated with 4.18 min of additional daily moderate-to-vigorous physical activity, assessed by accelerometer. For many exercise practitioners, the link between pleasure and subsequent exercise behavior is something they have learned from experience. Cardiac rehabilitation specialists have noted that "[managing] anxieties from the fear of overexertion causing an event, and attaining enjoyment from the exercise" are crucial contributors to adherence. Unless these are addressed, "the required longer-term changes of behavior for maintaining physical activity at appropriate levels are less likely" (p. 48).[54] Likewise, physical therapists working with individuals with chronic pain or fatigue use the construct of "kinesiophobia" to describe the fear that some of their patients have that exercise may exacerbate their symptoms. Once this fear develops, it tends to predict reduced physical activity participation.[55,56]

Second, when individuals who manage to remain active are asked in an open-ended fashion about the reasons behind their adherence; variants of pleasure (such as enjoyment, energy, relaxation, or pride) are among the most commonly reported factors. Conversely, variants of displeasure (such as exhaustion, pain, disappointment, or embarrassment) are ubiquitous in the reports of those who have dropped out. For example, Hendry et al.[57] interviewed patients with osteoarthritis about their exercise habits. Among the themes that most strongly distinguished those who were consistently active from those who had given up on exercise were statements related to pleasure versus displeasure or enjoyment versus aversion. Those in the former category used statements such as "I really do enjoy the gym; I look forward to going." Those in the latter category used statements such as "I can't enjoy exercise because it's so painful." According to a review of this literature,[58] constructs such as fun and enjoyment (or lack thereof) "were reported more often as predictors of participation and non-participation than perceived health benefits" (p. 832).

Third, several studies, particularly during the last decade, have examined the relationship between the dose characteristics of physical activity and the degree of pleasure that participants report. This research has shown that relative intensity, in particular, seems to exert a strong influence on pleasure. To illustrate this close linkage, Lind et al.[59] designed a study to simulate a scenario in which an exercise professional prescribed a level of intensity that was just 10% higher than that which participants would have selected if given this option. A sample of middle-aged women who were exercising for the first time in at least a year (but, in many cases, much longer) reached 84.17% ± 12.86% of their peak heart rate at the end of a 20 min treadmill bout, with the range recommended by the ACSM[26] extending from 64% to 94%. In contrast, imposing a treadmill speed that was just 10% faster than the self-selected caused the women to reach 91.14% ± 13.83% of their peak heart rate. Although both intensities were within the ACSM-recommended range, ratings of pleasure remained positive and stable during the bout at self-selected intensity but declined continuously and significantly when the speed was raised by just 10%. In this study, the women spontaneously selected an intensity that did not differ significantly from their ventilatory threshold (reached 98.07% ± 24.79% at the 20th min). In contrast, when the speed was raised by 10%, the women significantly exceeded their ventilatory threshold (115.40% ± 31.04%). In general, when adults are allowed to self-select their intensity, in most cases, they choose levels well within the range recommended by the ACSM for the development and maintenance of cardiorespiratory fitness. Furthermore, ratings of pleasure tend to remain stable and positive.[60]

Such findings support a reconceptualization of the constructs of "exercise prescription" and "physical activity recommendation." Instead of constantly revising the boundaries of the recommended heart rate range and risking massive confusion, it might be more effective to prescribe or recommend activity based on a constant and easy-to-understand reference

criterion: the intensity should be such that it does not cause a significant decrease in pleasure. Although this may sound simplistic, it represents an evidence-based approach to reaching the "compromise between the ideal physiological prescription and a manageable behavioral prescription" that was envisioned decades ago by Dishman[37] (p. 248). An intensity that does not induce a decrease in pleasure is, in most cases, close to the ventilatory threshold.[60] Such an intensity allows the maintenance of a physiological steady-state and can thus be continued over a prolonged period of time. Furthermore, since the ventilatory threshold typically occurs at approximately 50%–60% of maximal aerobic capacity in healthy nonathletic adults,[61,62] this intensity is within the range currently recommended by the ACSM.[26] Therefore, maintaining a steady level of pleasure during exercise can benefit motivation without compromising effectiveness or safety.

Calling for the maintenance of pleasure as a central consideration does not mean that monitoring intensity by objective means should be eliminated. The relationship between intensity and pleasure varies between, and even within, populations of exercisers with different physiological and psychological characteristics. It is also subject to situational influences, such as the perceived features of the social environment in which the exercise or physical activity takes place (e.g., whether the individual appraises the context as threatening by emphasizing competition or evaluation).

The presence of interpopulation and interindividual variability presents challenges and necessitates some radical changes in the way that exercise practitioners are trained (e.g., educational curricula will have to place at least as much emphasis on the psychology of exercise and physical activity as they do on the physiology). Furthermore, there is a need to direct resources toward a broad research agenda. The range of research topics that will have to be investigated in the years ahead includes (a) population-specific variations in the relationship between intensity and pleasure-displeasure responses (e.g., among individuals who are overweight or obese, patients with various exercise-limiting conditions), (b) physiological and psychological bases of interindividual differences in pleasure–displeasure responses, (c) the link between pleasure and exercise behavior (e.g., what aspects of pleasure–displeasure experiences may be more strongly predictive of subsequent behavior), (d) the mechanisms underlying pleasure–displeasure responses during exercise, and (e) the effectiveness and limitations of interventions aimed at increasing pleasure or decreasing displeasure during exercise.

AN ILLUSTRATIVE EXAMPLE: THE BOOM–BUST HYPOTHESIS OF EXERCISE BEHAVIOR IN OBESITY

Although the majority of the population in many industrialized countries is presently overweight or obese, how overweight or obese individuals feel when they exercise remains largely unexplored. Perhaps not coincidentally, the failure to increase physical activity among obese individuals has been nearly absolute. As noted earlier, according to data from the 2000 BRFSS, only 3.0% of obese women and 6.4% of obese men trying to lose weight report averaging 60 min of physical activity daily,[19] which is the minimum amount recommended by most agencies for effective weight management. As was also mentioned earlier, position statements by European and American scientific societies address how much exercise people should be doing for weight management but make no mention of the fact that the vast majority of people cannot or do not follow these guidelines.[29,30]

The ACSM[26] recommends that, initially, training intensity for obese individuals should be "moderate," defined as 40%–60% of oxygen uptake or heart rate reserve, with eventual progression to 50%–75%. This intensity should be maintained initially for 30–60 min and eventually for at least 60 min, with the option of performing the activity intermittently, as long as each period is at least 10 min long. If weight loss is desired (which is the case for the majority of obese women and men), then 60–90 min/day is deemed necessary.

To put these figures into perspective, a group of obese and sedentary, but otherwise healthy, middle-aged women reached 61% of their maximal oxygen uptake after walking at a relatively slow speed (2.50 miles/h, corresponding to approximately 3.0 metabolic equivalent units) for only 2 min.[63] A group of more active and fit obese women reached 56.0% of their maximal oxygen uptake after walking at a similar speed (2.65 miles/h) for only 4 min.[64] These figures illustrate that, at least when walking is chosen as the mode of physical activity, it may be impossible to maintain intensity within the recommended range of 40%–60% of maximal oxygen uptake for more than a few minutes. The challenge of accumulating 60–90 min of activity daily under these circumstances should become evident.

Studies have also shown that, unlike normal-weight individuals who typically show significant declines in pleasure at intensities that exceed the ventilatory threshold, obese individuals feel worse across most of the range of intensity.[63] Furthermore, obese participants may exhibit an attenuated "rebound" in pleasure (typically experienced as an increased sense of energy and reinvigoration) after exercise is stopped.[63]

Taken together, these data compose a likely scenario that could shed some light on the reasons behind the low levels of physical activity participation among obese individuals. It appears that many obese individuals, because of low cardiorespiratory fitness relative to body mass, need to raise intensity to fairly high percentages of maximal capacity in order to perform activities that may appear to be fairly "manageable" on paper (such as walking at 2.50 miles/h). This entails that most activities, at least after the first few minutes, would require effort that exceeds the ventilatory threshold. Because of the inability to maintain a physiological steady-state, these activities cannot be continued over extended periods of time, making the accumulation of 60–90 min on a daily basis a very challenging undertaking. Because initial attempts are likely to produce decreases in pleasure that are essentially unavoidable, giving up after a few trials is a phenomenon that should be considered predictable. This pattern can be

described as a series of "boom–bust" cycles that eventually serve to associate the idea of physical activity with displeasure. Because it is inherent in human nature to gravitate toward pleasant options and avoid unpleasant ones, activities associated with displeasure are avoided.

While this "boom–bust" hypothesis certainly requires considerable empirical testing and theoretical elaboration, it is interesting to use it as a possible frame of reference in evaluating recent calls for high-intensity exercise not only for weight management[33] but also for health promotion in general.[34,35] The main argument in support of these proposals is that, by using high intensity, the same fitness and health benefits can be accomplished within a shorter period of time compared to exercise of lower intensity. Although this argument may seem reasonable, it ignores some important empirical observations. First, with weekly energy expenditure fixed, given a choice between higher intensity or longer duration as a method of facilitating adherence, more obese individuals chose a reduction in intensity and a prolongation of duration.[65] Second, with daily duration fixed at 30 min, higher intensity was negatively associated with adherence (proportion of prescribed activity that was completed), whereas higher frequency (and, therefore, additional overall time investment) was not.[66] Third, higher intensity (specifically, intensity above the ventilatory threshold) produced a significant reduction in pleasure, whereas longer duration did not.[67]

Considering the persistent failure to promote physical activity to a larger segment of the public, it seems reasonable to suggest that prescriptions or recommendations for a given dose of exercise or physical activity should be accompanied by careful consideration of the possible impact on pleasure and adherence. The model of the exercising human without a head and without feelings is a relic of the dualistic past of biomedicine. The pressure to solve the problem of physical inactivity should accelerate its long-overdue decline into obsolescence.

With this in mind, the latest *Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults*,[68] issued by ACSM, should be considered a development of historical significance. According to this position stand, "moderate-intensity exercise and exercise that is enjoyable can enhance the affective responses to exercise, and may improve exercise adherence" (p. 1335). Moreover, "limited evidence suggests that pleasant affective responses to exercise (i.e., how enjoyable or pleasant is the exercise) may enhance future exercise behavior and vice versa" (p. 1347).

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120 Determinants of Physical Activity
Research to Application

Claudio R. Nigg, PhD, Ryan E. Rhodes, PhD, and Katie R. Amato, BS

CONTENTS

Individual/Psychological Determinants 1435
Attitude 1436
Changing PA Attitude in Practice 1436
Decisional Balance (Pros and Cons) 1436
Changing Decisional Balance for PA in Practice 1437
Self-Efficacy 1437
Changing Self-Efficacy for PA in Practice 1437
Social/Interpersonal Determinants 1437
Social Support and Subjective Norm 1438
Peers 1438
Parents 1438
Changing Social Support for PA in Practice 1438
Professional Support 1439
Environmental Determinants 1440
Changing the Environment for PA in Practice 1441
Conclusion 1441
References 1441

Despite the numerous benefits associated with moderate to vigorous physical activity (PA), more than half of U.S. adults are not meeting participation recommendations (i.e., 30 min of moderate PA per day, 5 or more days of the week, or vigorous PA at least 20 min/day, 3 or more days a week) [1]. Approximately 25% report that they engage in no PA for exercise in their leisure time [2]. Although physical inactivity is common among Americans, rates are higher among women, minorities, and those having little or no social capital [3]. Individuals who lead sedentary lifestyles as they age considerably increase their risks of developing psychological problems, cardiovascular disease, diabetes, obesity, some types of cancer, and premature death ([4]; see also other chapters in this book). It is therefore imperative to better understand variables or determinants that explain variation in PA in efforts to design effective interventions that increase the adoption and maintenance of PA [5].

To understand, promote, and maintain PA, we need to look at a comprehensive approach. The list of PA determinants is long and includes age, sex, education, income, ethnicity, body weight, climate, smoking status, health status, previous PA behavior, attitudes, perceived control, self-efficacy, intentions, motivation, commitment, enjoyment, perceived benefits and barriers, knowledge, skills, distance from a fitness facility, aesthetics, having home exercise equipment, amount of park space, time spent outdoors, spousal and peer support, number of children at home, extraversion, neuroticism, cohesion, group norms, class size, muscle fiber type, and genetic predispositions [6–9]. However, in this chapter, the focus is on modifiable psychological, social, environmental, and policy determinants. The rationale of this focus on modifiable determinants is a practical consideration—so that programs and practitioners know what they can change. The summary of these determinants provides the tools for application, enables plotting trends of generalized beliefs, and generates ideas for creative intervention approaches and research directions.

The social ecological framework [10] provides the framework to present the PA determinants. This ecological perspective highlights people's interactions with their physical and social/interpersonal environments, with the individual shaping their environments, as well as being shaped by their environments [11] (Figure 120.1).

INDIVIDUAL/PSYCHOLOGICAL DETERMINANTS

Many psychological determinants of PA have been documented, and the ones with the best evidence or the most practical promise are highlighted here. There are several

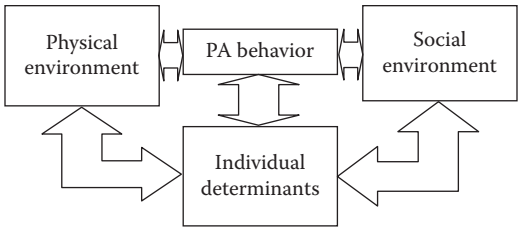


FIGURE 120.1 A conceptualization of the social ecological framework for physical activity (PA).

resources that present more comprehensive summaries and the reader is encouraged to explore these more in depth [12–15].

ATTITUDE

Attitude is the overall appraisal or evaluation concerning a behavior [16]. A recent meta-analysis confirmed the effect that PA attitude has on PA intention (d = 1.07) [17]. In particular, attitude was conceived as having affective (pleasure, enjoyment) and instrumental (utility, benefit) qualities [18,19] and this theoretical separation has been empirically supported [20], and subsequent meta-analyses show that affective attitude is clearly the largest predictor of intention [21]. Thus, the affective qualities of PA are the driving factor of PA intentions, which appears distinct from several other behaviors in health and social behavior [22].

Changing PA Attitude in Practice

Health care practitioners have opportunities to influence affective attitudes about PA by specifically building positive attitudes toward PA. One way to do this is to focus on physical activities that bring out positive (or less negative) attitudes. Have the individual/client list sedentary activities for which they have negative attitudes. Then encourage them to reward themselves (or their children) with active activities for which they have positive feelings. Concern should be given to the time, context, and amount and feeling of the PA. The PA should also be clearly defined in terms of moderate to vigorous activity (Table 120.1).

For example, an individual reports they enjoy working in their garden. For this to be a usable reward, it is important to specifically define the metrics: work on and harvest the garden for 1 h, in the afternoon to relax and make something fresh and healthy for dinner. Using the General Physical Activities Defined by Level of Intensity worksheet [23], define with the patient both moderate to vigorous gardening activities and describe their examples in detail:

> Gardening and Yard Work: raking the lawn, bagging grass or leaves, digging, hoeing, light shoveling (less than 10 lbs per minutes), or weeding while standing or bending. Planting trees, trimming shrubs and trees, hauling branches, stacking wood, pushing a power lawn mower or tiller.

In this manner, PA takes on a positive value (i.e., becomes a reward) and therefore facilitates positive affective attitudes about PA. People enjoy achieving or receiving awards. For children, a teacher might reward her/his entire class's academic achievements with 1 free day/hour of outdoor games, which is acknowledged by a certificate to be displayed in the classroom (Figure 120.2).

Likewise, parents may reward completion of chores with a trip to the park with friends. By clearly defining and changing the value of moderate to vigorous PA, affective attitudes will lead to increased intention and motivation for PA.

TABLE 120.1
Examples of Active Rewards for Completing Sedentary Activities to Build Positive Attitudes

Sedentary Things I Must Do	Active Rewards for Completion
1. Format the reference section	1. Go for a brisk walk at sunset
2. Do my homework	2. Bike to the park with a friend
3. Pay bills	3. Harvest the garden



FIGURE 120.2 Physical activity award certificate for a class.

DECISIONAL BALANCE (PROS AND CONS)

Decisional balance captures how individuals' weigh the consequences of a specific behavior in terms of gains and losses [24]. The importance of decisional balance has been documented in a recent meta-analysis, individuals who adopt health behaviors (including PA) increase their pros and decrease their cons in this process [25]. The decisional balance sheet (DBS) is the practical application of this concept, asking participants to record the anticipated pros and cons associated with the adoption of a preventive health behavior. As a health promotional tool, the DBS provides basic health knowledge and introduces personal control over one's own health. This approach has been supported within the PA domain [26,27].

TABLE 120.2
Decisional Balance Sheet

	Self	Others
Gains		
Losses		
Approval		
Disapproval		

Changing Decisional Balance for PA in Practice

The DBS is a simple method to get people to think about the pros and cons of engaging in PA [28]. Individuals list the pros in terms of gains and approval to self and to others incorporating instrumental and affective components at the individual and social levels. The mechanism at work here is to convince oneself. Similarly, by listing the cons for these same categories, it prepares the individual for these negative outcomes, and by being prepared, one can deal with them. This mechanism can be seen as an inoculation. The DBS technique is very useful for helping individuals start to exercise regularly, and for maintaining regular exercise may have to be redone with a specific focus on the pros and cons of maintaining PA (Table 120.2).

SELF-EFFICACY

Self-efficacy can be viewed as, and has been found to be, both a determinant and consequence of PA participation [29,30]. As a determinant, self-efficacy has shown an overall correlation of $r = 0.35$ with PA behavior in a recent meta-analysis [31]; this represents a medium effect size [32] and one of the largest overall correlates of PA [33].

In PA, two types of self-efficacy commonly used are barrier/coping efficacy and task efficacy [34]. Barrier efficacy is the confidence to overcome and navigate the possible barriers that interfere with performing PA, while task efficacy is the confidence to perform the specific PA act itself. In general, it appears that barrier efficacy is the critical predictor of PA participation, with the exception of clinical or physically compromised populations [34,35]. In these cases, it appears that task self-efficacy is the best predictor. This makes theoretical sense, as confidence in performing the task itself would seem necessary before one concerns themselves with confidence to regulate their daily barriers in order to act. Several other self-efficacy measures have emerged in the PA literature to define the specific barriers or behaviors that contribute to regular PA participation (proxy, scheduling, planning, etc.). Because self-efficacy is situation and behavior specific, multiple efficacies are theoretically valid and could all aid in promoting PA.

A similar concept to self-efficacy is perceived behavioral control (PBC), which refers to an individual's perception of the ability that they have to perform a behavior. This can include barriers or facilitators, such as resources, skills, and opportunities (i.e., time, fatigue, weather, access to facilities, money, etc.) needed to perform a behavior. It is thought to predict behavior directly because intention is less likely to be translated into an actual behavior under conditions of low PBC, and PBC acts as a proxy measure of actual behavioral control [16]. A meta-analysis reported a large effect size between intention and PBC ($d = 0.90$) [17].

TABLE 120.3
How to Build PA Self-Efficacy

Self-Efficacy Determinant	How to
Mastery experience	Enabling the person to succeed in attainable but increasingly challenging performances of desired behaviors For example, start out with 5 min walks once a week, then each week add another day, then after the 7th week at 2 min per day for each 2 weeks gradually progressing to 30 min of walking per day
Social modeling	Showing the person that others like themselves can do it. For example, providing examples of active coworkers
Improving physical and emotional states	Making sure people are well rested before attempting a new behavior. For example, reduce stress/depression, increase positive emotions
Verbal persuasion	Telling the person she or he can do it. For example, "Yes you can work out for 10 minutes"

Changing Self-Efficacy for PA in Practice

There are four determinants of self-efficacy: mastery experiences, social modeling, improving physical and emotional states, and verbal persuasion. Experiencing performance mastery has the strongest influence on self-efficacy beliefs. How to build self-efficacy through these four concepts is shown in Table 120.3.

Attitudes, decisional balance, PBC, and self-efficacy also influence intention to be PA. This is important to be aware of as changes in PA were positively predicted by changes in intentions [36], which is supported by a recent meta-analysis reporting a large effect size between intention and PA ($d = 1.01$) [17].

SOCIAL/INTERPERSONAL DETERMINANTS

Our interactions with others are central to our health and well-being [37]. Clearly, the social environment helps shape our behaviors, yet the concepts that comprise our social environment are complex and not widely agreed upon. McNeil et al. [38] summarized social concepts into three basic categories for use with PA: interpersonal relationships, social inequities, and neighborhood and community characteristics. From this categorization, it is clear that the scope of social determinants spans from the individual to

policy-level considerations. In the following section, we highlight social support and subjective norm, the two most prevalent constructs in PA research within the categorization of interpersonal relationships. The categorizations of social inequalities and community characteristics are discussed in the individual and environmental sections, respectively.

SOCIAL SUPPORT AND SUBJECTIVE NORM

Social support is a term that has seen great use in lay conversations and research literature over the last 20 years, but it was seldom used prior to the latter part of the twentieth century. There is no singular or formal definition of the construct, but many researchers can agree that social support involves multiple dimensions that encompass attachment to others, a sense of integration, and assistance or aid [39,40]. By contrast, subjective norm involves the perceived sense of pressure from others, either in the form of injunctive (psychological perception of others) or descriptive (behavioral acts of others) means [16,41].

The two constructs have seen considerable research attention with PA [7,33,42], and much of this work has resided from their application within psychological theories. Specifically, social support features prominently in social cognitive theory [43] and to a lesser extent in the transtheoretical model of behavior change (under the term helping relationships; [44]) and self-determination theory (under the term relatedness; [45]), while subjective norm resides within the theories of planned behavior [46] and reasoned action [47]. Of the two, social support has had superior validation as a determinant of PA. In prior reviews, Trost et al. identified social support as a reliable correlate of PA among adults [33], and similar conclusions were found with children [7]. By contrast, subjective norm has repeatedly been found as a small or trivial correlate of PA [17,48]. This has also been identified in direct comparison of the two constructs [49] when predicting PA.

Courneya et al. [50] suggest that subjective norm may be relevant for behaviors that are under complete volitional control because for such behaviors a person only needs to know whether important others approve of the behavior. By definition, they do not need any help. For behaviors that are not entirely volitional, however (e.g., regular PA), it is likely that assistance from others for performing the behavior (i.e., social support) in lieu of other time demands [51] would be helpful beyond knowing that they approve of the behavior.

Another potential way to view interpersonal determinants of PA involves the assessment of support or norms for specific referents [16,51]. In this case, specific people such as family members, friends/peers, and health professionals may have different influences upon one's PA behavior. In the subsequent sections, we highlight these three types of referents and the state of the evidence for their effect as PA determinants.

Peers

When one considers the constructs of subjective norm and social support generally, peers are the most likely candidates for these judgments. Indeed, peers followed by family members are the central consideration for subjective norm and social support as highlighted in focus groups [16,51]. Thus, it should not be surprising that peer influence, young children notwithstanding, is the critical interpersonal referent in PA. In terms of norms, peers show a larger correlation with PA than other social referents [52–54]. A similar result has also been identified with social support [7,33,55]. The likely reason for this powerful influence is due to the proximity and similarities of peers in day-to-day lifestyle. First, peers are in a position to interact, and thus influence, our behaviors daily. For repeated behaviors like regular PA, this offers the constant presence for both norms and support to take place. Second, peers, whether in the form of friends, partners, or coworkers are often selected for their similarities or values; thus, social influence to PA is a relatively natural extension of the social arrangement one has with their peers. The positive results in the PA domain appear to support this logic [16,33,56].

Parents

For children and adolescents, their parents and/or guardians represent pivotal social influences on behavioral, moral, and personal development. Indeed, parents are considered the primary gate control to exposure of almost all behaviors, and certainly health behaviors like PA. A review by Gustafson and Rhodes [57] of 34 studies pairing children and their parents highlighted the relative contribution of parental social influence. This review demonstrated that social norms, in the form of symmetry between the PA patterns of parents and their children, had mixed evidence. The results thus suggest that descriptive norms are not particularly powerful indicators of the parent–child PA relationship. By contrast, all but one study supported the importance of parental support on child PA behavior. The evidence suggested that the key factors for social support included encouragement (e.g., verbal), involvement (e.g., coaching of kids teams), and facilitation (e.g., driving children to events). These factors lend strong evidence for the notion of gate control of parents and youth PA and demonstrate that while parents may not need to be active themselves to influence their children's PA, they do need to foster active support.

Changing Social Support for PA in Practice

An example of a tool that encourages obtaining social support along with the individual/psychological determinants is provided (Figure 120.3).

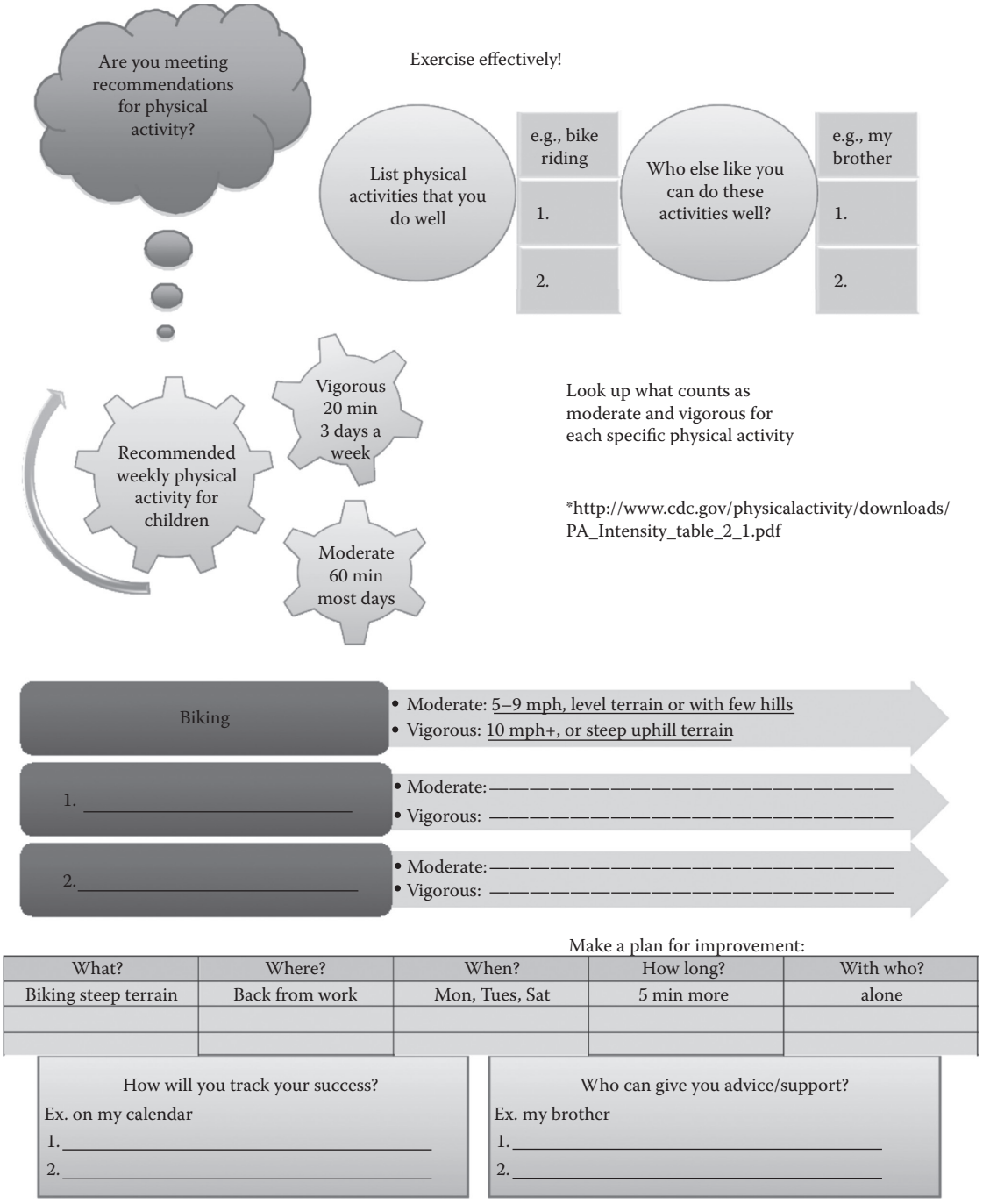


FIGURE 120.3 A tool to promote individual/psychological and interpersonal/social determinants.

Professional Support

It would seem like physicians and other health providers/practitioners are placed in a pivotal position for influencing PA. First, these individuals are considered credible in terms of health outcomes, and health behaviors could also act as a natural extension of this credibility. Second, people visit health professionals with the primary purpose of seeking information to health conditions; thus it would seem that they have an aperture for influencing health behavior. Still, there are limitations to the potential influence of health professionals. The most obvious is the low frequency of this visit; unlike peers and family, physician interactions are often extremely brief. Further, physician and health care models are often diagnostic and include passive recommendations to treat conditions (e.g., use of medications, surgery) that complement the brevity of these visits and the interpersonal distance between a patient and health care provider. These factors do not provide a strong climate for behavior change. To examine the effectiveness

of health care professionals on influencing PA, Williams et al. [58] conducted a systematic review and meta-analysis of 18 studies in this domain. The results showed modest evidence (OR = 1.2 times more likely than control participants) that physician/health care providers can influence PA among their patients. The complicated issue of exercise adherence, far exceeding what can be achieved in a short medical visit, was the main reason for these modest findings. Overall, it seems that health care professionals, while in a natural position to affect PA change, are not always able to do so within the context of the current health care structure due to the complications of sustained behavior change.

ENVIRONMENTAL DETERMINANTS

Environments contain a range of behavior settings that are seen to provide, in different degrees, "opportunities" or "affordances" for desired behaviors; the extent and the ways that those behaviors occur are further dependent on factors

TABLE 120.4
How to Change the PA Environment

Environmental Context	How to Change It
Policies	• Involve local communities and experts at all stages of policy development to maximize PA potential • Advance assessment of impact (intended and unintended) of the proposals on PA levels • New developments always prioritize PA • Local facilities and services be easily accessible on foot, bicycle, and other modes of transport involving PA • Ensure children can participate in PA play
Transport	• Reallocate road space to support physically active modes of transport (e.g., widen pavements and introduce bicycle lanes) • Restrict motor vehicle access (e.g., close or narrow roads to reduce capacity) • Implement road-user charging schemes • Introduce traffic-calming schemes (using signage and changes to highway design) • Develop safe routes to schools (e.g., traffic-calming measures by schools and create/improve walking and cycle routes to schools) • Plan and provide a comprehensive routes network for walking, cycling, and using other modes of transport involving PA, which should be convenient, safe, and attractive • Access workplaces, homes, schools, and other public facilities—shops, play and green areas, and social destinations be built and maintained to a high standard
Public open spaces	• Ensure public open spaces and public paths can be reached on foot, by bicycle, public transport, and other modes of transport involving PA • Should be safe, attractive, welcoming to everyone, and maintained to a high standard
Buildings	• Campus sites (two or more related buildings set together—e.g., hospitals and universities) should be linked by walking and cycling routes • Link new workplaces to walking and cycling networks improving the existing walking and cycling infrastructure by creating new, through routes (and not just links to the new facility) • Staircases should be designed and positioned to encourage use • Clearly signpost staircases and make staircases attractive (e.g., well lit and well decorated)
Schools	• Ensure that school playground designs encourage varied, PA play • Schools should create areas to promote individual and group PA such as hopscotch and other games (e.g., use different colors)

Source: National Institute for Health and Clinical Excellence, Promoting or creating built or natural environments that encourage and support physical activity, 2008, http://www.nice.org.uk/PH008, accessed February 10, 2011.

that are conceptualized as "filters" (e.g., perception, cognition, motivation) and "antecedent conditions" (e.g., opening hours, income, physical ability) [59,60]. Regular walking can be predicted by the proximity to retail and shopping [61], and dog ownership [62]. An environment that is not aesthetically appealing and is inaccessible to walking has been shown to be a barrier to engaging in PA [63]. Similarly, Brownson et al. [64] also listed adequate neighborhood characteristics as a motivator for PA, in addition to lacking energy, motivation, and time.

Proximity or nearness to PA resources from one's residence is a primary characteristic of environmental resources that support active transport [65], demonstrating a strong positive association with PA and walking across numerous examinations [66]. Density, which is commonly operationalized as the number of PA resources within a certain area or distance from residence was documented as a significant contributor to increased PA among adults in six of six review articles [66].

Environments exert, therefore, probabilistic influences, making behavior more or less likely. Thus, they vary in the support they provide for activities, enabling or promoting some, while preventing or discouraging others [67].

Changing the Environment for PA in Practice

To facilitate changing the environment to promote PA, key stakeholders need to be involved in addition to the health professional including planning and transport agencies (regional and local authorities), architects, designers, developers, employers, facility managers of public buildings, children's services, school governing bodies, principals, and PA coalitions. Practical suggestions are provided in Table 120.4.

What is important to consider when beginning the journey of changing the PA environment is to also be aware of the perceptions that the people have of the environment. To illustrate, families may feel very unsafe in a neighborhood due to a perception of high crime rates, whereas the police already implemented a frequent surveillance schedule, and the crime rate has been minimized. The perception in this case is the barrier, not the environment itself.

CONCLUSION

Research also suggests that environmental modifications will have greater effects when combined with strategies that target individual and social factors to foster participation in PA [69]. Social and environmental factors like an unsupportive partner and a lack of access to PA opportunities predict a return to previous PA levels after an intervention is completed [70,71]. A recent review of 22 interventions suggests a synergistic approach considering physical and social environmental and individual factors may be an effective strategy for initiation *and* maintenance [72]. Therefore, interventions aimed at simultaneously impacting individual and environmental PA determinants are likely to have the strongest and sustained effects.

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Part XXII

Injury Prevention

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121 Injuries and Lifestyle Medicine*

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CONTENTS

Introduction 1447
Burden of Injuries 1447
Trends and Variations 1448
Disproportionate Impact 1448
Injury or Accident? 1449
Causes of Injury 1450
Public Health Response 1450
Axioms in Injury Prevention 1451
Public Health, Preventive Medicine, and Injury Control 1452
How Lifestyle Medicine Practitioners Can Help Prevent Injuries 1453
Future Challenges 1453
Conclusions 1454
References 1454

INTRODUCTION

Today, chronic diseases and injuries have replaced infectious diseases as the leading causes of death in America, but no vaccines are available for these maladies. Injuries, which include both unintentional injuries and violence (e.g., homicide and suicide), are a major public health problem that affect patients, families, and the communities in which they live. This chapter will focus on unintentional injuries, which account for two-thirds of the public health injury burden.

The Centers for Disease Control and Prevention (CDC) and the Lifestyle Medicine Association share a common goal: to increase awareness of lifestyle-based causes of disease and injury in the general public and to assist in the integration of health professionals working in lifestyle-related disease and injury management and prevention. In addition to the many preventable diseases that are seen in medicine, there is one health threat that the public still accepts as a *fait accompli*: injuries. We have not yet fully integrated injury prevention into preventive medicine, and patients are not as educated on how to lower the risks of injury as they are on how to lower the risks of cancer or heart disease. Perhaps this is in part due to the belief that injuries are "accidents," acts of fate, random events, or acts of God.

The science of injury prevention teaches us that injuries are not accidents, they are predictable and they are preventable.[1,2] Lifestyle Medicine can be an important source to dispel the myth of "accidents" and help patients and the public recognize that injuries are preventable if only certain steps were taken to reduce the risks at home, on the road, at work, and in the community.

The ways we drive, walk, use alcohol and drugs, play sports, organize our home environment, select a car, use playground equipment, take prescription and over-the-counter medications, and supervise our children at play all affect the likelihood of injury. Effective interventions may include education and behavior change but also environmental supports such as legislation/enforcement and technology, engineering, and the environment. Interventions that support prevention include using individual protective devices; reducing risky driving behaviors; purchasing and using safety equipment; promoting regulations and legislation; supporting enhanced enforcement; and improving practices of physicians, providers, and other health care workers. A growing body of scientific evidence has demonstrated that lifestyle interventions for injury can and do work to lower risks.[1,2]

BURDEN OF INJURIES

Injuries are a large, predictable, and preventable national and international problem affecting individuals, families, and communities. In the United States, unintentional injuries are the fifth leading cause of death for people of all ages and the leading cause of years of potential life lost before age 65 years.[3] The consequences of injuries can be extensive and wide ranging. The effects are physical, emotional, and financial; and in the case of disabling injuries, the

* Disclaimer: The opinions expressed in this chapter are those of the authors, and do not necessarily represent any official position of the Centers for Disease Prevention Control and Prevention.

consequences are enduring. In 2007, nearly 123,706 people died from unintentional injuries in the United States; and in 2009, approximately 1 in 10 people or 27,632,781 experienced a nonfatal injury serious enough to require a visit to the emergency department.[3] Approximately one-third of all emergency department visits[4] and 6% of all hospital stays[5] are due to injuries. Today, millions of people in the United States suffer from chronic disability that was caused by injury.

The costs of all injuries are staggering.[6] In 2005 alone, injuries (unintentional and violence) cost $355 billion. This includes estimates of $77 billion in medical care costs and $278 billion in work loss costs.[3] In 2007, 9 of 10 deaths and more than two-thirds of disabling injuries suffered by workers occurred off the job, while 75 million days were lost to work injuries.[7] Moreover, costs associated with treatment of injuries and their long-term effects account for 12% of the total U.S. medical spending.[8]

The impacts to communities are equally enormous and multidimensional. Not only do communities suffer the emotional and psychological impacts of injury-related deaths (consider the death of a young teen driver) but also the economic and social strain injuries can cause. Loss of a job, care for the injured person, costs of rehabilitation, family disruption, medical care visits, insurance claims, marital difficulties, etc., all have enormous economic and social costs.

Injuries are also an international problem, especially among children and in developing countries. According to the 2008 WHO/UNICEF *World Report on Child Injury Prevention*,[9] the lives of more than 2000 families are torn apart every day around the world by the loss of a child to an unintentional injury or what is sometimes referred to as an "accident" that could have been prevented. Once children reach 5 years of age, unintentional injuries are the biggest threat to their survival. The pattern for children is similar in the United States. According to a 2008 CDC report,[10] about 33 children die every day from an unintentional injury and an estimated 9.2 million are rushed to the emergency department every year to be treated for an unintentional injury.

TRENDS AND VARIATIONS

Incident rates for injuries, like those for diseases, demonstrate long-term trends and geographic, socioeconomic, and seasonal variations. Injury rates also vary according to characteristics among individuals (e.g., age, sex, income) and environments (e.g., neighborhood, workplace, home). Injury epidemiology helps us understand and explain these variations, identify groups at higher risk for injury, and target specific interventions.

Table 121.1 compares the 10 leading causes of death in 2007 by age group. In the United States, injuries are among the top 10 causes of death in each age group throughout the lifespan. Unintentional injuries are the leading cause of death for people of ages 1–44 years. Within the 15 to 24-year-old age group, the top three leading causes of death (unintentional injuries, homicide, and suicide) accounted for 25,588 deaths. The total number of deaths from the remaining seven leading causes of death for this age group total only 3825. Unintentional injuries dominate the picture across all age groups, and violence from homicide and suicide occupies the second position as the major cause of death for those between the ages of 15 and 34.[3]

Among persons aged 1–44 years, unintentional injuries claim more lives than any other cause. In 2007, 42,031 motor vehicle traffic fatalities accounted for 3% of unintentional injury deaths (Table 121.2). Poisoning 29,846 (24%), falls 22,631 (18%), suffocation 5997 (5%), drowning 3443 (3%), and fire/burns 3375 (3%) together accounted for approximately 53% of deaths.[3]

Deaths are only a part of the devastating effect of injury on society (Table 121.3). Falls are the leading cause of injury-related emergency department visits for people of all ages, accounting for an estimated 8.8 million visits in 2009 or 32% of all injury visits. Another 4.4 million visits are for being struck by or against and 4.2 million are transportation related.[3]

An estimated 1.4 million people in the United States sustain a traumatic brain injury (TBI) annually. Falls and motor vehicle traffic crashes are leading causes of TBI. Fifty thousand die, 235,000 are hospitalized, and 1.1 million are treated and released from emergency departments.[11] CDC estimates that at least 5.3 million Americans currently have long-term or lifelong need for help to perform activities of daily living as a result of a TBI.[12] Additionally, it is estimated that 11,000 people are hospitalized with spinal cord injuries each year, and currently, nearly 200,000 people in the United States are living with these injury-related disabilities.[13] Out of the more than 50 million Americans with disabilities, about 10 million require personal assistance to carry out everyday activities; over 80% of the people who take on the role of primary helper are relatives.[14]

DISPROPORTIONATE IMPACT

As with many public health problems, injury disproportionately affects those who can least afford to suffer from it. In the United States, Native Americans 19 years and younger are at greater risk of preventable injury-related deaths than other populations in the same age group. Compared with blacks and whites, this group had the highest injury-related death rates for motor vehicle crashes, pedestrian events, and suicide. Rates for these causes were two to three times greater than rates for whites of the same age. During 1989–1998, injuries and violence caused the deaths of 3314 Native American children living in Indian Health Service areas.[15] In 2007, American Indians/Alaska Natives (AI/AN) have the highest age-adjusted rate of all injury deaths in the United States at 76.1. Blacks have the second highest rate at 65.1, while whites have an age-adjusted rate of 59.6.[3] According to the U.S. Census Bureau, the 3 year average poverty rate (2003–2005) for people who reported

TABLE 121.1
Ten Leading Causes of Death, Including Unintentional and Intentional Injury, by Age Group, All Race/Ethnicities, Both Sexes—United States, 2007

10 Leading Causes of Death by Age Group, United States – 2007

	Age Groups										
Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Congenital Anomalies 5,785	Unintentional Injury 1,588	Unintentional Injury 965	Unintentional Injury 1,229	Unintentional Injury 15,897	Unintentional Injury 14,977	Unintentional Injury 16,931	Malignant Neoplasms 50,167	Malignant Neoplasms 103,171	Heart Disease 496,095	Heart Disease 616,067
2	Short Gestation 4,857	Congenital Anomalies 546	Malignant Neoplasms 480	Malignant Neoplasms 479	Homicide 5,551	Suicide 5,278	Malignant Neoplasms 13,288	Heart Disease 37,434	Heart Disease 65,527	Malignant Neoplasms 389,730	Malignant Neoplasms 562,875
3	SIDS 2,453	Homicide 398	Congenital Anomalies 196	Homicide 213	Suicide 4,140	Homicide 4,758	Heart Disease 11,839	Unintentional Injury 20,315	Chronic Low. Respiratory Disease 12,777	Cerebro-vascular 115,961	Cerebro-vascular 135,952
4	Maternal Pregnancy Comp. 1,769	Malignant Neoplasms 364	Homicide 133	Suicide 180	Malignant Neoplasms 1,653	Malignant Neoplasms 3,463	Suicide 6,722	Liver Disease 8,212	Unintentional Injury 12,193	Chronic Low. Respiratory Disease 109,562	Chronic Low. Respiratory Disease 127,924
5	Unintentional Injury 1,285	Heart Disease 173	Heart Disease 110	Congenital Anomalies 178	Heart Disease 1,084	Heart Disease 3,223	HIV 3,572	Suicide 7,778	Diabetes Mellitus 11,304	Alzheimer's Disease 73,797	Unintentional Injury 123,706
6	Placenta Cord Membranes 1,135	Influenza & Pneumonia 109	Chronic Low. Respiratory Disease 54	Heart Disease 131	Congenital Anomalies 402	HIV 1,091	Homicide 3,052	Cerebro-vascular 6,385	Cerebro-vascular 10,500	Diabetes Mellitus 51,528	Alzheimer's Disease 74,632
7	Bacterial Sepsis 820	Septicemia 78	Influenza & Pneumonia 48	Chronic Low. Respiratory Disease 64	Cerebro-vascular 195	Diabetes Mellitus 610	Liver Disease 2,570	Diabetes Mellitus 5,753	Liver Disease 8,004	Influenza & Pneumonia 45,941	Diabetes Mellitus 71,382
8	Respiratory Distress 789	Perinatal Period 70	Benign Neoplasms 41	Influenza & Pneumonia 55	Diabetes Mellitus 168	Cerebro-vascular 505	Cerebro-vascular 2,133	HIV 4,156	Suicide 5,069	Nephritis 38,484	Influenza & Pneumonia 52,717
9	Circulatory System Disease 624	Benign Neoplasms 59	Cerebro-vascular 38	Cerebro-vascular 45	Influenza & Pneumonia 163	Congenital Anomalies 417	Diabetes Mellitus 1,984	Chronic Low. Respiratory Disease 4,153	Nephritis 4,440	Unintentional Injury 38,292	Nephritis 46,448
10	Neonatal Hemorrhage 597	Chronic Low. Respiratory Disease 57	Septicemia 36	Benign Neoplasms 43	Three Tied* 160	Liver Disease 384	Septicemia 910	Viral Hepatitis 2,815	Septicemia 4,231	Septicemia 26,362	Septicemia 34,828

*The three causes are: Complicated Pregnancy, HIV, Septicema
Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, CDC.

American Indian and Alaska Native was 25.3%; the poverty rate for blacks was 24.9% between 2004 and 2005; and for Hispanics was 21.8%, non-Hispanic whites had a poverty rate of 8.3%.[16] The combination of high injury rates, high poverty rates, and high rates of uninsured people among AI/ANs created a demand for action, which has led to the development of targeted interventions and implementation of capacity building programs for tribes and communities to reduce and prevent injuries.

INJURY OR ACCIDENT?

An injury is distinct from an accident. Accidents are not usually considered predictable or preventable. In fact, The Oxford English Dictionary defines the term *accident* as "an unusual event, which proceeds from some unknown cause … unexpected … happening by chance or fortune."[17]

The word *injury* has its root in the Latin term *injuris*, which literally means "not right." The dictionary defines injury as "harm of any kind, done or sustained." Injury in public health is defined as unintentional or intentional damage to the body resulting from acute exposure to thermal, mechanical, electrical or chemical energy, or from the absence of such essentials as heat or oxygen.[18] These exposures are affected by lifestyle.

Most injuries can be prevented through changes to products, behaviors, and environments.[2] Using terms such as *injury prevention* rather than *accident prevention* helps make clear that injuries are controllable and can be prevented. Former U.S. Surgeon General C. Everett Koop underscored this distinction when he said: "We must accept that the injuries associated with motor vehicles are not 'accidents' and that much can be done to reduce them. We must realize that violence in the forms of abuse, assault or suicide is within the purview of the health system. An informed and aroused public can change the behavior of each of us, but more importantly it must lead to community outrage and action in regard to unsafe playgrounds, automobiles, highways, work places, toys, homes and use of handguns."[18]

TABLE 121.2
Unintentional Injury Deaths, All Ages, All Race/Ethnicities, Both Sexes—United States, 2007

Cause of Death	*N*	Percentage
Motor vehicle traffic	42,031	34.0
Poisoning	29,846	24.1
Falls	22,631	18.3
Suffocation	5,997	4.8
Drownings	3,443	2.8
Fire and burns	3,375	2.7
Natural disasters, animals, and environmental exposures	1,449	1.2
Pedestrian	1,138	0.9
Struck by or against a person or object	832	0.7
Machinery	659	0.5
Firearms	613	0.5
Pedal cyclist	242	0.2
Cut or pierced by sharp object	111	0.1
Overexertion	13	0.0
Other transportation[a]	2,656	2.1
Other and unspecified causes[b]	8,674	7.0
Total deaths	123,706	100.0

Source: National Center for Health Statistics, Vital Statistics System.

[a] The number and percentage of other transportation deaths include the following subcategories combined: other land transport and other transport.

[b] The number and percentage of other and unspecified causes of death include the following subcategories combined: unspecified; other specified, classifiable; and other specified, not elsewhere classifiable.

TABLE 121.3
Leading Causes of Nonfatal Unintentional Injuries Treated in Hospital Emergency Departments, All Ages, All Race/Ethnicities, Both Sexes—United States, 2009

Mechanism	*N*	Percentage	Rate[a]
Unintentional injuries	27,632,781	100.0	9058.6
Falls	8,765,597	31.7	2831.3
Struck by or against a person or object	4,435,906	16.1	1489.0
Transportation[b]	4,200,980	15.2	1379.3
Overexertion	3,207,877	11.6	1065.3
Cut or pierced by sharp object	1,997,752	7.2	656.1
Bite or sting other than dog bite	1,067,922	3.9	350.21
Poisoning	708,318	2.6	229.3
Foreign body	540,180	2.0	178.0
Fires and burns	371,577	1.3	121.6
Dog bites	333,669	1.2	110.6
Machinery	207,125	0.7	66.9

Source: National Electronic Injury Surveillance System-All Injury Program (NEISS-AIP), U.S. Consumer Product Safety Commission.

[a] Age-adjusted per 100,000 population.

[b] The number, percentage, and rate of transportation-related injuries include the following subcategories combined: motor vehicle occupant, motorcyclist, pedal cyclist, pedestrian, and other transportation.

[c] Injuries inflicted by law enforcement personnel during the course of official duties.

CAUSES OF INJURY

The terms *injury* and *trauma* are often used interchangeably. Although there are many kinds and causes of injury, two main categories prevail;

1. *Acute exposure to energy* refers to injuries resulting from falls, motor vehicle crashes, and sports injury (kinetic energy); fires and burns (thermal energy); poisonings (chemical energy); electrocution (electrical energy); and from radiation
2. *Absence of essentials* includes lack of oxygen (as in asphyxiation, strangulation, or drowning) and lack of heat (as in hypothermia or frostbite)

PUBLIC HEALTH RESPONSE

According to the National Academy of Sciences, injury is the most under-recognized public health problem facing the nation today.[19] The science of injury control demonstrates that using the public health approaches can be effective in injury prevention. Injuries, like diseases, result from interactions between persons (host factors), agents or vectors (e.g., energy exchange), and the environment (physical and social environmental factors).[20] This approach is the foundation for understanding injury prevention.[21–23]

In response to the public health burden of injuries, the National Center for Injury Prevention and Control (Injury Center) was established at the CDC to prevent premature death and disability and to reduce the human suffering and medical costs caused by injuries.[8] To do this, the Injury Center uses the public health approach (Figure 121.1)—a systematic process to (1) define the injury problem, (2) identify risk and protective factors, (3) develop and test prevention interventions and strategies, and (4) translate and disseminate effective interventions to assure widespread adoption.

The mission of the Injury Center at CDC is to prevent injuries and violence and reduce the consequences so that people can live to their full potential.[24] The CDC Injury Center

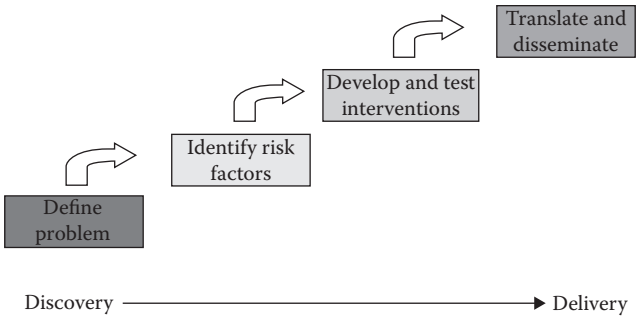


FIGURE 121.1 Steps in the public health approach to injury prevention.

is the only organization in the federal government with the responsibility to address all phases of the injury problem from foundational research to implementation of interventions and widespread adoption of effective strategies.

Control of injuries requires preventing the occurrence or reducing the severity of the injury event. In the case of an injury to an older adult falling, damage to the host (the person harmed) is brought about through a rapid transfer of kinetic energy. Changing this pattern of energy transfer can be modified in many ways, for instance, by making the host more resistant to it (by increasing injury tolerance through exercise and diet), by reducing the amount of energy transferred to the host (by landing on a softer surface or wearing hip protectors), or by creating a safer home environment (by removing trip hazards and installing proper lightening on stairs or installing grab bars in the bathroom). These are lifestyle changes within reach of most patients, manufacturers, homebuilders, governments, and parents.

The practice of successful injury prevention requires the application of lifestyle change and health promotion strategies that modify individual and population behavioral risks, reduce exposure to hazardous environment, and remove or modifying harmful products in the marketplace.[1,21] Individual and community actions are required for these strategies to succeed, and they are fostered by education, stimulated by social and organizational change, and encouraged through public policy, legislation, and enforcement activities. These actions, by their diversity alone, require the involvement of many professionals including physicians, nurses, coaches, designers, product engineers, and many others.

AXIOMS IN INJURY PREVENTION

Several axioms for injury prevention can help guide efforts in controlling injuries.[21,25,26]

1. *Injury results from interactions between people and the environment*: There are both human and environmental determinants of injury. The agent of injury will cause relatively little damage if the amount reaching tissues is within the limits of human tolerance. Tap water can scald in seconds or not at all depending on its temperature. The importance of this interaction is recognized in approaches that control the environment by reducing hot water temperatures at the tap and approaches that simultaneously target parents of small children and the elderly about hot water scald risks (including the need for reduced tap water temperatures).
2. *Injury-producing interactions can be modified through changing behavior, products, or environments*: Injuries can be reduced by modifying the weakest or most adaptable link in the chain of causation. Unsanctioned swimming in a home swimming pool is more easily reduced by placing an isolation fence or barrier between the child and the pool than by supervising the child's behavior at all times. During sanctioned swimming, while in the pool, close supervision is the most important strategy. Changing the environment, the laws, the person, or the product can all lead to reductions in injuries.
3. *Environmental changes have the potential to protect the greatest number of people*: Changes to the environment that automatically provide protection to every person have the potential to prevent the most injuries. This includes automatic protection built into roads (such as barriers), into buildings (such as fire sprinkler systems), into automobiles (such as shatter-proof glass), into homes (such as fuses), and into products (such as child-resistant packaging on medicines). Few "passive" interventions succeed without an active behavioral component (such as replacing lids on medicines) and succeed better when the public is informed and convinced of their need and benefit.
4. *Effective injury prevention requires a mixture of strategies and methods*: Three primary strategies—education/behavior change, technology/engineering, and legislation/enforcement—are widely recognized as effective in preventing injuries. Individual behavior change, product engineering, public education, legal requirements, law enforcement, and changes in the physical and social environment work together to reduce injuries. The challenge in intervention planning is to select the most effective combination of strategies to produce the desired result.
5. *Public participation is essential for community action*: Effective public policy requires the support and participation of people. Local problems and resource availability often determine the direction of injury prevention programs. Factors influencing success in injury prevention are best identified by public feedback and participation

in the process. Without public support, effective laws designed to protect the public (such as mandatory motorcycle helmet use laws) may be ignored, or worse, repealed.

6. *Intersectoral collaboration is necessary*: Injury prevention requires coordinated action by many groups. Participation by community leaders (in addition to health officers, hospital administrators, and others) is necessary in planning and implementing injury prevention programs. Different sectors can play different roles—ranging from identifying problems to mobilizing community action, evaluating intervention effectiveness, and advocating for change. Identifying and building a constituency and shifting or sharing resources require collaboration across many different sectors.

An illustration of these axioms can be seen in the following case study involving burn prevention and modifications to cigarette lighters to make them child-resistant.

PUBLIC HEALTH, PREVENTIVE MEDICINE, AND INJURY CONTROL

Injury prevention has received less than its share of coverage in the public health and preventive medicine literature.[25] As injury prevention and lifestyle medicine become more closely aligned, the potential benefits of comprehensive injury prevention strategies, including behavioral and environmental change, will become clearer and more widely accepted.[22] Health promotion approaches using a combination of approaches including educational, behavioral, engineering and technology change, and legislation, policy, and enforcement provide the greatest chance of success.[1,21,25]

There are many examples[1,2] of successful strategies to reduce risky behaviors, change policies to promote safer practices, support stronger enforcement efforts, and change products to make them safer (as in the case study). Working with community leaders and advocates and implementing low-cost but effective interventions to reduce preventable injuries is also a common theme in injury prevention.[1,2] Translating successful strategies for use in primary care settings is more challenging (even in traditional prevention arenas such as

CASE STUDY: BURN PREVENTION AND CHILD-RESISTANT CIGARETTE LIGHTERS

After seeing many children suffering from burns, Diane Denton, an emergency room nurse in Louisville, Kentucky, began asking parents how these tragic burns occurred. She learned that a large number of cases were the result of children playing with disposable cigarette lighters. The lighters are small enough to fit in the palm of the child's hand, are brightly colored, and become "sparking toys" when moved rapidly along a carpet or mattress. Ms. Denton documented these case findings within her own community and then, armed with the data, petitioned the U.S. Consumer Product Safety Commission (CPSC) to investigate more widely the risks posed by disposable cigarette lighters. Others in the burn prevention community nationally joined her plea for action to either ban the lighters or modify them to make them child-resistant.

Impressed with the data Ms. Denton provided, the CPSC-funded research to examine cases nationwide in which children had been badly burned while playing with disposable cigarette lighters. It found that children playing with lighters ignited 5900 residential fires that resulted in an average of 150 deaths and 1100 injuries annually. Average annual property damage from such fires totaled almost $70 million. As many as 190 burn-related deaths among children younger than 3 years could be prevented, they estimated, by a simple and inexpensive childproof device costing less than nine cents.

Ten years after Denton's efforts, with CPSC prompting, the major cigarette lighter manufacturers complied with a request to make disposable lighters childproof, reengineered them so that small children could not operate them, and marketed them to the public as safer for the protection of children. CPSC finally set a standard (effective in 1994) requiring disposable and novelty lighters to be child-resistant. Since the standard took effect, there has been a 58% reduction in fires caused by children under 5 years of age, representing the prevention of hundreds of deaths and injuries and thousands of fires. However, in a recent year, there were still 2400 fires resulting in 70 deaths and 480 injuries because of children under age 5 years playing with lighters. Back as far as 2004 to the present, CPSC was still recalling novelty lighters (digital wristwatch lighters, lighters made into shapes of toy cars) that are sold in the United States but do not meet the current child-resistant standard (see http://www.nonoveltylighters.com for a website dedicated to these activities in Arkansas).

Manufacturers and marketers who disable or tamper with the childproof feature in lighters, or import nonstandard lighters have been jailed and fined. In this example, the actions of one emergency care nurse and a small community of injury prevention advocates from the medical community changed an entire industry, saving hundreds of lives and preventing thousands of children from being seriously burned.

cancer prevention and women's health,[27,28]) but it is critical in injury control where using known and effective interventions can save lives almost immediately. The challenge now is to stimulate primary care physicians and family practitioners to become more engaged in using and adapting the evidence with patients and families to save lives and prevent injuries.

One additional benefit to preventing unintentional injury is that it not only saves lives but also saves dollars. Many low-cost safe practices that protect children and adults will help reduce economic costs to society.[29] For example,

- A child safety seat can save $100 in direct medical costs and an additional $1360 in other costs.
- A bicycle helmet can save $440 in direct medical costs and other costs.
- A smoke alarm can save $15 in direct medical costs and an additional $710 in other costs.
- Every dollar spent on poison control centers can save $6.70 in medical costs.

Among the most urgent priorities is the area of motor vehicle injury prevention where more than 35% of the injury deaths occur (Table 121.2). Examples of evidence-based strategies to prevent motor vehicle occupant injuries can be found in the Guide to Community Preventive Services (Community Guide) and recent reviews.[30–33] The guide summarizes what is known about the effectiveness, economic efficiency, and feasibility of interventions to promote community health and prevent disease, and it makes recommendations for the use of various interventions based on the evidence gathered in the rigorous and systematic scientific reviews of published studies.

HOW LIFESTYLE MEDICINE PRACTITIONERS CAN HELP PREVENT INJURIES

Lifestyle medicine physicians often see patients and their families after an injury has occurred, or meet practitioners responsible for managing, implementing, or evaluating injury prevention programs. These are opportunities to share effective strategies and build traffic injury prevention opportunities into clinical care. Physicians can also influence decision makers to enact or strengthen legislation or to set health care and reimbursement policies that promote prevention. Health care professionals who serve on medical school or nursing faculty and teach courses on trauma prevention or public health can also help prepare their students with material related to injury prevention.

Reducing injuries will also require a shift in how society thinks about hazards, the environment they live in, their personal risk behaviors, and the value of prevention. Lifestyle medicine can contribute to this shift by a variety of actions:

1. At the individual level
   a. Include injury prevention in all your health promotion and disease prevention activities with patients
   b. Expand your record keeping to collect and monitor patient risk factors for injuries (e.g., chart reminder about teens counseling about driving or unintentional poisoning among middle-aged adults).
   c. Assess the safety practices of patients and their families (e.g., helmet use, texting while driving, use of life jackets).
   d. Set goals for your patients to change risky lifestyles that predispose to injuries.
   e. Collect data on the clinical and health care costs and consequences of the injuries you treat.
   f. Have information available on how patients can access resources in the community for injury prevention (e.g., local safety council, MADD, bicycle helmet programs).
   g. Screen for alcohol misuse, using existing tools such as brief intervention and motivational interviewing.
   h. Screen for use of age-appropriate child safety seats and booster seat use.
   i. Support improvements in prehospital and hospital care for injured victims and support comprehensive trauma care systems in your community.
   j. Talk to parents of teenage drivers about the importance of graduated driver licensing.
2. At the community level
   a. Support efforts to strengthen policies in your state that prevent injuries such as primary seat belt laws, stronger teen driving policies, smoke alarm policies, and motor cycle safety.
   b. Discourage efforts to repeal legislation that has had a positive safety benefit.
   c. Strengthen collaboration with local coalitions, such as Safe Kids, a local drowning prevention coalition, the National Safety Council, or State Offices of Highway Safety.
   d. Support efforts to build injury prevention into initiatives into health care reform.
   e. Testify at hearings and town meetings about evidence-based strategies that work.
   f. Support research on risk and protective factors and interventions to reduce all forms of injury and trauma, including injury prevention on and off the job.

FUTURE CHALLENGES

The National Academy of Sciences Institute of Medicine Report, Reducing the Burden of Injury[8] reemphasized the importance of using a scientific approach to injury prevention and called on CDC and others to work with medical care organizations, health care providers, states and communities, businesses, and other federal agencies to pursue

alliances that would help reduce injuries. Lifestyle medicine practitioners and the Lifestyle Medicine Association can be important partners in this prevention solution. It's time to add *injuries* to the broad range of conditions resulting from lifestyle choices and engage the primary caregivers and other gatekeeper health care professionals in advocating for lifestyle choices that reduce injuries from all causes.

CONCLUSIONS

Although injuries have plagued societies since the beginning of time, preventive and lifestyle medicine have only recently recognized these events as important public health problems that are both predictable and preventable. Injuries are seldom distributed randomly—they are concentrated in physical space and time, and they affect definable populations at risk. Using ecological public health approaches that are based on sound epidemiology,[34] human factors research[35] and behavioral and social science theories[1] stand the best chance of succeeding. Targeting the host, agent, and environmental factors, including hazardous products that contribute to injury, will help reduce overall injury rates. Approaches will need to be adapted to different populations, lifestyles, and life stages. Because there are so many different injuries with varied causes, tailored strategies are necessary.

Reductions in injury and their costs to patients and their families are possible, but will need support, collaboration, and partnering from policy makers, clinicians, and health care practitioners. Lifestyle medicine and primary care family practitioners are important allies in encouraging lifestyle choices that reduce injuries and in advocating for medical and public health policies related to injury prevention. Primary caregivers and other health care professionals can help reduce injuries from all causes using clinical-based prevention skills[36] and advocating in the community for changes that reduce injury potential.

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122 Patient Counseling for Unintentional Injury Prevention*

Michael F. Ballesteros, PhD and Andrea Gielen, ScD

CONTENTS

Who Gets IPC? 1457
Does It Work? 1458
Barriers to IPC 1459
The Injury Prevention Program 1459
Guidelines for Adolescent Preventive Services 1461
Conclusion 1461
References 1462

Unintentional injuries are a leading cause of morbidity and mortality in the United States. In 2007, unintentional injury accounted for over 123,000 deaths and over 27 million emergency department visits. Unintentional injury is the leading cause of death for individuals who are 1–44 years of age, the fourth leading cause of death for all ages combined, and the leading cause of years of potential life lost before 65 years [1].

The most common causes of injury death are motor vehicle traffic crashes, poisoning, fall, suffocation, drowning, and fire and burns, while the most common causes of nonfatal injury are fall, struck by/against, overexertion, motor vehicle crashes, and cut/pierce [1]. The toll on the health care system is dramatic, with injuries in a single year resulting in $406 billion in lifetime medical expenses and lost productivity [2].

Many injuries are preventable through the application of proven effective interventions. These interventions include policy changes, environmental modification, and personal protective behaviors. For example, graduated driver licensing policies, the presence of home smoke alarms, and the use of car seats, seat belts, and bike helmets have all demonstrated their risk-reducing potential [3]. How to communicate risk-reduction messages and get proven effective safety products into the hands of those who need them remains a challenge for injury prevention [4,5].

The purpose of this chapter is to explore one solution to this challenge, injury prevention counseling (IPC) by health care providers. This is one strategy to reduce risk by encouraging people to modify their environment or their personal behaviors to protect themselves or their loved ones.

Physicians and other health care providers are trusted sources of health information [6] and can play an important role in injury prevention. This is particularly true of pediatricians who often see infants and their parents multiple times in the first years of life [7]. IPC is included in the American Academy of Pediatrics (AAP) recommendations for well-child visits [8] and in the U.S. Preventive Services Task Force *Guide to Clinical Preventive Services* [9]. The aims of this chapter are to describe the prevalence and effectiveness of IPC and to suggest which elements of an IPC program are associated with greater success. The results can be used to inform future efforts to strengthen this injury prevention strategy.

WHO GETS IPC?

Despite the professional endorsements of IPC, recent national surveys have found that few patients are receiving IPC. Only 1 in 5 adults who visit a health care provider reported receiving counseling on any injury topic and only 1 in 10 was counseled on seat belt safety and 1 in 17 was counseled on home smoke alarms. Other than seat belt use, there has been little change in these percentages over the past 10 years. Prevalence of IPC differed by age, sex, race/ethnicity, household poverty status, education level, health insurance status, and presence of children in the household [10].

Pediatricians have been more successful. Over 40% of children with a medical visit reported receiving IPC delivered either to themselves or their parents; however, this percentage decreased with increasing patient age (0–1 year: 62.8%; 2–6 years: 44.6%; 7–12 years: 39.0%; 13–14 years: 27.3%). Overall, the percentage of U.S. children with reported IPC for any injury topic has not changed over time, but there have been modest increases in IPC on home smoke alarms, bicycle helmets, and car seats for children 6 years of age or younger [11].

* Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

DOES IT WORK?

The evidence of IPC being effective at increasing safety practices comes mostly from the pediatric literature and is inconsistent. A review of studies from 1964 to 1991 by Bass et al. found that IPC taking place in pediatric primary care settings can change parents' knowledge, attitudes, and behavior related to motor vehicle, household, and environmental injuries [12]. The studies in this review included various methodologies including randomized controlled trials, non-randomized studies, multiple time series (before and after), and descriptive approaches. The Centers for Disease Control and Prevention's Second Injury Control and Risk Survey examined IPC through a nationally representative random-digit-dial telephone survey, which asked respondents if they or their children had received any IPC during visits to health care providers. Additionally, specific safety practices and behaviors related to children were also assessed. This study found that IPC improved safety behaviors for posting the poison control center number and always using a bicycle helmet; there was no association between IPC and having a working smoke alarm in the home or always using a seat belt [11]. However, another review looking exclusively at 22 randomized controlled trials of IPC delivered in a variety of settings such as physician offices, clinics, emergency departments, and hospitals. They found that safety practices, which may have been self-reported or observed, improved for motor vehicle restraint use, smoke alarm ownership, and maintenance of a safe hot tap water temperature; but there was not added protection for general injury prevention at home or bicycle helmet use [13].

There are several possible reasons why some IPC efforts have been shown to be effective while others have not. Choices in study designs and outcomes examined (i.e., change in knowledge, change in behavior, and occurrence of an injury) may limit the ability of individual studies to demonstrate an effect. In some instances, IPC may have a true benefit, but that benefit may not be clear in the short term or measureable. Furthermore, counseling recommendations for some injury issues may involve more effort, cost, or inconvenience by the patient or parent compared with other injury issues. For example, a recommendation to check the temperature of the hot water heater and turn it down if it is over 120°F is a one-time action versus the recommendation to always wear a bicycle helmet, which must be demonstrated each time one cycles. Additionally, perceived risk and consequences also vary by injury issue and can affect the impact of counseling. Counseling to prevent drowning or a motor vehicle injury may be perceived as more serious than counseling to prevent a sports injury. A person's beliefs about their susceptibility to an injury, the severity of the injury should it occur, the effectiveness of the recommended action, and the benefits versus the costs of the action (as described by *the Health Belief Model*) all affect behavior change and thus the receptivity to the counseling efforts [14].

Counseling that is based on behavior change theories used in health education, health promotion, and health communication is likely to be the most effective [15]. DiGuiseppi and Roberts [13], using the theoretical planning framework of the PRECEDE-PROCEED model [16], suggest addressing three types of factors that health education can modify, based on (1) *predisposing factors* (these include knowledge, beliefs, values, attitudes, and confidence; use these to motivate the patient to change behavior), (2) *enabling factors* (allow the motivation to be realized; these factors include skills mastery, accessibility of resources, and product design and legislation), and (3) *reinforcing factors* (reinforce and reward implementation and maintenance of safety behaviors—e.g., follow-up visits or calls, incentives, reminders, media messages, and legislative enforcement). IPC effectiveness can be improved by combining these strategies, or by combining education with demonstrations, the provision of subsidized safety devices, and reinforcement.

Consideration of other theories of behavior change could also improve counseling approaches and effectiveness. For example, the *Protection Motivation Theory* addresses protection motivation through individual appraisals of threat and coping (e.g., parents must be convinced that teen driving poses a personal and serious threat and that actions they could take would protect against this threat) [14]. The *Theory of Reasoned Action* and the related *Theory of Planned Behavior* examine factors related to behavioral intention (which predicts behavior). Intention can be influenced by attitudes toward behavior (e.g., my child would be safer in a car seat), subjective norms (e.g., my spouse would approve of using a car seat), and perceived behavioral control (e.g., I can put my child in a car seat successfully) [14].

The effectiveness of patient counseling that addresses other health issues varies by topic area. Data exist that patient counseling to prevent sexually transmitted infections [17], promote healthy diet [18], reduce risky or harmful alcohol use [19], and promote smoking cessation can be effective [20]. Evidence is inconclusive about the effectiveness of counseling to increase physical activity [21].

Reviews of studies on these topic areas suggest other factors for why some counseling is effective. Counseling done in truly low-risk populations show minimal benefit, so physicians should consider concentrating their counseling efforts on patients at higher risk. This may involve screening patients to understand this level of risk. Identification of high-risk patients can be done through the appropriate use of validated screening instruments (e.g., CAGE to detect alcoholism [22]) in conjunction with clinical assessment and judgment. It is important to note that counseling interventions differ from screening interventions in that counseling may address complex behaviors and be influenced by multiple contexts (i.e., family, peers, school, work, and community) [23].

Intervention intensity also seems to be an important factor in effectiveness. Higher intensity interventions take more time, and may involve more patient contacts (such as follow-up visits) and individual risk-based counseling, which could include tailored risk-reduction plans.

The evidence for effectiveness of counseling for these other health areas is based on systematic reviews of individual studies. Some of these studies used specifically trained professionals, such as nutritionists or dieticians in counseling interventions that addressed dietary changes, and study protocols often involved the use of study-specific clinics and staff to provide screening and assessment services. In practice, access to these resources may not be available, so translating effective interventions done in a research context may be challenging.

BARRIERS TO IPC

Health care providers who want to include IPC in the care of their patients also face a number of additional barriers. The most obvious barrier is a lack of time. The health care provider may be seeing a patient for a health maintenance visit, to treat an injury, or to treat another medical problem in an inpatient or outpatient setting. It can be difficult for a provider to balance the time needed to manage the reason for the visit with the time needed for IPC or counseling for other health issues. Additional barriers include the feeling that they have more important things to do, fear of patients' or parents' reactions to discussion of some aspects of injury prevention, and a sense that this problem is too big to be solved by a provider working one-on-one with a patient or family [24,25]. In fact, injury prevention often is perceived as more outside the physician's role compared to other clinical preventive services, and therefore, many physicians are unprepared to deliver IPC [26].

These gaps and challenges can be addressed with more emphasis during medical education on the importance of injuries as a health issue and how to conduct IPC. A broader effort is needed to improve the attitudes of providers, parents, and patients that it is within the purview of individual health care providers to discuss the prevention of injuries from motor vehicle travel, in sports and recreation, at work, in the home, and in the community.

There may be a unique opportunity at this time to increase IPC because of health care reform efforts, which have raised the visibility and importance of preventive services. While insurance programs typically cover preventive services such as vaccines, they do not cover IPC or safety products. It's estimated that Medicaid could save $1 million per 100,000 children by supporting child safety seat distribution and education [27].

Gielen found that coupling pediatric counseling with convenient access to low-cost safety supplies and personalized information can improve home safety practices among low-income urban families [28]. The IPC utilized here was developed specifically for this project and involved the SAFE Communication Framework, which was found to increase physician counseling and improve parent satisfaction with the medical visit [29]. This framework involved four steps: (1) *solicit information* (i.e., ask what patient or parent knows, does, and is concerned about regarding specific injury issues), (2) *advise* (i.e., explain safety practice and provide information on how to do it), (3) *focus on risks and barriers* (i.e., help patient or parent understand the injury risk, acknowledge barriers to safety practice, and help problem solve), and (4) *encourage compliance* (i.e., reinforce intentions and efforts and plan to follow up). Pediatric residents received specific instruction on SAFE that included practice in role playing as well as demonstration skill stations. Part of this comprehensive approach was a standard 1 h seminar on the problem of injuries and an overview of the AAP's The Injury Prevention Program (TIPP).

THE INJURY PREVENTION PROGRAM

TIPP is an educational program for parents of children from newborns through 12 years of age [30,31]. It addresses the prevention of common injuries from motor vehicles, drownings, burns, firearms, poisoning, falls, bicycle crashes, choking, and pedestrian hazards. TIPP is designed to assist pediatricians with a systematic method to counsel parents and children about adopting behaviors to prevent injuries. There are three major elements in TIPP: (1) a policy statement on injury prevention approved by the APP [32], (2) Childhood Safety Counseling Schedules for early and middle childhood, and (3) a package of materials consisting of Safety Surveys and age-specific, color-coded Safety Sheets for use in providing anticipatory guidelines to parents and children (Table 122.1).

TIPP can be integrated into a physician's practice through the following steps:

1. Have a parent answer a Safety Survey in the reception room. The child can complete the survey at 10 years of age.
2. Have the completed survey placed in the child's medical chart for review by the physician.
3. Note "at-risk" answers on surveys that have been completed.
4. Counsel the parent or child on specific injury prevention behaviors using the Safety Sheets and the counseling guidelines prompted by the "at-risk" answers obtained from surveys.
5. Reinforce the counseling by giving the parent or child an age-appropriate Safety Sheet emphasizing the targeted safety messages of the counseling schedule.
6. Document the counseling in the child's medical record.

There is some evidence that TIPP is also a cost-effective method of preventing childhood injuries. Miller and Galbraith estimated that pediatric IPC for parents of children younger than 5 years can achieve an estimated savings of $880 per child or $80 per visit. Each dollar spent of TIPP targeting this age group returns nearly $13 [33].

TABLE 122.1
TIPP Counseling Guidelines

The first year of life

Household hazards

- Keep crib sides raised
- If you leave, even for a moment, place your baby in a playpen or crib with the sides up
- Provide constant supervision
- Keep plastic bags and balloons away from your children
- Do not put anything around a baby's neck—objects around the neck may strangle the baby
- Do not allow your child to play with small objects
- Select an experienced babysitter
- Check heating systems and fireplaces at least once a year
- Place operable window guards on all windows in your home
- Do not place your child in a walker

Burns

- About one-third of home fires involving fatalities are caused by smoking
- Develop an escape plan in the event of a fire in the home
- Buy a fire extinguisher for the home
- Install smoke alarms in your home
- Do not drink or carry hot liquids when holding your child or when children are nearby
- Erect barriers around space heaters

Water safety

- Never leave a child alone in or near a tub, pail, toilet, or pool of water
- Fence in your pool or hot tub on all four sides

Auto safety

- Your child should ride in a car safety seat during every trip, even if you will be traveling a short distance
- Never place an infant in front of an air bag
- Seat a child in the rear seat of the car

Bicycle safety

- Do not carry children younger than 12 months on bicycles

Firearms hazards

- Remove all guns from places children live and play

From 1 to 4 years

Household hazards

- Never leave small children alone in the home
- Select an experienced babysitter
- Keep plastic bags and balloons out of reach
- Small objects and solid foods such as hot dogs, peanuts, grapes, carrots, or popcorn may block your child's airway
- Mechanical garage doors may crush a child
- Place operable window guards on all windows in your home
- Keep small children out of the yard while the lawn mower is in use
- Use gates on stairways
- Place your baby's crib away from windows
- Check for hazards in homes your child may visit
- Report any history of injuries to the pediatrician

Firearm hazards

- Remove all guns from places children live and play

TABLE 122.1 (continued)
TIPP Counseling Guidelines

Poisonings

- Keep medicines and hazardous products out of the sight and reach of children
- Dispose of old medicines
- Purchase medicines with child-resistant safety caps
- Inspect walls for peeling paint
- Learn first aid for poisoning
- Heating ventilation systems and fireplaces should be checked at least once a year

Burns

- Do not leave electrical appliances within the reach of a child in the bathroom
- Keep electrical cords out of a child's reach
- Keep matches and lighters out of the reach of children
- Most deaths due to home fires are caused by smoking
- Develop an escape plan in the event of a fire in the home
- Buy a fire extinguisher for your home
- Install smoke alarms in your home
- Check hot water temperature
- Keep hot pots and pans out of the reach of children

Water safety

- Do not leave your child alone in a tub, even for a moment
- Always wear a Coast Guard-approved life jacket
- Fence in your pool or hot tub on all four sides
- Do not let children swim without supervision

Bicycle safety

- Use an approved child carrier

Auto safety

- Children of this age should always be properly restrained in a car safety seat. Select a car safety seat that fits your child's size and weight and that can be installed properly in your car
- Never leave a child alone in a car
- Seat a child in the rear seat of the car
- Never put children in front of passenger air bags
- Buckle up and lock up!
- Young children should not play in driveways or near busy streets

Toy safety

- Inspect toys for safety hazards

From 5 to 9 years

Firearm hazards

- Do not keep guns in your home

Household hazards

- Never let children this age operate a lawn mower or ride with you on one
- Report any history of injuries to the pediatrician
- Heating ventilation systems and fireplaces should be checked at least once a year

Burns

- Develop an escape plan in the event of a fire in the home
- A third of deaths due to home fires are caused by smoking
- Do not let children play with fire
- Buy a fire extinguisher for your home
- Do not let children play with fireworks
- Install smoke alarms in your home

TABLE 122.1 (continued)
TIPP Counseling Guidelines

Water safety
- Teach children how to swim
- Teach and enforce the rules of swimming and diving safety
- Be sure your child wears a life jacket when on a boat

Auto safety
- A booster seat should be used on every trip by all children who have outgrown their car safety seats with harnesses (usually around 40 lb) until the seat belt fits correctly (usually around 4 ft 9 in. tall or between 8 and 12 years old)
- Never seat a child in front of a passenger air bag

Pedestrian safety
- Teach your child pedestrian safety skills

Bicycle safety
- Teach and enforce bicycle safety rules
- Wear a bicycle helmet

Recreational safety
- Wear protective gear during sports
- All children should wear an approved equestrian helmet when riding a horse

From 10 to 12 years

Firearm hazards

Do not play with guns!

Burns
- Check to see that your home has smoke alarms

Bicycle safety
- Never ride with passengers on your bike
- Always wear a helmet when riding a bike

Auto safety
- Buckle up
- Do not sit in front of a passenger air bag
- The safest place for you to ride is in the back seat, buckled up

Pedestrian safety
- Follow safety rules when crossing the street

Water safety
- Never play near water without an adult nearby

Farm safety
- Farm equipment is very dangerous to children

Source: AAP, The Injury Prevention Program (TIPP): A Guide to Safety Counseling in Office Practice, American Academy of Pediatrics, Elk Grove Village, IL, 1994.

GUIDELINES FOR ADOLESCENT PREVENTIVE SERVICES

The Guidelines for Adolescent Preventive Services (GAPS) is a comprehensive set of recommendations developed by the American Medical Association's Department of Adolescent Health that are intended to be applied to 11- to 21-year-old patients. The rationale for GAPS is that at an early age, high-risk behaviors and negative lifestyle patterns can be identified and interventions can reduce premature morbidity and mortality [34].

GAPS is organized into four types of service that address 14 separate topics or health conditions, including injury prevention. GAPS consists of 24 recommendations that encompass health care delivery, health guidance, screening, and immunizations.

GAPS recommendation 6 states, "All adolescents should receive health guidance annually to promote their *reduction of injuries*" [35]. The GAPS health guidance for injury prevention includes counseling to

- Avoid the use of alcohol or other substances while using motor or recreational vehicles or where impaired judgment may lead to injury
- Use safety devices, including seat belts, motorcycle and bicycle helmets, and appropriate athletic protective devices
- Resolve interpersonal conflicts without violence
- Avoid the use of weapons and/or promote weapon safety
- Promote appropriate physical conditioning before exercise

While the physician is responsible for making decisions on how to apply GAPS during interactions with adolescents in their offices, GAPS provide the framework for the organization and content of these preventive health services. The use of the GAPS model can increase clinicians' detection and discussion of risk behaviors [36].

CONCLUSION

Physician counseling can play a critical role in efforts to prevent unintentional injuries. IPC is a promising, but underutilized, prevention strategy. Evidence suggests that it is most effective if based on behavior change theory and used in conjunction with other strategies such as providing access to affordable low-cost safety resources and equipment. The research base is limited relative to the broad array of IPC opportunities, which span the lifecourse from car seats for infants for which much work has been done to falls prevention strategies for older adults where little is known about the role of IPC. There is a particular need to understand if IPC is effective for adult patient populations. Barriers for delivering IPC can be overcome by improving physician medical education to include injury prevention and counseling skills and by providing incentives, such as reimbursement for IPC and safety products distribution as part of covered preventive services. Materials and recommendations from TIPP and GAPS can be used to guide clinicians who wish to incorporate IPC into their practices.

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123 Preventing Traffic Injuries
*Strategies That Work**

Ann M. Dellinger, MPH, PhD and David A. Sleet, PhD, FAAHB

CONTENTS

Traffic Injury and Lifestyle 1463
Epidemiology 1464
Effective Interventions 1465
Alcohol-Impaired Driving 1465
Zero Tolerance Laws 1466
Minimum Legal Drinking Age Laws 1466
Sobriety Checkpoints 1467
Lower BAC 1467
Ignition Interlocks 1467
Server Intervention Training 1467
Screening and Brief Intervention 1467
Increasing Alcohol Taxes 1467
Occupant Protection 1467
Seat Belts 1467
Child Safety Seats 1468
Booster Seats 1468
Rear Seating Position 1468
Motorcycle Helmets 1468
Bicycle Helmets 1468
Graduated Driver Licensing Systems 1468
Parental Monitoring of Young Drivers 1469
Automated Enforcement: Speed Cameras 1469
Interventions with Limited Evidence of Effectiveness 1469
Legislation to Restrict Cell Phone Use While Driving 1469
Designated Driver Programs 1469
Implications for Primary Care Practice 1469
References 1469

Traffic-related injuries have only recently been recognized as a fundamental part of public health practice. With an eye toward the health of populations, but clinical practice at the individual level, primary care providers can have a positive influence on their patients' behavior and help prevent one of the leading causes of death in America. There are many effective strategies to address these preventable deaths and injuries that are closely related to lifestyle factors and can be incorporated into clinical assessments. For example, clinicians can support primary prevention by screening for alcohol dependency and counseling patients about drinking and driving or support secondary prevention by counseling patients about the need for seat belts for themselves and child safety seats (CSS) for their young children. This chapter will describe the current traffic environment, the epidemiology of traffic-related deaths and injury, and review what is known about effective prevention strategies with an emphasis on strategies that are most applicable to lifestyle medicine.

TRAFFIC INJURY AND LIFESTYLE

Traffic-related injury and lifestyle are inextricably linked. Our culture values independence, and for many, independence comes with the ability to drive. The motor vehicle dominates all other modes of travel in the United States. In the span of 100+ years, the number of registered automobiles grew from 8000 in 1900 to 259 million in 2009 [1]. In 2009, 20% of households reported three or more vehicles and

* Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

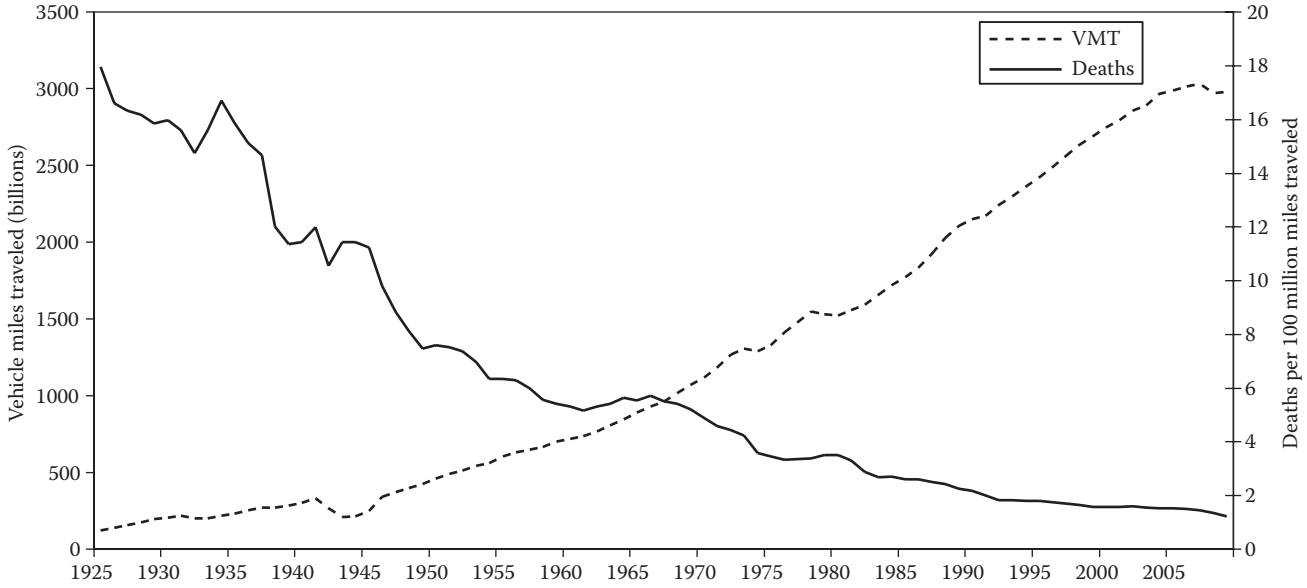


FIGURE 123.1 Annual vehicle miles traveled and motor vehicle-related deaths, United States 1925–2009. (From National Safety Council, *Injury Facts*, National Safety Council Press, Itasca, IL, 2011.)

only 9% reported zero vehicles [2]. A high degree of mobility is integral to our lifestyle. There are more than 200 million licensed drivers in the United States and they drive an average of 14,000 miles/year on 4 million miles of roads [3].

Figure 123.1 indicates that while exposure to the road environment has increased, there has been a long-term decline in the rate of traffic-related deaths, over 90% since 1925 [1], primarily due to advances in the safety of vehicles, roads, and improvements in driver behavior [4], which have mitigated the negative effects of increased motorization. In spite of these declines, traffic crashes remain the leading cause of death among children, adolescents, and young adults and fall within the top 10 causes of death among all age groups combined [5].

EPIDEMIOLOGY

Traffic crashes result in about 33,000 deaths and more than 3 million nonfatal injuries treated in hospital emergency departments each year [5,6]. The risk of death or injury varies by many factors including sex, age, race/ethnicity, type of road user (e.g., occupant, pedestrian, motorcyclist, cyclist (nonmotorized)), and state. There is a significant risk difference by sex. Males have death rates at least twice that of females overall; for vehicle occupants, motorcyclists, pedestrians, and cyclists; and for all age groups after the age of licensure (age groups 15–19 years and older). The difference is especially high for motorcyclists (death rate 10.7 times higher among males) and cyclists (8 times higher among males). For nonfatal injuries, males have higher injury rates than females except in the case of motor vehicle occupants where the injury rate among females is 1.27 times that among males [5].

Death rates vary widely by age with the lowest rates among children aged 0–14 years and the highest rates among those aged 15–24 years and 80 years and older [5]. Young drivers represent 6% of all licensed drivers but are involved in 11% of all fatal crashes [7]. Young drivers have higher crash involvement rates than any other age group; this holds true for fatal crashes, injury crashes, and property damage only crashes [6]. Novice teen drivers have especially high death rates given their lack of experience driving and risk-taking behaviors. Defined later in this chapter, graduated driver licensing (GDL) systems are an effective crash prevention strategy for teen drivers and are the likely reason fewer teens are currently licensed. In 2000, 37% of 16 year olds were licensed drivers compared with 31% in 2009, among 17 year olds, the decline was from 57% to 49%, and among 18 year olds, the decline was from 70% to 64% [8,9].

Older drivers, aged 65 years and older, represent a fast growing segment of the driving population. In just 10 years time, from 2000 to 2009, the number of older licensed drivers grew 20% to 33 million, nearly 16% of the driving population in the country. The proportion of the population who are licensed drivers has also increased in this age group: in 2000, 88% of 65–69 year olds were licensed drivers; in 2009, this had increased to 94%. Similar increases were seen in all older age groups, including those aged 85 years and older, who increased from 48% to 58% [8,9].

Per mile traveled, fatal crash rates increase starting at age 75 years and increase notably after age 80 years. This is largely due to an increased susceptibility to injury and medical complications among older drivers rather than an increase in crash involvement [10]. However, age-related declines in vision and cognitive functioning, as well as physical changes, may affect some older adults' driving abilities. The American Medical Association has resources for physicians to assess and counsel their patients [11].

There are also racial and ethnic differences in crash-related deaths. Generally, American Indian and Alaska

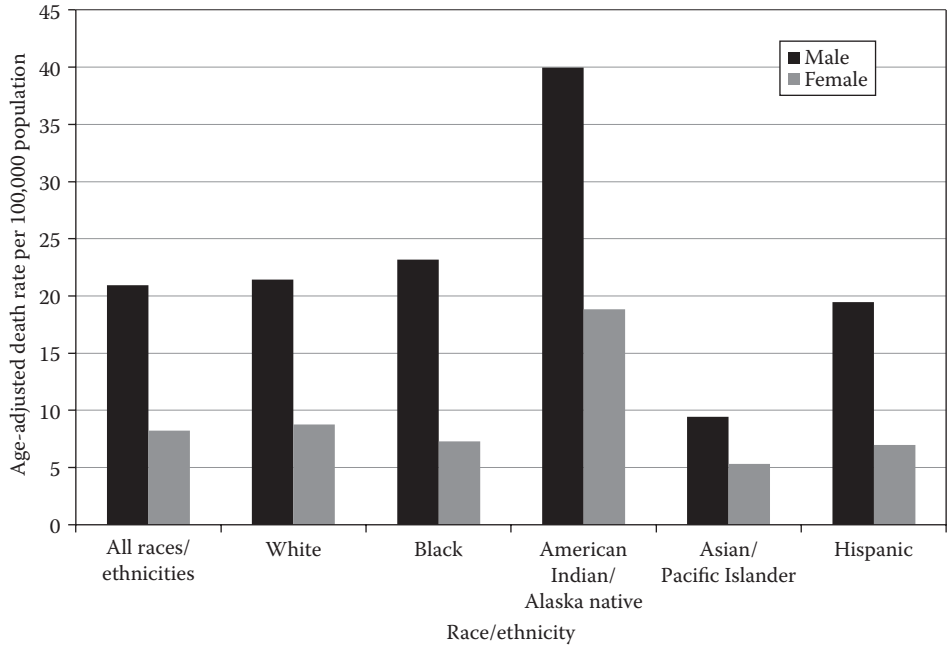


FIGURE 123.2 Motor vehicle-related death rates by race/ethnicity and sex, 2007. (From Centers for Disease Control and Prevention, Web-based Injury Statistics Query and Reporting System [WISQARS].)

Native populations have the highest death rates, while Asian and Pacific Islander populations have the lowest; African American and white populations have similar death rates [5]. However, when adjusting for time on the road, or vehicle miles traveled, vehicle occupants who are African American and Hispanic have higher death rates than whites [12]. Racial and ethnic minorities are disproportionately affected by motor vehicle crashes; approximately 7% of all deaths among American Indian and Alaska Native populations are due to crashes, 5% of all deaths among Hispanics are due to crashes, while less than 2% of all deaths among African American and white populations are crash-related [13]. Figure 123.2 shows age-adjusted motor vehicle-related deaths rates by race/ethnicity and sex. For all racial/ethnic groups, males have higher death rates than females; American Indian and Alaska Native males have higher deaths rates than all other groups [5].

Death rates vary by road user type. Motor vehicle occupants (drivers and passengers) represent the majority of crash deaths, 72%, motorcyclists represent 13%, pedestrians 12%, cyclists 2%, and others 1% [14]. However, these unadjusted statistics do not incorporate exposure to the road environment into their calculation. For example, motorcyclists represent 13% of the crash deaths but only 3% of all registered vehicles and 0.4% of all vehicle miles traveled. Per vehicle mile traveled, motorcyclists are 37 times more likely than a passenger car occupant to die in a crash [15]. Alcohol is prevalent in crashes among motorcyclists; the percentage of drivers with a blood alcohol concentration (BAC) of 0.08 g/dL in fatal crashes was highest for motorcyclists at 29% [16]. For nondrivers, the prevalence of alcohol impairment in fatal crashes was also considerable. Among cyclists killed in crashes, 24% had a BAC of 0.08 g/dL or higher [17]. Among pedestrians killed in crashes, 35% had a BAC of 0.08 g/dL or higher [18].

States vary in the number and rate of traffic crash deaths, the use of seat belts, the incidence of self-reported drinking and driving, the proportion of urban versus rural area, the coverage of level one trauma care centers, safety legislation, and many other factors related to the risk of a crash and the risk of death or injury given a crash has occurred. Consequently, as shown in Figure 123.3, there is nearly a fivefold difference in death rates [5].

EFFECTIVE INTERVENTIONS

While this chapter focuses primarily on strategies designed to modify personal behaviors, it also includes some information on vehicle safety devices and public policies (such as legislation and enforcement) that address other countermeasures. Most strategies, however, are ultimately designed to change the behavior of drivers, passengers, or pedestrians. The intent is to provide a practical review of interventions designed to reduce traffic crash deaths and injuries that can be supported by clinicians, whether through patient education in clinical settings or by advocacy to support effective public policy.

Alcohol-Impaired Driving

In 2009, 32% of all traffic deaths (around 11,000) involved a driver with a BAC of 0.08 g/dL or higher, a level illegal in every state [16]. Each year, millions of adults admit to an estimated 147 million episodes of alcohol-impaired driving [19], yet only a small proportion, 1.4 million, are arrested for this offense [20]. Progress has stalled in this area; while the

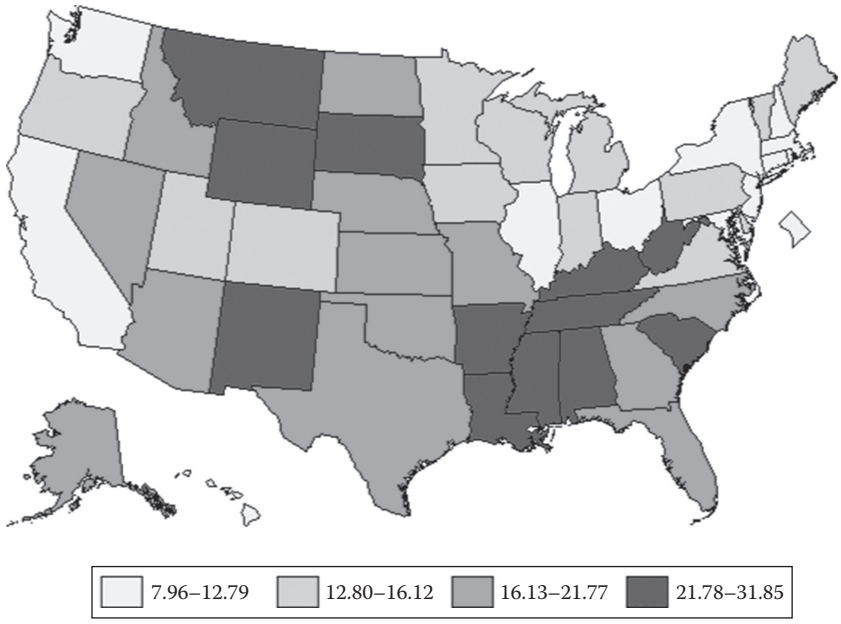


FIGURE 123.3 Age-adjusted death rates per 100,000 population by state. (From Centers for Disease Control and Prevention, Web-based Injury Statistics Query and Reporting System [WISQARS].)

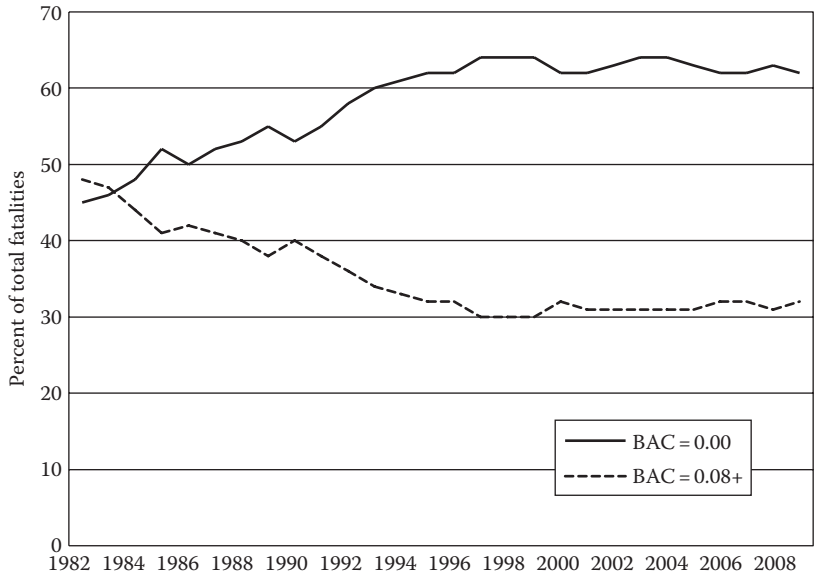


FIGURE 123.4 Proportion of persons killed, by highest driver blood alcohol concentration (BAC) in the crash, 1982–2009. (From National Highway Traffic Safety Administration, Traffic Safety Facts 2009, Early Edition.)

number of alcohol-related traffic deaths has declined with the overall decline in all traffic deaths, the proportion of traffic deaths that are alcohol-related has stabilized. Figure 123.4 shows that since the late 1990s, this proportion has hovered around 30% [21].

Interventions to reduce alcohol-impaired driving include the following:

Zero Tolerance Laws

These laws make it illegal for persons younger than 21 years to drive after any drinking, but the threshold is usually set at 0.02 g/dL BAC. These laws have been associated with declines in alcohol-related deaths [22,23]. Voas et al. found declines from 19% to 24% in underage drinking drivers in fatal crashes [24]. All states have passed zero tolerance laws for young drivers.

Minimum Legal Drinking Age Laws

Minimum legal drinking age (MLDA) laws are effective in reducing alcohol-related crashes and injuries [23,25]. This type of law is especially important given the high crash and death rates of young drivers [24,26–28]. At the same blood alcohol level, crash risk is higher for young drivers than older drivers [29]. All states have increased their MLDA to 21 years, the National Highway Traffic Safety Administration (NHTSA) estimates more than 600 lives saved in 2009 due

to MLDA laws [30]. Lowering the MLDA so that younger people can legally purchase alcohol can increase alcohol-impaired crashes by a median of 10% [23].

Sobriety Checkpoints

Alcohol roadside checkpoints, whether randomly or selectively implemented, are an effective law enforcement intervention. Sobriety checkpoints are generally paired with media efforts to publicize the effort, which helps to increase the perceived risk of arrest. Sobriety checkpoints have been shown to decrease fatal and nonfatal injury crashes [31].

Lower BAC

BAC laws make it illegal "per se" to operate a motor vehicle at or above a specified BAC. Originally set at 0.10 or 0.15, these laws have had their limits lowered over time; 0.08 g/dL BAC laws have been found effective in reducing alcohol-impaired driving [22,23,28]. All 50 states have passed 0.08 g/dL BAC laws that place the legal "per se" limit for driving after drinking (for adults) below 0.08 g/dL. The United States lags behind many other countries that have reduced their legal BAC limit for drivers to under 0.05 g/dL [32].

Ignition Interlocks

These devices prevent a drinking driver from starting the vehicle by requiring the driver to provide a breath sample before starting the vehicle. If the breath sample exceeds a specified blood alcohol content, the ignition is locked, and the vehicle will not start. Reports that have combined data from multiple studies estimate that interlocks account for 65% reductions in driving while impaired (DWI) recidivism, a beneficial effect that is usually limited to the period of installment [33–35]. Because drivers with a prior (DWI) violation are seven times more likely to have a subsequent violation than drivers without a history of DWI [36], ignition interlocks should be considered for all convicted DWI offenders—even first-time offenders.

Server Intervention Training

Server intervention and training programs are designed to prevent patron intoxication and alcohol-impaired driving by offering food with drinks, delaying service to rapid drinkers, and refusing service to intoxicated patrons. Evidence for effectiveness comes from studies of establishments that volunteered to participate in training servers; therefore, management support was well established, and server training was intensive, high quality, and face-to-face (not video training) [23].

Screening and Brief Intervention

Screening for heavy alcohol use and subsequent brief intervention has been found effective in emergency departments [37], trauma centers [38], and primary care settings [39]. A study by Fleming et al. found that two 15 min sessions with a physician followed by two 5 min telephone calls from an office nurse resulted in sustained effects. The treatment group had significant reductions in 7-day alcohol use, number of binge drinking episodes, and frequency of excessive drinking compared to controls. In addition, the treatment group had fewer days of hospitalization and fewer emergency department visits. The largest cost benefit was due to fewer motor vehicle-related events [39]. These results indicate that a modest investment in time and resources can have a clinically important effect that is maintained over several years.

Increasing Alcohol Taxes

Alcohol excise taxes affect the price of alcohol and are intended to reduce alcohol-related harms, raise revenue, or both. Alcohol taxes are implemented at the state and federal level and are beverage specific (i.e., they differ for beer, wine, and spirits). A systematic review of 73 studies looking the relationship between either tax rates or total price on measures related to excessive alcohol consumption and its harms found consistent evidence that higher alcohol prices were associated with less youth drinking. The bulk of the studies showed higher prices were related to fewer traffic crashes and deaths, less alcohol-impaired driving, less mortality from liver cirrhosis, and less all-cause mortality. Effects were also demonstrated for outcomes of violence, sexually transmitted diseases, and alcohol dependence [40].

Occupant Protection

Occupant restraints, including lap and shoulder belts, CSS, and booster seats, are among the most effective injury prevention interventions available. Seat belts reduce the risk of death and serious injury in a crash by about half [41]. CSS are 71% effective in reducing fatalities among infants and 54% effective among toddlers. An estimated 284 children younger than 5 years were saved in 2009 by CSS [42]. Booster seats are 59% more effective than adult belts alone in reducing injury in age- and size-appropriate children [43].

Interventions to increase occupant protection include the following:

Seat Belts

Seat belts provide the greatest protection available to drivers and occupants. The National Occupant Protection Use Survey conducted in 2010 found belt use to be 85% nationwide [41]. To date, 49 states, the District of Columbia, Puerto Rico, and all U.S. territories have adult seat belt use laws in place. Primary enforcement laws allow a law enforcement officer to stop a motorist based on a belt violation alone, while secondary enforcement laws require another reason to stop a motorist other than a seat belt infraction. Both primary and secondary enforcement laws are effective in increasing belt use and reducing fatal and nonfatal injury, with primary laws showing the greatest effectiveness [44–46]. As of January 2011, 19 states do not have primary enforcement laws [47]. Enhanced enforcement programs of seat belt laws, through more officers on patrol, or by increasing the number of citations issued, are also effective in reducing fatal and nonfatal injuries and increasing belt use [44].

Child Safety Seats

All states require children to be restrained, although the specifics of coverage vary [48]. CSS use laws require children to be restrained in federally approved safety seats appropriate for the child's age and size. CSS use laws decrease fatal and nonfatal injury and increase CSS use. Distribution of safety seats, plus CSS education programs, in combination, have been found to decrease fatal and nonfatal injury, increase CSS use, and increase possession of CSSs. Community-wide information plus enhanced enforcement campaigns have also been found to increase CSS use. Finally, incentive plus education programs (including rewards for either parents or children for correctly using CSS) have been shown to increase CSS use [49,50].

Booster Seats

Booster seats are designed to raise a child so that the vehicle lap and shoulder belts fit properly. They are recommended for children until they reach 4 ft 9 in. tall, usually between ages 8–12 years [51]. A systematic review of the impact of various legislative, educational, and promotional interventions among children aged 4–8 years found that interventions that combined education with distribution of booster seats or incentives such as discounted coupons had the greatest positive impact [52]. Moreover, booster seat legislation has been shown to reduce injury and save costs [53,54].

Rear Seating Position

The number of children sitting in the front seat is declining. Although the catalyst for moving children to the rear seat was the danger from passenger-side air bags, rear seating position is still the safest place for children whether or not there is a passenger-side air bag present [55–57]. A recent study found that children in the rear row(s) of the vehicle were one-half to two-thirds as likely to sustain injury than those in the front [58].

Motorcycle Helmets

Motorcycle helmets are estimated to be 37% effective in preventing fatal injury to motorcyclists [59], and 72% effective in reducing head injury [60]. Helmet use is especially important since, per vehicle mile traveled, motorcyclists are about 37 times more likely to die in a crash than passenger car occupants. Motorcycle helmet use laws are effective. In states with mandatory or universal (covers riders of all ages) helmet use laws, 76% of motorcyclists wear them—without a law, use is 40%. In 2010, 20 states plus the District of Columbia required helmet use by all operators and passengers. An estimated 71% of motorcyclists wore helmets in 2000, compared with only 54% in 2010 [61].

Bicycle Helmets

Bicycle helmets are effective in preventing head injury, brain injury, facial injury, and death [62–64]. However, only about half of children aged 5–14 years always wear their helmets when riding, and less than half the states in the United States have statewide helmet laws in place [65]. Interventions designed to increase bicycle helmet use generally target children and adolescents, as does legislation requiring helmet use. Legislation with supporting helmet promotional activities has successfully increased observed helmet use and reduced injury and death in the United States and abroad [66–69]. Community-based interventions that included free helmets and an educational component had the strongest evidence of effectiveness, along with school-based interventions and those that subsidized helmets [70].

Graduated Driver Licensing Systems

Motor vehicle crashes are the leading cause of death among teenagers in the United States. GDL systems address the high risks faced by new drivers by requiring an apprenticeship of planned and supervised practice (learners permit stage) followed by a provisional license that places temporary restrictions on unsupervised driving [71]. Two commonly imposed restrictions are limits on nighttime driving and passenger limits. These restrictions are lifted as new drivers gain experience and teenage drivers mature (full licensure). Although the specific requirements for advancing through the three stages of GDL vary across jurisdictions, they provide a protective environment, while new drivers become more experienced. GDL has proven effective in reducing new driver crash risk, and the stronger the policy the stronger the effect [72–76]. The most restrictive GDL policies were associated with a 38% reduction in fatal crashes among 16 year old drivers [77]. Figure 123.5 shows the number of states with GDL plotted by the fatal crash rate involving 16 or 17 year old drivers and indicates that the more states with GDL systems, the better the outlook for young novice drivers [21,78].

An issue related to GDL and teen driver safety is driver education resulting in early licensure. Early licensure can lead to increased exposure of inexperienced drivers and to

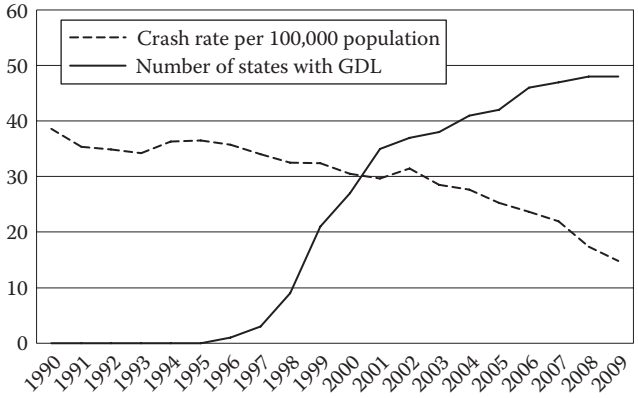


FIGURE 123.5 Fatal traffic crashes involving 16 or 17 year old drivers, United States, 1990–2009 and number of states with a graduated driver licensing (GDL) system. **GDL is defined as a graduated driver licensing law that includes an intermediate stage (From National Highway Traffic Safety Administration Traffic Safety Facts 2009; Insurance Institute for Highway Safety, Highway Loss Data Institute.)

more crashes. School-based driver education training can often lead to earlier licensure, which can be harmful. Studies by Levy, Vernick et al., and Roberts and Kwan [79–81] have consistently indicated that young drivers who take driver education tend to get their licenses earlier than young drivers who do not. Any potential safety benefit from the driver training may be offset by the increase in exposure of teens to unsupervised driving.

Parental Monitoring of Young Drivers

Although not definitive, there are studies of the effect of parental monitoring on young driver safety. Results have varied from indicating no effect to modest effects on risky driving behaviors [82]. However, parents are in a strong position to delay licensure and to restrict driving under higher risk conditions, such as nighttime driving and driving with teenage passengers [83,84], whether or not these restrictions are part of their states' GDL law. Research has shown that teens whose parents set and maintain strict limits are less likely to engage in risky driving behaviors, have traffic violations, or to crash during the first year of licensure [84]. Clinicians are in a unique position to counsel parents about their responsibility and effectiveness in keeping their teens safe on the road.

Automated Enforcement: Speed Cameras

Speed affects both the likelihood of a crash and the severity of a crash. Crashes at higher speeds are more severe and, therefore, the risk of injury is greater. For vulnerable road users, such as pedestrians and cyclists, this is especially problematic. Automated enforcement is one way to obviate conventional enforcement, which requires law enforcement officers to stop drivers and issue citations and the likelihood of being caught speeding is relatively low. Automated speed enforcement has been shown to reduce speeds and speeding violations [85]. Reviews of the effectiveness of speed cameras have found decreases in both crashes and injuries [62,86,87].

INTERVENTIONS WITH LIMITED EVIDENCE OF EFFECTIVENESS

Legislation to Restrict Cell Phone Use While Driving

Research has shown that drivers using cell phones are four times more likely to be involved in a serious crash [88]. Research by the AAA Foundation found that 69% of drivers reported that they had talked on a cell phone while driving in the past 30 days [89]. Cell phone legislation varies with some states or localities banning handheld devices, some banning use among young drivers or bus drivers, and some state bans including texting while driving. Although most people agree that using a cell phone while driving is unsafe, the effectiveness of legislation to address this problem has yielded inconsistent results [82]. A paradox for safety researchers is the increasing use of cell phones during a time of declining crashes.

Designated Driver Programs

A designated driver is a person who agrees to either abstain or limit alcoholic consumption and drive others home. Designated driver promotion programs set in restaurants or drinking establishments encourage individuals to act as designated drivers by offering incentives such as free nonalcoholic drinks, food, or free admission. Despite their widespread use in the United States, relatively few programs have been thoroughly evaluated. A systematic review of designated driver programs in drinking establishments found insufficient evidence of their effectiveness in reducing alcohol-impaired driving or alcohol-related crashes [90]. A more recent review by Nielson and Watson found that while awareness and use of designated drivers may increase, evidence of a reduction in drinking and driving or alcohol-related crashes has not been well documented [91].

IMPLICATIONS FOR PRIMARY CARE PRACTICE

Despite the great success in reducing motor vehicle-related death rates in the past 50 years, motor vehicle crashes remain the leading cause of injury-related deaths in the United States. Primary care practitioners have the opportunity to reduce death and injury using a variety of strategies, including screening and counseling [92–94]. Practitioners also can help patients understand the importance of reducing their exposure to risk on the road and the importance of safety behaviors. In clinical practice, traffic injury prevention can become a regular part of the practice of lifestyle medicine and integrated into care and preventive services. Science tells us that traffic injuries are not "accidents"—they are predictable and preventable. Through efforts to educate and change behaviors, promote stronger traffic safety legislation and enforcement, and encourage more effective use of technology and engineering, lifestyle medicine can contribute to reducing traffic injuries and help promote a culture of safety [95].

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124 Child Injury
The Role of Supervision in Prevention

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CONTENTS

What Is "Supervision"?....1473
What Is "Adequate" Supervision?....1474
How Should Supervision Be Measured?....1474
Supervision and Injury: A Complex Process....1475
Supervisor Presence Influences Children's Risk Taking....1475
Supervisory Behaviors and Child Injury....1475
Environmental Risks....1478
Strategies to Promote Supervision....1478
Conclusion and Future Directions in Research....1479
Acknowledgments....1480
References....1480

Unintentional injury poses a significant health threat for children. In most industrialized nations,[1] including the United States, unintentional injuries are the leading cause of death for children older than 1 year of age.[2,3] In fact, the number of injury-related child deaths in the United States exceeds that of the next nine causes combined.[2] Approximately 12,000 Americans of 0–19 years die annually from an unintentional injury, about 33 children per day.[4] The financial burden is staggering. For example, in 2000, injuries to American children cost an estimated $24 billion in lifetime medical expenses and $82 billion in present and future work losses, including the caregiver's income loss.[5] Of course, these costs do not even account for the burden of suffering and reduced quality of life that can result from injury. There is a pressing need to identify the key factors that influence the risk of injury to children so that interventions can be developed to address these issues.[6–8]

Caregivers can substantially influence children's risk of injury,[9] particularly for toddlers and preschool-aged children whose injuries often occur in the home when they are presumably being supervised by a caregiver.[10–12] Because many of these injuries have been judged to be preventable,[13] there has been considerable interest aimed at understanding what caregivers do, why they make the choices they do about safety practices, and how to motivate them to make better choices in order to reduce children's risk of injury at home. Historically, this research has focused primarily on environmental modifications by caregivers (e.g., use of safety devices, hazard removal practices)[14–18]; however, recognition that not all risks can be addressed by environmental modifications has fueled interest in studying supervision as a risk management strategy.

WHAT IS "SUPERVISION"?

For the most part, past research on "supervision" did not specify a definition of the term. And those definitions that have been published are often vague and not based on any conceptual framework about supervision. Moreover, often in past research, the *act of supervising* (i.e., directly observing and attending to the child) and *monitoring* from a distance based on prior knowledge of the child (i.e., the child is not in view but the supervisor has sufficient prior experiences to surmise where the child is likely to be and what she or he is probably doing) have been used interchangeably as indicators of "supervision" even though it has never been confirmed that a supervisor's past knowledge about a child's behavior is an adequate substitute for directly observing and attending to that child's actual behavior. Given that studies of childhood injuries have highlighted how unpredictable young children's behavior can be,[19] Morrongiello has argued that direct "attention" to confirm what the child is doing is an essential aspect to defining "supervision" if one is interested in relating the construct to injury risk.[20] Monitoring from a distance, therefore, may be more developmentally appropriate and commonplace than direct observation for older school-age children, but this is not likely to yield as many protective benefits as direct observation in which one frequently confirms the child's location and activity.[21] Consistent with this view, low levels of monitoring (i.e., awareness of a child's activities and location) have been associated with high levels of problem and risk-taking behaviors,[22] as well as with more frequent injuries.[23]

Drawing on this developmental literature, Morrongiello recently proposed a definition of supervision to guide

research on children's risk of injury.[20] Three dimensions of behavior are considered in the definition: *attention* (extent of watching and listening, which is relevant for determining when to intervene), *proximity* (within versus beyond arm's reach, which is relevant to readiness to physically intervene with a child who may not comply with a verbal directive[24]), and *continuity* of attention and proximity (coded as constant, intermittent, not at all). Maximum supervision and lowest risk of injury occur when a supervisor is attentively watching and listening to the child, is in the closest proximity possible (i.e., touching), and these behaviors are sustained and constant over time. Any change in one or more of the three dimensions (e.g., being farther from the child, lack of constant attention) would result in lower levels of supervision and, therefore, increase injury risk. The usefulness of this definition has been confirmed in studies that have found that distinct patterns of supervision systematically relate to children's frequency of injury (see the following literature).

WHAT IS "ADEQUATE" SUPERVISION?

A number of factors influence the level of supervision needed to ensure a child's safety, making it difficult to determine what constitutes "adequate" supervision. A child's developmental level, often indexed by age, is one such factor. Not surprisingly, young children require continuous, close supervision to ensure their safety in most situations, and the need for continuous, direct supervision declines with increasing age during childhood.[23,25] There are no guidelines or minimal standards for supervising children at different ages, however, and professionals do not agree about possible guidelines.[25] The most common approach, therefore, is to set a minimum legal age at which children can remain at home unsupervised. It should be emphasized, however, that these cutoff ages are not based on any scientific evidence, which is probably why they vary so much across jurisdictions (e.g., some states set this cutoff as young as 8 years and others as old as 13 years).

Situational context is another variable that impacts what constitutes "adequate" supervision. When environmental risk is high, it is generally accepted that time unsupervised should be minimal to ensure a child's safety,[25,26] and evidence based on studies of pediatric farm injuries confirms this.[27] Furthermore, Morrongiello and her colleagues examined supervision at the time of farm injuries[19] and found that one-third of the children who were injured were receiving what would typically be considered "adequate" supervision (i.e., acceptable levels of attention, proximity, and continuity). This increased injury risk under presumably adequate supervision reflects the fact that when children are on a farm, being in *close proximity* to an adult often means *greater* exposure to hazards (e.g., machinery, animals) because the adult is working. Findings such as these highlight the challenge of determining what constitutes "adequate" supervision. Simply stated, if both child age and situational context interact to influence the risk, it may be unrealistic to create one set of guidelines that aims to protect all children in all circumstances.

HOW SHOULD SUPERVISION BE MEASURED?

A variety of approaches to measuring supervision have been used in research, including questionnaires, naturalistic observations, and self-report diary measures. When questionnaires are used, parents are often asked to describe how they supervise their own children[24,28–36] or how they would supervise a child in particular situations.[25,26,37,38] Sometimes parents have listened to story vignettes or watched videos about children engaging in risky behaviors and then reported on how they would react if they were supervising the child shown.[39] A handful of studies have used participant event-monitoring, in which parents have been asked to keep track of their actual supervision over a 24 h period and over days.[26,35,40–44] Supervision at times when children happened to be injured can then be compared to times when the child was not injured, providing insight into patterns of supervision that are associated with injury. Although a potential limitation of self-report measures is the possibility of response bias in that parents may be reluctant to report information if they feel it could reflect poor parenting skills, the fact that parents readily report leaving their child unsupervised (see next section) suggests that this concern may not apply in these research studies.

Morrongiello has suggested an alternative approach to self-reports about supervisory practices, namely, to focus on measuring parent attributes (e.g., attitudes toward supervising closely, beliefs about children's need for close supervision, parenting values related to safety, personality traits that impact parent practices such as conscientiousness) that provide a foundation for parenting decisions and supervisory "styles" (i.e., consistent behavioral patterns or approaches to supervising). Applying this approach, she developed the Parent Supervision Attributes Profile Questionnaire (PSAPQ[29]), which measures parental attributes that have been shown to influence supervision decisions. Psychometric evaluations have shown that the measure is both reliable and valid.[30] High scores on the PSAPQ have been shown to predict closer supervision and low scores to predict poorer supervision in naturalistic observation situations, and these scores positively relate to children's frequency of both risk taking and injuries. Recently, this approach was extended to develop a similar measure (Supervision and Risk Taking Questionnaire) that applies to the supervision of elementary school children[45]; preliminary testing of the measure shows good validity and that scores relate as one would expect to measures of actual parental supervision and children's frequency of injuries.

Observational studies are also an excellent approach to measuring supervision as they provide insights into how caregivers supervise in typical situation.[46–50] For example, Harrell conducted a series of naturalistic observations of children and their supervisors in the grocery store and found reliable variations in child risk behaviors depending on supervision patterns.[51–55] Although observational studies are high on ecological validity, they are very time and labor intensive and not applicable to all settings (e.g., home). An alternative

approach that has been developed is to conduct naturalistic observations in a laboratory setting that contains "contrived" hazards, that is, hazards that appear real but that have been modified to pose no real risk of injury (e.g., blue water in a Windex bottle, glue-shut sharp scissors).[24,56] This approach creates a "simulated" risk situation, and if supervisors' reactions are unobtrusively video recorded, then one can obtain a highly accurate index of "typical" supervision practices in situations that pose some risk of injury. Although not all injury risks are amenable to being recreated in a contrived situation, this is an excellent approach to measuring supervision under seemingly natural conditions for those hazards that can be so represented.

Supervision and Injury: A Complex Process

It has long been assumed in the child injury literature that supervision must serve a protective role and prevent injury, particularly for preschool children who have limited capacity to keep themselves safe.[9,57,58] Some have gone so far as to argue that if an injury can be attributable to inadequate supervision, then this should be reported as child abuse/neglect.[59] Most of this speculation about supervision, however, is fueled by "indirect" evidence, such as the fact that there is increased frequency of injuries for children living in families with only a single parent[69] or with multiple siblings at home.[70] Although insufficient caregiver attention has been mentioned as a contributing factor for a variety of types of childhood injuries (drowning,[60] pedestrian injuries,[61,62] poisoning,[63] choking,[32] playground injuries,[64] dog bites,[65] escalator injuries,[66] falls,[51] and injuries from handling dangerous substances in grocery stores[54] or at home[67]), this is based on logical arguments rather than evidence.[68] Studies aimed at directly examining links between supervision and child injury risk have only recently been conducted, and the findings suggest a more complex interrelation than previously thought.

SUPERVISOR PRESENCE INFLUENCES CHILDREN'S RISK TAKING

Not surprisingly, individuals behave differently depending on whether or not a supervisor is present. School-age children have been shown to behave more cautiously when a supervisor is nearby.[71,72] Similarly, young children have been shown to engage in more risky play activities at supermarkets and playgrounds when supervisors are more distant physically.[29,51] Even adult and child swimmers have been shown to violate more rules in public pools when there are fewer lifeguards present.[55]

Sex differences in how boys and girls behave when a supervisor is present also have been noted. For example, in a prospective study of home injuries and caregiver supervision patterns, the intermittent appearance of a parent supervisor was sufficient to reduce girls' risk taking to the low level observed when the supervisor was continuously present. In contrast, boys' risk taking was as high in frequency as when they were completely unsupervised for an extended period of time.[35] Similarly, unobtrusive observations of parent–child dyads in injury-risk situations revealed that boys do more ignoring of supervisors than girls, resulting in caregivers needing to enact increasingly more effortful supervision strategies (e.g., when verbal redirections are ignored, they then need to physically redirect the child) to ensure that boys do not interact with hazards.[24]

In summary, the presence of a supervisor often reduces children's risk taking, and for girls even the intermittent appearance of a supervisor achieves this outcome. Generally, even if the supervisor is continuously present, boys require more effortful supervision efforts than do girls to keep them safe.

SUPERVISORY BEHAVIORS AND CHILD INJURY

Ideally, parents should engage in the highest level of supervision possible (i.e., continuous watching, close proximity); however, this is not often the case. Consistent with social-cognitive models of health behavior,[73] research indicates that parents are "strategic" in allocating effort. Hence, the safety strategies they implement vary with their injury-risk appraisals (likely occurrence of the injury, beliefs about their child's personal vulnerability, the potential injury severity, and the extent to which they attribute injuries to bad luck), as well as parent characteristics (e.g., personality characteristics such as conscientiousness, parenting style such as permissiveness), environmental context (e.g., presence of hazards), and perceived child attributes (e.g., age, personality).[35,44,74–79] For example, parents engage in more child safety practices if they believe that resulting injuries are likely to be severe and their child is particularly vulnerable (e.g., due to age or personality); the level of inconvenience to the parent is low in terms of time, cost, or effort; and they feel they have the potential to lower risk and actually prevent injury. In fact, drawing on research on the determinants of parents' safety practices, Morrongiello developed an evidence-based conceptual model (see Figure 124.1) that illustrates the multi-determined nature of childhood injury risk and how factors often interact to influence parent safety decisions and determine injury risk.[20] Similarly, complex interactions among risk factors are emerging in research relating caregiver supervisory behaviors to children's risk of injury.

Evidence that supervision relates to frequency of children's injuries has been reported in a number of studies. For example, in a prospective study of children's minor injuries in the home, examining the patterns of supervision provided by parents to 2–3 year-olds at the time of injury revealed five levels of supervision, and as supervision level decreased, there was an increase in the frequency of children's injuries.[35,79] Similarly, research relating reports of supervision on a questionnaire measure (PSAPQ[29,30]) to children's injury histories revealed that mothers who more strongly endorsed statements indicative of supervision (e.g., "I keep a close watch on my child") had children with a history of fewer injuries. Most recently, applying a case–control design, the supervision

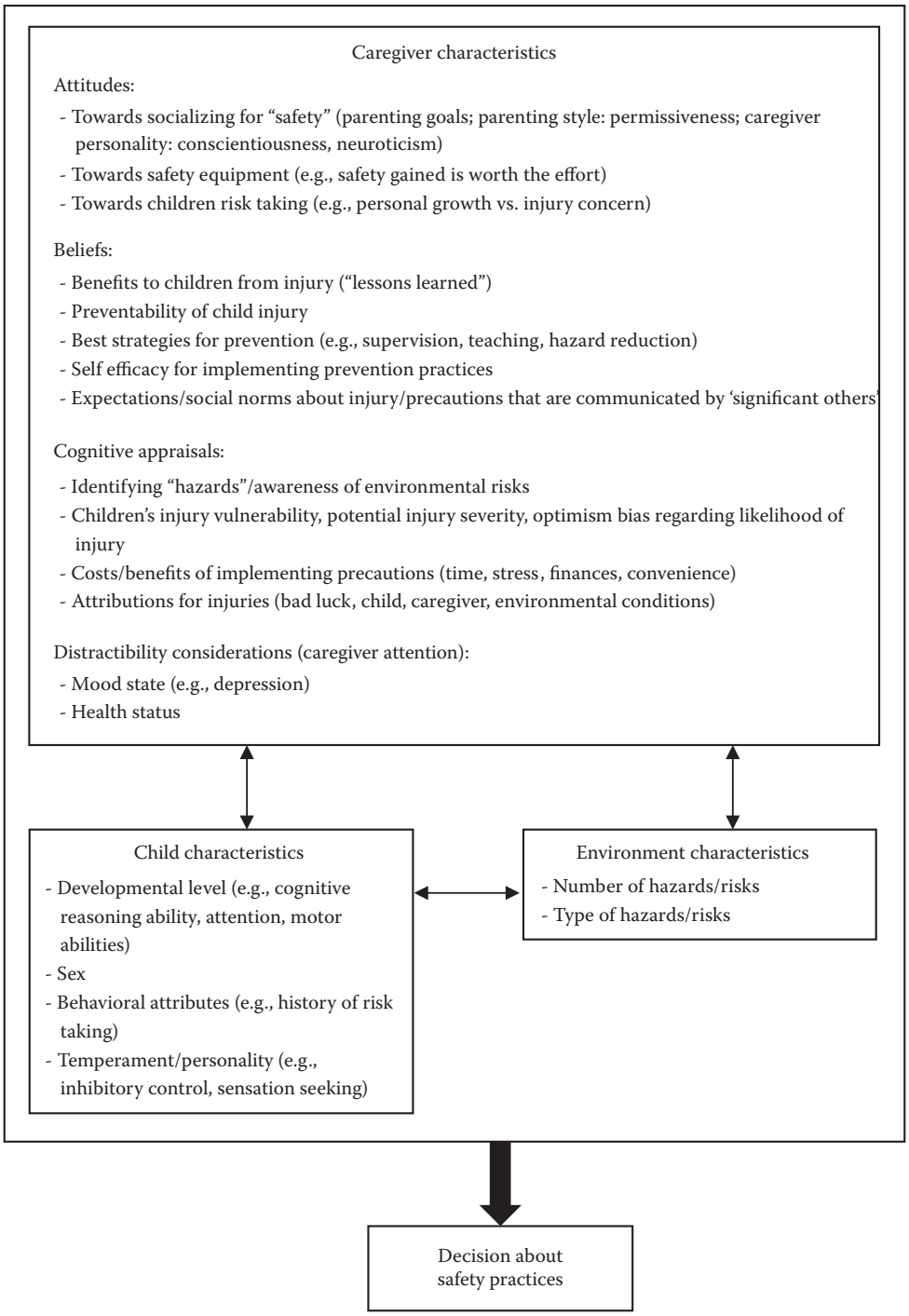


FIGURE 124.1 Empirically derived conceptual model representing the dynamic interplay of factors that affect caregivers' decisions about whether or not to implement safety precautions to prevent injury to young children. (Adapted from Morrongiello, B.A. and Corbett, M., *Health Psychol. Rev.*, 2, 191, 2008.)

provided "injured children" (cases) at the time of injury was compared with that experienced by same age/sex-matched "uninjured ill children" (controls) the last time they did the activity that resulted in injury to their matched case, with all children recruited at the same hospital emergency department to match for demographic characteristics.[80] Results revealed significantly lower levels of supervision for injured than uninjured children, and this pattern emerged across several measures of supervision. Thus, a number of studies have now confirmed that at the time of injury (minor or medically attended), there is often a reduced level of supervision relative to noninjury times.

Complexity in the relation between supervision and injury risk emerges, however, when one considers the more general question of "how caregivers *routinely* supervise" on a day-to-day basis. This research reveals that young children are

unsupervised (i.e., parent does not know where the child is or what the child is doing) for up to 8% of their awake time when at home with a parent and they are completely out of view of supervisors an additional 20% of their awake time.[44] The fact that not all children incur injuries under reduced supervision conditions, however, raises questions about why reduced supervision poses injury risk for some children more so than for others.

Exploring the possibility that child behavioral attributes *interact* with supervision to increase injury risk for some children, Morrongiello and her colleagues found mothers altered their level of supervision according to their beliefs about their child's behavioral attributes.[35,78] Moreover, supervision statistically moderated the relation between several of children's behavioral attributes and injury outcomes, confirming that injury risk arises from an *interaction* between child behavioral attributes and caregiver supervision level.[81] Children who scored high in behavioral intensity had a history of more medically attended injuries when their parents reported reduced supervision but not when their parents reported close supervision. Thus, more intense supervision counteracted the elevated risk of injury typically found for temperamentally difficult children.[82,83] On the other hand, the child attribute of inhibitory control (e.g., child can exercise self-control and resist doing things prohibited by a caregiver) always served a protective function; thus it predicted fewer medically attended injuries even under conditions of *reduced* supervision. Children high in sensation seeking (i.e., the tendency to seek novel and excitement-eliciting risky activities),[84] experienced increased risk of medically attended injury *regardless* of the level of supervision, whereas for children low in sensation seeking, less supervision was associated with more frequent injuries. Figure 124.1 illustrates the dynamic interplay of these various risk factors.

Overall, the pattern of these findings suggests that high levels of supervision can counteract the potential negative effect on injury risk of some child attributes, thereby serving a protective or risk-reducing function. However, there are some attributes (sensation seeking) for which this is less likely to occur and there are other attributes (inhibitory control) for which supervision is less relevant for children's injury risk. Thus, relations between supervision and injury are complex, and it is not always the case that more supervision is necessary or sufficient to reduce children's risk of injury. This type of complexity mitigates against formalizing guidelines about "adequate" supervision that can apply broadly to all children in all circumstances.

Additional evidence that supervision interacts with child behavioral attributes to influence injury risk can be found in the limited research examining siblings as supervisors. Younger siblings are one-third more likely to be injured when supervised by an older sibling, particularly when the supervisee is less than 2 years of age and there is less than a 2 year interval between children.[85] Although few studies have explored how often siblings act as primary supervisors in North America, one study in the United States found that this occurred 8% of the time after school[86] and another in Canada reported 11% of the time when sibs were awake and at home together.[87] The general assumption in the literature has been that the risk arises because older children who supervise younger siblings lack the judgment[85] and cognitive skills[88] to effectively deal with young children and they are, therefore, poorer supervisors than adults. Recent evidence, however, reveals a more complex process than this and suggests that both supervisee *and* supervisor behaviors elevate the risk of injury to the supervisee.

Research examining injury history scores of supervisees and relating these to the extent of sibling supervision has shown that the more often siblings (approximately 6 years of age) supervised, the more frequently younger children (approximately 2 years of age) experienced minor and moderately severe injuries.[87] When parents were asked to comment on this finding, they believed that older siblings supervised in similar ways to parents but that younger children were less compliant with sibling supervisors. And, in fact, parents' ratings of their younger child's compliance when the older sibling was supervising predicted the younger child's frequency of injury better than how often the older sibling supervised. Consistent with this finding, recent evidence comparing how young children behave with sibling versus parent supervisors reveals greater noncompliance by supervisees in response to sibling than parent supervisors.[89] In fact, negative cyclical interactions between younger and older siblings occurred often when siblings supervised, fueled by both noncompliance from the supervisee and a high frequency of prohibitions from the supervisor, and this often then detracted attention from the actual safety issue.

Direct comparisons of the supervisory practices of sibling and parents when looking after a younger child in the family have shown, in contrast to what parents believe (see earlier text), that older siblings are *poorer* supervisors than parents. Specifically, parents engaged in more proactive safety behaviors by removing hazards, whereas older siblings more often modeled injury-risk behaviors by interacting with interesting hazards and this then led supervisees to interact with these same hazards. Although supervisees displayed more injury-risk behaviors when supervised by a sibling, sibling supervisors were less attentive to supervisee risk behaviors than parents,[90] sibling supervisors reacted to only one-third of risk behaviors by supervisees, whereas parents were more vigilant and reacted to stop most of these risk behaviors. And sibling supervisors reacted to risk behaviors with more forceful prohibitions, whereas mothers adopted a teaching orientation and gave more explanations and directions in response to risk behaviors by the supervised.[90] This was fueled, sibling supervisors were generally mostly concerned with controlling the immediate behavior by the supervisee rather than with promoting understanding about any underlying safety- or rule-based issue. In contrast, mothers' reactions to risk and rule violation behaviors balanced prohibitions

with teaching, and they emphasized explaining about risk and rules to reinforce the supervisee's understanding for the prohibition. From a learning perspective, the reactions of maternal supervisors are more likely to promote understanding by the supervisee and, therefore, to increase the likelihood a young child might avoid the behavior in the future. Moreover, research relating childrearing practices to compliance reports that children who receive more directives and prohibitions by caregivers react with more defiance and noncompliance.[91–94] Thus, frequent forceful prohibitions by sibling supervisors, even when these are appropriately delivered in response to a risk or rule violation by the supervisee, are likely to result in greater noncompliance by the supervisee that then fuels the delivery of further prohibitions and leads to an escalating cycle of negative interactions that increases risk of injury to the supervisee. In summary, the process leading to elevated injury risk among young children when supervised by older siblings is a fairly complex one that involves interactions of behaviors by both the supervisor (poorer supervision) and the supervisee (noncompliance).

ENVIRONMENTAL RISKS

In addition to supervision interacting with child attributes to influence the risk of injury, level of environmental risk is another factor to be considered. Generally, proximity to a supervisor enhances readiness to intervene and, therefore, reflects a high level of supervision that is associated with reduced risk of injury to children. Exceptions to this finding, however, illustrate that the extent of environmental risk matters too.[19]

Based on a retrospective review of the circumstances of 334 pediatric farm injuries that resulted in death or hospitalization, patterns of supervision were coded according to attention, proximity, and continuity. Surprisingly, approximately one-third of injuries occurred under what traditionally would be interpreted as "adequate" supervision, namely, supervision was available, proximal, and continuous. Further analyses revealed that such injuries occurred because, on farms, children who are proximal to adults are typically in the vicinity of environmental hazards (e.g., machinery, animals) because supervising adults are also engaged in farmwork. Hence, while proximity to a supervisor usually increases readiness to intervene and improves supervision, in farm contexts, it often increases exposure to environmental hazards. Coupled with normative unpredictability in how young children behave, this creates risk of injury by increasing the likelihood they will interact with hazards, particularly preschoolers.[27] Thus, defining "adequate" supervision is more complex than assuming greater attention, proximity, and continuity will necessarily translate into a reduction in children's risk of injury. What constitutes "adequate" supervision will likely need to reflect a consideration of the interactions between the environment and child characteristics, and different definitions of "adequate" are likely to be needed for different types of children in different risk environments.[25]

Interestingly, for certain activities and contexts, such as in organized sports, there is debate about not only what constitutes "adequate" supervision but whose responsibility it is to provide this supervision. Should an older child be expected to consistently follow safety rules that have been stated by a coach, making close supervision not essential? Should parents who are present assume responsibility for supervising their children during organized/team sports activities? Are coaches substituting for parents and responsible for supervising every child at all times?[95] Many of these issues remain to be resolved, but there is increasing interest in them given the frequency of children injured when participating in organized sports activities.

Strategies to Promote Supervision

Surprisingly, despite how often supervision is mentioned as a risk factor for injury in the pediatric literature and the relevance it has for parenting neglect,[96,97] there are no published prevention programs that aim to improve supervision. Much is known about strategies to increase caregivers' safety knowledge and/or their use of safety devices for hazard reduction in the home.[14–16,18,98,99] However, supervision probably matters at least as much as household hazards for preventing childhood injury because not all hazards can be removed from the environment.[100] Interestingly, parents do not seem to realize this. For example, in a study of caregiver perceptions of factors that led to child injury in/around the home, poor supervision was not even mentioned as a contributing factor. Instead parents focused on hazards in the physical environment, citing passive prevention approaches as primary ways to improve a child's safety at home.[101] Thus, despite the fact that caregivers recognize that close supervision can promote children's safety,[37] they do not seem to recognize (or are unwilling to admit) that supervisors are implicated when young children are injured. These opinions probably arise out of a need to preserve self-esteem and a positive parental identity[102] and to reduce guilt after a child is injured.[103] It is particularly important, therefore, that messaging aimed at improving caregiver supervision does not evoke defensiveness or challenge parenting identity. In fact, several recent advances have been achieved with regard to identifying messaging that is effective to motivate parents to more closely supervise.

A recent study explored parental reactions to different types of messages about supervision and identified several that were effective to elicit caregivers' commitment to supervising children more closely. Because parents prefer parenting information in a video format[104,105] and this has the added benefit of standardizing message delivery across individuals, the investigators used this approach to present the different types of messages to parents.[106] The 20 min video comprised three phases and incorporated different messaging strategies that were aimed at eliciting distinct cognitive and emotional reactions that would promote a readiness to change and culminate in parents' commitment to changing their supervisory patterns and more closely attending to their child when at home. Focus group testing of the video with

TABLE 124.1
Summary of Key Messages That Parents Endorsed as Promoting a Commitment to More Actively Supervise Their Child

Aim of Message	Messaging Approach
1. Educate about unintentional injuries (i.e., falls, drowning, burns, and poisonings) and evoke interest in knowing more	• Injury statistics • Injury images • Long-term consequences of injury • Mood-inducing sound effects • Discuss unique hazards • Parent testimonials • Questions posed to viewer
2. Empower parent	Reinforce that: • Children depend on their caregivers to keep them safe • Do not ignore "doubts" about leaving child alone • Parents have many positive characteristics, but no one is perfect • Most parents are capable of making even better choices about supervising their children
3. Acknowledge potential barriers to behavior change and suggest strategies to address these and encourage viewers to problem-solve too	• Suggest solutions to common barriers • Normalize parental concern about injuries and emphasize each parent's need to problem-solve to more actively supervise

TABLE 124.2
Mean Ratings (SD) for Each Cognition (Ratings Scale: 1–8) Given by Intervention (n = 40) and Matched Control (n = 40) Parents before and after the Intervention

	Pre-Intervention		Post-Intervention	
Cognition	Intervention	Control	Intervention	Control
Injury severity	7.41 (0.82)	7.33 (0.78)	7.96 (0.50)	7.03 (0.91)
Injury vulnerability	7.05 (0.78)	6.90 (0.93)	7.73 (0.42)	6.76 (0.83)
Injury preventability	5.12 (0.83)	5.14 (0.86)	5.96 (0.96)	4.93 (0.83)
Value of supervision	4.78 (0.68)	4.89 (0.72)	5.35 (0.72)	4.56 (0.86)
Self-efficacy to supervise	5.86 (1.00)	5.62 (0.91)	6.53 (0.75)	5.73 (0.98)

TABLE 124.3
Average Percent of Time (SD) Child Was in View and Out of View of Intervention (n = 40) and Matched Control (n = 40) Parents before and after the Intervention

	Pre-Intervention		Post-Intervention	
Group	In View	Out of View	In View	Out of View
Intervention	80.65 (15.66)	19.35 (15.66)	88.03 (15.55)	11.97 (15.55)
Control	80.86 (14.62)	19.14 (14.62)	79.53 (15.78)	20.47 (15.78)

ethnically diverse parents of children 2–5 years provided a number of insights into what messaging was most effective and what should be avoided. A summary of these key messages appears in Table 124.1.

These findings were then used to finalize the videotape for inclusion as part of the *Supervising for Home Safety Program* in a randomized control trial.[107] Preliminary analyses (based on over half the sample) from this ongoing intervention study reveal a number of positive findings and confirm no differences in demographic characteristics between intervention and control parents at baseline. First, pre- and post-measures of parental cognitions relevant to child injury (vulnerability, severity, and preventability) and supervision (self-efficacy, value of close supervision) were taken. As shown in Table 124.2, parents in the intervention group, but not the control group, showed significant ($p < 0.05$) changes in their beliefs about injuries and supervision in reaction to viewing the videotape. Thus, the video produced the desired changes in beliefs and attitudes related to childhood injury and caregiver supervision.

Most importantly, analyses of the actual supervision shown by parents revealed significant ($p < 0.05$) improvement in supervision (greater watching and keeping the child in view) during the post-intervention phase for the intervention but not the control group; there were no group differences in the extent of supervision scores obtained during the pre-intervention or baseline phase. Thus, the intervention is having a positive impact on parents' beliefs about supervision and their actual supervisory practices. Assuming that these preliminary findings are replicated when the full sample is completed, the *Supervising for Home Safety Program* will be the first intervention that has proven to positively impact caregiver supervision (Table 124.3).

CONCLUSION AND FUTURE DIRECTIONS IN RESEARCH

There is now clear evidence to confirm what has long been assumed in the child injury literature, namely, that the nature and extent of caregiver supervision influence children's risk of injury.[108] Research reveals too that this influence is not just relevant to very young children but operates across a broad age range throughout childhood. While it is generally true that increased supervision is associated with decreased risk of injury, evidence also indicates that other factors can interact to influence this process, including child behavioral attributes, parent characteristics, and level of environmental risk. The complexity of factors that can influence how supervision relates to child injury makes it difficult to prescribe a fixed set of guidelines for what constitutes "adequate" supervision. It may be, for example, that any definition of "adequate" supervision may need to vary for high- versus low-risk environments.[27]

With regard to future research, additional work is needed comparing mothers' and fathers' appraisals of injury risk and their supervisory practices. The few studies that have been

conducted have found no differences between mothers and fathers in their beliefs about the need for supervision of their young children[109] and reactions to their toddlers' risk-taking behaviors.[110] However, school-age children believe that fathers are more likely than mothers to tolerate risks when supervising children.[111] It may be, therefore, that differences in supervision styles between mothers and fathers emerge as children develop and become increasingly independent or in reaction to children behaving differently with mothers and fathers (e.g., differences in compliance, play activities, disclosure about risk taking). Longitudinal research examining bidirectional parent–child interactions is needed to address this issue because the findings could have important implications for developing programs that aim to improve the supervisory practices of parents; possibly, programs would need to target different determinants of supervisory decisions for mothers compared with fathers.

An additional direction for future research is in the area of sibling supervision, which is a very common occurrence in families. It is important that we now know both supervisor and supervisee behaviors contribute to elevate injury risk when siblings supervise. There now needs to be research aimed at identifying ways to modify the behaviors of both the supervisor and the supervisee so that injury risk is reduced. Interventions that achieve this goal might be as simple as having the parent make explicit to both children that the older child is to watch the younger one and the younger one is to comply with directives from the older one.[112] More extensive interventions might involve online training programs for older children that aim to improve supervisory skills and behavior management skills.[113] Thus, research is needed to determine the nature and scope of interventions that are effective to reduce injury risk when siblings supervise younger children in their family.

To conclude, as outlined in this article, there have been many recent advances to our understanding of how supervision influences children's risk of injury. These findings have important implications for clinical practice and anticipatory guidance. The development of effective programs and appropriate counseling strategies to improve supervision of children is critical, especially because most caregivers do not provide continuous, proximal, and focused attention to their children at all times. The recent identification of effective messaging approaches and the positive outcomes noted of an intervention based on these messaging approaches could serve as the first evidence-based approach to improving supervision as a means of reducing childhood injuries.

ACKNOWLEDGMENTS

Preparation of this chapter was supported by grants to the first author from the Social Sciences and Humanities Research Council of Canada and the National Center for Injury Prevention and Control and by a scholarship to the second author from the Canadian Institutes of Health Research.

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113. Schell SL, Morrongiello BA. Evaluating an on-line program to improve sibling supervision (In preparation).

125 Preventing Injuries at Home

Karin A. Mack, PhD and Karen DeSafey Liller, PhD

CONTENTS

Epidemiology and Burden of Home Injuries 1485
Leading Causes of Home Injury 1485
Falls 1485
Poisonings 1486
Fire/Burns/Carbon Monoxide Poisoning 1486
Choking/Suffocation 1487
Drowning 1487
Excessive Heat–Cold Exposure 1487
Animal and Insect Bites 1487
Prevention of Home Injuries: Practice Considerations 1488
Children 1488
Adults 1489
Older Adults 1489
Conclusions 1490
References 1491

EPIDEMIOLOGY AND BURDEN OF HOME INJURIES

The burden and cost of home injuries are substantial. There are approximately 18,000 injury-related deaths at home each year,[1] and there are an average of 21 million medical visits made each year due to home injuries.[2] The home is the second most common location for deaths from injuries in the United States following motor vehicle injuries.[1] There are approximately 49 home injury deaths every day (Figure 125.1) and the leading causes of these deaths include falls (33%), poisonings (26.8%), fire/burns (18.8%), choking/suffocations (6.1%), and drownings (4.6%). Together, these comprise 90% of all home injury deaths.[1] Children younger than 15 years and adults older than 70 years are at high risk for injuries in the home. Among children ages 0–14 years, the leading causes of home injury deaths are fire/burns, choking/suffocations, drownings, firearms, and poisonings. Among older adults, the leading causes of home injury deaths are falls, fire/burns, poisonings, natural/environmental exposures (primarily exposures to excessive heat or cold), and choking/suffocations.[2]

Home injuries are not equally distributed across population groups or geographic regions. Individuals with disabilities are at higher risk for home injuries.[3,4] Males experience many more home injury deaths than females.[1] Home injuries death rates are greatest in New Mexico followed by Mississippi and Arizona.[2] Southeastern states have high death rates due to residential fires, whereas drownings are highest in Florida, Arizona, Nevada, and California.

Home injuries pose a substantial cost burden to society. In 1998, these injuries cost at least $217 billion[5]: $34 billion for deaths from injuries and $183 for nonfatal injuries. The proportion attributed to medical costs totaled $22 billion. This chapter provides practitioners with an overview of the epidemiology and burden of home injuries (focusing on the leading causes of injury death), evidence for prevention by life stage, and conclusions about best practices. For the purpose of this chapter, home is broadly defined as a structure and includes the garage and yard.

LEADING CAUSES OF HOME INJURY

Falls

Falls alone account for 53.7% of all home injury deaths,[1] 36%–45% of all nonfatal home injuries, and almost 4 million emergency department (ED) visits annually.[6] Falls are the most common cause of injury death among adults aged 65 years and older.[7,8] More than one-third of all adults 65 years of age and older fall each year—with women 67% more likely to have a nonfatal fall than men.[7–9] As a result of falls, many older adults experience devastating consequences such as fractures and head trauma.[10,11] Important fall-related hazards for older adults in the home include poor lighting on stairs, lack of handrails on stairs, lack of grab bars in bathroom areas, use of throw rugs, and individual conditions such as impaired balance and vision.[7]

Falls also are a major cause of nonfatal injury in children and resulted in an estimated 2.5 million emergency room visits in 2007 for children ages 0–18 years.[9] Fall rates

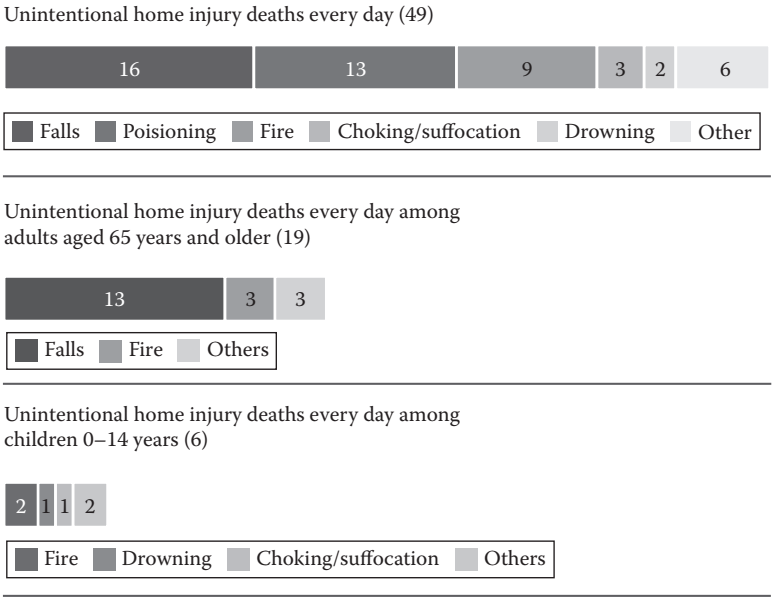


FIGURE 125.1 Unintentional injury deaths at home by cause.

among children younger than age 5 years are second only to those observed among adults aged 65 years of age and older.[12] Young age (children 0–6 years), male gender, and low socioeconomic status have been shown to be risk factors for fall injuries.[13] Important fall-related hazards for children in the home include baby walkers, stairs, windows above ground level, bathrooms, and furniture.[14,15] Beds have been identified as the leading product involved in injuries in infants and as the leading product in the percentage of nonfatal home injury costs for children younger than 5 years of age.[5,16] In particular, an estimated 23,000 children ages 0–9 years are treated in EDs annually for bunk bed-related injuries.[17] Outside play equipment, including play sets and trampolines, can also be dangerous for children. Most injuries occur when a child falls from the equipment onto the ground.[18]

Poisonings

Poisoning deaths and injuries continue to rise.[19] More than two-thirds of all home poisoning deaths occur among adults aged 30–49 years, and males have higher rates of poisoning death than females across all age groups.[1] Data from the American Association of Poison Control Centers show that in 2008, there were 2,491,049 human exposures to substances reported.[20] Almost all exposures (94%) occurred in the home. For children aged 5 or younger, the leading substances were

- Cosmetics and personal care products (13.5%)
- Analgesics (9.7%)
- Cleaning substances (9.7%)
- Foreign bodies (7.5%)
- Topical preparations (6.9%)

The leading substances involved in exposures across all age groups were

- Analgesics (13.3%)
- Cosmetics/personal care products (9.0%)
- Household cleaning substances (8.6%)
- Sedatives/hypnotics/antipsychotics (6.6%)
- Foreign bodies (5.2%)[20]

Poisonings led to 732,316 ED visits in 2008, and approximately 25% of the ED visits resulted in hospitalization or transfer.[9] In 2000, poisonings led to $26 billion in medical expenses and made up 6% of the economic costs of all injuries in the United States.[19]

Fire/Burns/Carbon Monoxide Poisoning

In 2009, house fires were responsible for approximately 2565 deaths and injuries to approximately another 12,650 persons (not including firefighters).[21] Most fire victims do not die from burns but from smoke or toxic gases.[22] Those at high risk of death because of fire or heightened difficulty in benefiting from smoke alarms include children 4 years and younger; older adults (65 years and older); those living in poverty; people with hearing, vision, or other physical or mental limitations or disabilities; and smokers.[23–26] Households with income below the poverty level, with lower levels of education attainment, or with older or no children were less likely to have a smoke alarm.[27] Additional groups at high risk for dying in a house fire include African Americans and people who live in substandard homes where emergency egress is often compromised.[28] Approximately $7 billion in property loss occurred in residential properties in 2009.[21]

A primary risk factor for death and injury in residential fires is absent or nonworking smoke alarms.[24,29,30] Studies show that even though over 90% of homes in the United States have smoke alarms, only about three-quarters of the alarms are functioning.[30,31] When a fire occurs in a home with a functioning smoke alarm, the death rate is decreased by 51%.[30]

Scalds and thermal and electrical burns also contribute to home injuries. Between 1997 and 2002, 78,000 infants and toddlers were treated annually in ambulatory care settings for injuries due to contact with a hot object or substance.[32] Exposure in an adult for 2 s to water at a temperature of 150°F can result in a third-degree burn and for children, it can happen even more quickly.[33,34]

Carbon monoxide (CO) is found in combustion fumes, such as those produced by stoves, lanterns, burning charcoal and wood, gas ranges, and heating systems. Each year, more than 400 Americans die from CO poisoning, more than 20,000 visit the emergency room, and more than 4000 are hospitalized.[35,36] Death rates are highest among older Americans.

Choking/Suffocation

More than 1000 suffocation/choking deaths occur in the home each year.[1] In 1998, costs from deaths and nonfatal choking/suffocation injuries totaled 3.2 billion.[5] Young children and older adults have the highest death rates from choking and suffocation. More than half (60%) of infant suffocation occurs in the sleeping environment.[15] Cribs and playpens are responsible for half of all nursery product-related deaths among children ages 5 years and younger.[15] Strangulation deaths from window cords happen in places such as in a crib or a bedroom. From 1991 to 2000, the U.S. Consumer Product Safety Commission received reports of 160 strangulations involving cords on window blinds.[37]

For older adults, predisposing factors for asphyxia of food include poor dentition, insufficiently chewing food, semisolid diet, alcohol use, sedative drug use, reduced motor coordination, dementia, and various neurological or other diseases.[38] Positional asphyxia is also a cause of suffocation-related death in older adults. Body position in these cases causes airway obstruction or impaired respiration. People who live alone may be at higher risk for choking because they may be less likely to enlist help when they are choking.

Drowning

Approximately 820 deaths occur in home settings each year due to drowning.[1] In 1998, costs from deaths and nonfatal drowning injuries totaled 2.1 billion.[5] The majority of residential pool drownings (61%) occur at the victims' home; however, 22% take place at the homes of neighbors, friends, and relatives.[39]

Drowning is the second leading cause of home injury death among children aged 1–9 years.[1] Among infants, 71% of drownings occur in bathtubs and 16% in buckets.[40] Among children ages 1–4 years, 56% of drownings are in pools, and among children ages 5–9 years, 31% are in pools.[40]

Males are 3.7 times more likely than females to die from drownings in the United States.[9] Between 2000 and 2007, the drowning death rate for African Americans across all ages was 1.2 times that of whites and for American Indians and Alaskan Natives, this rate was 1.7 times that of whites.[9] In the summer, between May and August, drowning deaths among children increased to 89% compared with the rest of the year.[41]

Excessive Heat–Cold Exposure

Extreme hot and cold temperatures (or environmental injury) are a leading cause of home injury death among older adults.[2] This may include illnesses, as well as injuries and conditions, related to excessive heat (e.g., heat cramps, heat exhaustion, heat syncope, heatstroke, or hyperthermia) or excessive cold (e.g., central nervous system depression, arrhythmias, and renal failure). In 1998, costs for natural and environmental exposures totaled approximately 1.5 billion,[5] and roughly 420 deaths occur in homes each year due to natural and environmental exposures.[1] Among all heat exposure deaths (inside and outside the home), males accounted for 66% of deaths.[42] Seven percent of the deaths were among those aged younger than 15 years, 53% were aged 15–64 years, and 40% were aged older than 65 years. The states with the highest average annual hyperthermia-related death rate were Arizona, Nevada, and Missouri.[42] Among all cold exposure deaths (inside and outside the home), males accounted for 67% of deaths.[43] Among those who died from hypothermia, 49% were aged 65 years or older. States with the highest average annual rates were Alaska, Montana, Wyoming, and New Mexico.[43]

Animal and Insect Bites

Although not a leading cause of injury death, bites and stings are the third leading cause of ED visits for young children, and many of these events occur at home. Dogs bite more than 4.7 million people/year in the United States with more than 800,000 Americans seeking medical attention.[44] The rate of dog bite-related injury is highest for children ages 5–9 and decreases as children age. Non-canine bites and stings (e.g., cats, bees, snakes) result in more than 900,000 ED visits annually, with nearly 90% of the injuries occurring in and around the home.[45] These numbers do not include deaths from bites or stings or the multitude of bite and sting injuries that are treated outside the ED by other health care providers or treated at home. Risk is typically greatest in the summer months, and injuries mostly occur to extremities of the body. According to the American Veterinary Medical Association, there were nearly 81.7 million pet cats, 72 million pet dogs, 11.2 million pet birds, 6 million pet rabbits, 1.2 million pet hamsters, and 586,000 pet snakes in the U.S. households in 2006.[46] As the practice of exotic pet

trade activity increases, practitioners are more likely to be treating injuries from these species.[46]

Mammalian bites are of particular concern for public health because they can lead to rabies exposure, rat-bite fever, and other zoonotic infectious diseases. The U.S. animal species that carry rabies include raccoons, skunks, bats, foxes, cats, dogs, and cattle. Distribution of hamsters and other pet rodents from centralized breeding facilities to pet stores located in various states and the distribution of imported, exotic pets have resulted in the diffusion of potential infectious exposures that may be infrequently seen by local physicians.

PREVENTION OF HOME INJURIES: PRACTICE CONSIDERATIONS

Health care professionals should be aware that educating about home safety in a clinical setting can be effective in increasing a range of safety practices, especially when partnered with the provision of home safety equipment.[47,48] Patient counseling can be a promising injury prevention strategy, especially if it is based on established behavioral and communication theories.[49] The following practice recommendations are arranged by three life stages: children, adults, and older adults. The recommendations for preventing injuries in children are meant to be provided to parents or caregivers. The topics covered were selected based upon contribution to the leading causes of injury deaths in the age group and practice recommendations established in the literature.

Children

Preparing and practicing a fire escape plan, especially teaching fire escape skills to children, can minimize injuries and death from fires.[15,50] Parents and caregivers should store all matches and lighters away from children up high in a locked cabinet and institute a "kid-free zone" of at least 3 ft around the stove and areas where hot food or drink is prepared or carried. Scald injuries can be prevented as well. Home safety education can be effective in increasing the proportion of families that have a safe hot tap water temperature.[47,51] Successful strategies to decrease scalds include reducing the temperature in water heaters to 120°F, installing hot water temperature limiters at the faucet, using roll-up cords for electric coffee pots, and using pots, pans, and kettles designed to be less likely to tip and spill hot liquids.[52] Five years after a 1983 Washington state law required new water heaters to be preset at 120°F at the factory, 77% of homes tested had safe tap water temperatures accompanied by a reduction in the frequency, morbidity, and mortality of tap water burn injuries in children.[53]

Parents and caregivers should be advised on the types of objects that pose a strangulation or suffocation risk for children and familiarized with methods to reduce this risk. For example, children younger than 4 years should not be fed round, firm foods (e.g., hot dogs, nuts and seeds, grapes, hard candy, raw vegetables) unless they are chopped completely. Dangerous household items include balloons, coins, magnets, marbles, and toys with small parts. Parents should be advised to learn and practice cardiopulmonary resuscitation (CPR) and basic first aid in case of emergencies at home.

Infants should be placed on their back on a firm sleep surface, such as a safety approved crib mattress, and soft objects or loose bedding should not be placed in a crib. Loop window blind and drapery cords should be tied up out of reach or the ends should be cut and retrofitted with safety tassels. The inner cords of blinds should be fitted with cord stops.[37]

Recent research suggests that formal swim lessons can reduce the risk of drowning in 1 to 4 year old children.[54] To help prevent drowning, parents might consider enrolling children in formal swim lessons, but they also need to be within arm's length of children who are bathing or playing around water.[55] Children should never swim alone or without adult supervision.[56] When combined with self-closing and self-latching gates, four-sided fencing provides a passive intervention that prevents unintended access to pools by residents and visitors.[57]

To protect children from poisonings, it is recommended that the poison control number, 1-800-222-1222, be kept on or near each home phone and saved on cell phones. Drugs and medicine should be kept in locked cabinets, and patients should be advised to follow all label instructions. Child-resistant packaging significantly reduces the morbidity and mortality of childhood poisonings. Studies show clear declines in poisonings after passage of the Poison Prevention Packaging Act (PPPA) in 1970.[58,59] One study revealed that a substantial number of the post-PPPA poisonings (as high as 40%) were due to either improperly secured safety caps or products that were not required to be packaged in a child-resistant container.[60] Clinicians should urge patients to keep medicines in original bottles and containers and to turn on a light at night when using medications. Adults should never leave children alone around medicines. Homes with pools should store pool chemicals away from children and animals as well as store them as recommended by the manufacturer.[61] Chemicals should be protected from mixing or getting wet.

While not a leading cause of injury death among children, falls are a leading cause of injuries and there has been substantial work on the topic. Residential hazards associated with falls among children include a lack of safety devices such as properly installed and used safety gates or window guards, use of bicycle helmets, and structural defects (e.g., uneven floors, insufficient surfacing under play equipment). Although few child fall prevention interventions have been rigorously evaluated, individual studies have suggested positive results. Interventions to increase stair gate use and reduce baby walker use have been shown to be effective.[62] Other interventions that may help to prevent childhood fall injuries include window guards,[63] balcony railings less than 4 inches apart, and window locks for windows above ground level.[15] The evidence that window guards reduce childhood morbidity and mortality from falls comes primarily from dramatic results following a community-wide program to

provide window guards in high-risk apartments where falls declined 50% in the 2 years after the program's inception.[64] Building codes that require window guards, safe stair and balcony design, and other modifications are likely to be effective for fall prevention because they remove the need for home dwellers to modify their home for safety.

Playground equipment should be properly sited within the yard, have appropriate surfacing beneath the equipment, and be age appropriate and well maintained.[65] Children should be adequately supervised when playing on the equipment. Children should use bike helmets when riding bicycles; indeed, many states and localities have laws requiring their use.[66]

Injuries to children from common household equipment can be extremely damaging. Recent reviews of injuries from equipment such as lawn mowers[67] and treadmills[68] demonstrate the potential harm. Although equipment redesigns to enhance passive safety measures might be the most effective way to prevent these injuries, clinicians can advise parents to keep children away from this equipment, especially when adult supervision is not present. Other measures, such as keeping keys for these devices out of reach of children, is also prudent. Furniture can also be a source of injury for children. Televisions were the most common item of furniture associated with injury among children aged 9 years or younger, whereas other items, such as desks, cabinets, and bookshelves, were the most common source of injury among children aged 10–17 years.[69] Clinicians can encourage parents to secure large furniture to a stable stand or a wall.

The American Academy of Pediatrics has anticipatory guidance available in The Injury Prevention Program. It is designed to provide a systematic method for clinicians to counsel parents and children about adopting safe behaviors during various child development stages to prevent injuries.[70] It targets the parents of children, newborn through 12 years of age, to help prevent common injuries from motor vehicles, firearms, bicycle crashes, drowning, poisoning, choking, burns, falls, and pedestrian hazards.

Adults

To prevent residential fire and burn deaths, smokers should be advised to quit since smoking is the leading cause of residential fire deaths. The U.S. Department of Health and Human Services, National Institutes of Health, and National Cancer Institute provide a free helpline (1–800-Quit Now) for smokers who want to quit and need help doing so. In addition, families should be counseled about fire and burn prevention. Home safety education has been effective in increasing the proportion of families with a functional smoke alarm.[47] Homes should have properly placed smoke alarms, and the batteries should be checked and replaced when appropriate. Patient reminders for new batteries can be timed to coincide with when clocks are reset to daylight standard time. In addition, residential sprinklers are a promising strategy to prevent deaths and injuries due to fires and are gaining greater acceptance as a feature of new home construction.[71–73] Only 23% of homes in the United States have a fire escape plan and practice it, and yet residents should be prepared to exit a home when a smoke alarm sounds.[27] The fire escape plan should include at least two different ways of escape for each household resident (and that egress routes are not blocked), and a safe place should be designated outside of the home to meet after escaping the fire.

Cooking is the leading cause of home fires and home fire injuries.[74] Food that is cooking should not be left unattended, and caution should be used when frying foods. The stove should be turned off if leaving the kitchen for even a short period of time. While cooking, it is prudent practice to roll up sleeves and use oven mitts. Grilling outdoors can cause house fires as well.[75] Grills should be placed well away from the house. Generators, camp stoves, and propane or charcoal grills should only be used outdoors to avoid fire and or CO hazards. Before using gas grills and propane tanks, the fuel lines should be examined to be sure they are working properly and not leaking.[76] To prevent CO poisoning, the heating system, water heater, and any other gas, oil, or coal burning appliances should be serviced by a qualified technician every year. Homes should have properly placed CO detectors, and the batteries should be checked and replaced when appropriate.[77]

Falls from ladders can result in serious injuries.[78,79] Prevention strategies for ladder safety include ensuring the ladder is on secure and level ground before climbing, spacing the base of the ladder 1 ft away from the wall for every 4 ft it extends up, and staying centered between the rails of the ladder.[80] Patients should be advised not to overreach or stand on the top two rungs of the ladder. To reach a roof, the ladder should be extended at least 3 ft beyond the edge of the roof. A folding step ladder should never be used when it is closed.

Older Adults

Older adult falls in the home can be prevented, in part, by taking note of home hazards and safety features. Structural residential hazards associated with falls among older adults include lack of handrails on stairs, lack of grab bars and nonslip surfaces in the bathroom, tripping or slipping hazards (e.g., throw rugs, waxed flooring), outdoor steps, inadequate lighting, and the presence of electrical or telephone cords in the walkway.[81] Individual behaviors and physical ability levels also are important factors contributing to falls in older adults.[82,83] Homes can be designed and constructed to protect older adults from fall-related injuries through installation of grab bars in bathtubs and showers and adding handrails and good lighting in stairwells. Many homes currently do not have these simple safety features. The evidence that structural modifications, such as installation of handrails, grab bars, and improved lighting, are promising interventions for reducing risk of falls among older adults comes from two systematic reviews.[84,85]

Similar to recommendations for children, preparing and practicing a fire escape plan can be beneficial for older adults.

Increased risk for death in fires for older adults may arise, in part, from decreased mobility, hearing loss, and confusion. Smoke alarms may be less effective at waking older adults who suffer hearing loss.[23] Older adults may want to consider alarms with flashing lights or vibration alerts. Clinicians should recommend that older adults stay in the kitchen when food is cooking on the stove and not wear loose clothing while cooking.

Periods of extreme heat or cold are potentially dangerous for older adults. During periods of extreme heat or cold, having a system in place for checking in with relatives or neighbors can be helpful. Air-conditioning is a key protective factor against heat-related illness and death.[42] If a home is not air-conditioned, older adults might consider spending time in public facilities that are air-conditioned. Clinicians can recommend the following during hot weather: staying cool indoors, drinking plenty of fluids, replacing salt and minerals, wearing appropriate clothing and sunscreen, and using a buddy system. The ability to feel a change in temperature decreases with age.[43] Also, older people are more susceptible to health problems caused by cold. Two practical measures to recommend for older adults include placing an easy-to-read thermometer in an indoor location where they can see it frequently and checking the temperature of the home often during the winter months.

CONCLUSIONS

All patients are entitled to a healthy and safe home. Clinicians can help patients and families take actions to change lifestyle behaviors and create safer home environments. The principles of healthy and safe homes have been previously explained,[86,87] but examples of the more important "best practices" to be encouraged by health professionals include the following:

1. Recommend installation, maintenance, and consistent use of safety devices (Figure 125.2):
   a. Smoke alarms
   b. Stair gates in homes where young children live or visit
   c. Grab bars in bathrooms
   d. Adequate lighting outside and on stairs
   e. Proper storage areas for medicines, cleaning solutions, automotive supplies, pool chemicals, and pesticides
   f. Four-sided isolation fencing with self-closing, self-latching doors around pools
   g. CO detectors
2. Recommend parents dispose of baby walkers—they are inherently dangerous
3. Have patients in homes where older adults live or visit complete a home fall prevention checklist (see http://www.cdc.gov/HomeandRecreationalSafety/Falls/pubs.html)
4. Encourage patients to prepare and practice an emergency fire escape plan (see http://www.usfa.fema.gov/campaigns/smokealarms/escapeplans/index.shtm)
5. Encourage homeowners and renters to set their water heater temperature at (or below) 120°F to prevent scalding
6. To reduce home fires, encourage patients to not smoke and provide active support for quitting (http://www.smokefree.gov)
7. Have patients complete a playground safety checklist if they have playground equipment in their yard (see http://www.cpsc.gov/cpscpub/pubs/pg1.pdf)
8. Have patients choose poison prevention packaging for all toxic products in the home
9. Provide advice to patients regarding basic first aid and recommend CPR and first aid classes to parents
10. Recommend that infants sleep on their backs on firm sleeping surfaces
11. Advise adults aged 65 years and older to exercise caution in extreme hot or cold weather (http://emergency.cdc.gov/disasters)

Homes injuries are not accidents. Most are predictable and, more important, preventable. Clinicians can help patients choose lifestyles that prevent home injuries by promoting safe behaviors and changing hazardous home environments.[88] Clinicians, however, cannot do this alone.

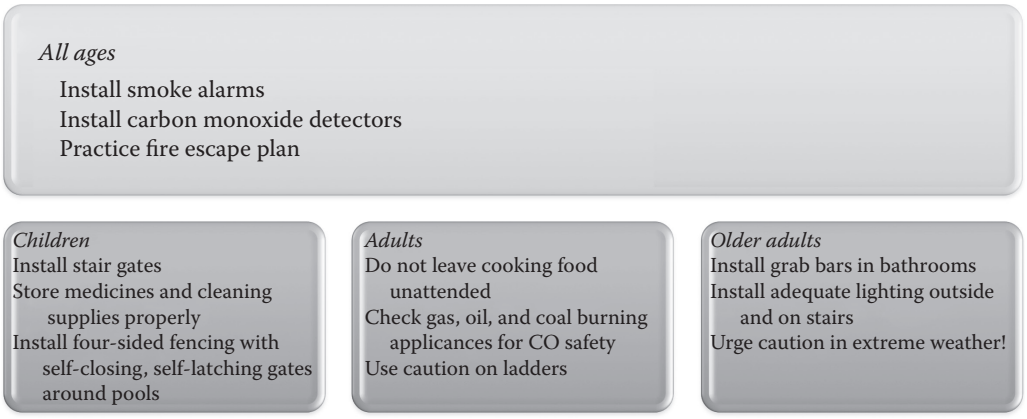


FIGURE 125.2 Help patients take actions to create safer home environments through safety devices.

It is important for home injury prevention messages to be embraced and advocated by teachers, schools, media, local health departments, advocacy groups, business, law enforcement, and policy makers.[89] Home injuries are related to many factors that span individual, interpersonal, organizational, community, and societal determinants. The costs and consequences of home injuries can be significant, both to families and society as a whole. Home injury prevention should be considered right alongside disease prevention as both predictable and preventable through changes in behavior, public policy, enforcement, environment, and product/engineering.[89,90] Although injury statistics guide our practice and research, a more powerful force are the people behind the statistics whose lives can be spared and disabilities prevented through the application of effective injury prevention strategies at home.

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126 Falls and Fall Injuries among Older Adults

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CONTENTS

Introduction 1495
Public Health Burden 1496
- Community Settings 1496
- Nursing Homes 1496
- Hospitals 1496

Epidemiology 1497
- Fatal Falls 1497
- Nonfatal Falls 1497

Fall Risk Factors 1498
- Biological Factors 1498
- Behavioral Factors 1498
- Environmental Factors 1499
- Socioeconomic Factors 1499
- Risk Factor Interactions 1499

Fall Interventions 1499
- Clinical Assessment and Risk Factor Reduction 1499
- Exercise 1499
- Medication Management 1500
- Vision Enhancement 1500
- Home Modification 1500
- Vitamin D 1500
- Multifactorial Interventions 1500

Perceptions of Risk 1501
Research Gaps 1502
- Future Directions 1502

Conclusion 1502
References 1502

INTRODUCTION

The U.S. population is aging rapidly. At present, 35 million people—one-eighth of the U.S. population—are 65 years of age or older, and by 2020, this number is expected to reach 77 million. The aging process typically involves cognitive and physical changes to the body's brain and nervous, cardiovascular, and sensory systems. These changes, in turn, may cause a reduction in functional abilities including decreased muscle strength and endurance, slower recovery times after exertion or stress, and delayed reaction times to different types of stimuli. Such physiological changes can make older adults (those aged 65 years and older) particularly susceptible to falling [1].

Falls among people who are 65 years or older are a major public health concern. More than a third of older adults fall annually [2] and those who fall are two to three times more likely to fall again within a year [3]. Although most falls do not result in injury, about 20% cause serious injuries such as head trauma, lacerations, and fractures [4]—injuries that can limit mobility, diminish quality of life, and increase the risk of premature death [5,6]. Although both men and women are susceptible to falls and fall injuries, women are disproportionately affected because they outnumber men in the older age groups and because they are more vulnerable to sustaining fall injuries such as hip fractures.

This chapter describes the magnitude of this health issue and highlights how falls and fall injuries are influenced by biological, environmental, and behavioral factors. It summarizes the epidemiology of older adult falls and describes our current knowledge about interventions that can reduce these injuries.

PUBLIC HEALTH BURDEN

Falls are the leading cause of both fatal and nonfatal injuries among people aged 65 years and older [7]. In 2007, there were 38,300 unintentional injury deaths among older adults, of which 48% were caused by falls. But fatal falls represent only the "tip of the iceberg." In the same year, 3.1 million nonfatal unintentional injuries among older adults were treated in emergency departments, of which 1.9 million (62%) were due to fall injuries. Sixty-nine percent of these fall injuries were sustained by women (Figure 126.1).

One of the most serious fall outcomes is hip fracture, an injury that often results in long-term functional impairment, nursing home admission, and increased mortality [9]. More than 90% of all hip fractures in older adults are caused by falls [10]. In 2006, there were 309,000 hospital admissions for hip fractures, and about three-quarters of these injuries were sustained by women [11].

In addition to physical injuries, falls can have significant psychological and social consequences. Many people who fall, whether or not they sustain injuries, develop a fear of falling. Studies show that 12%–39% of older adults report they are afraid of falling [12]. This fear can cause them to restrict their activities, leading to reduced mobility, muscle weakness, and subsequent increased fall risk [13]. Fear of falling is strongly associated with future falls and has been found to lead to deteriorating health, a decline in physical and social functioning, and nursing home admission [14].

The financial burden of falls is substantial. In 2000, the direct medical costs of fall injuries among adults 65 years and older totaled $19.2 billion [15] or $30.0 billion in 2010 dollars. About two-thirds of these costs were for people who were hospitalized.

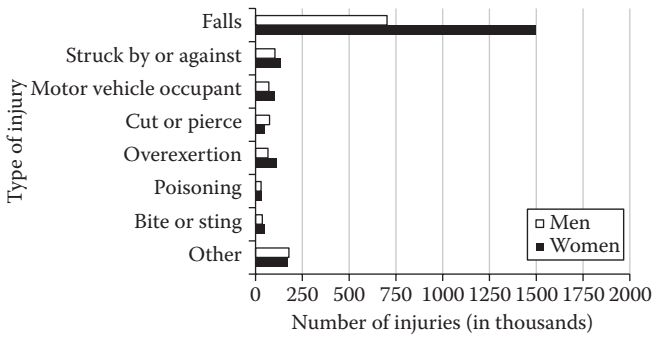


FIGURE 126.1 Leading causes of unintentional nonfatal injuries among men and women aged 65 years or older, United States, 2009. (Data source from NEISS-AIP, 2009.)

Community Settings

Although older adults reside in a variety of settings, including assisted living facilities and nursing homes, approximately 96% of the 35 million adults aged 65 years and older live independently in the community. In a 2006 national survey, about 5.8 million (15.9%) community-dwelling adults aged 65 years and older reported falling at least once during the preceding 3 months [16]. Of those who said they had fallen, 23.1% reported falling three or more times. People who fall repeatedly are at greatly increased risk of sustaining a serious injury [17].

Many older adults living in the community spend much of their time at home, so it is not surprising that between one-half and two-thirds of all falls, and about half of fatal falls, happen in or around the home [18,19]. Studies show that most people fall from a standing height (e.g., by slipping or tripping while walking) [20], and most falls happen on the same level rather than from heights (e.g., down stairs or off ladders) [21]. Berg et al. found that the majority of falls (82%) occurred during the day; 14% happened in the evening and only 4% happened at night [18].

Nursing Homes

In 2004, there were 1.3 million persons aged 65 years and older living in nursing homes; half were 85 years and older and three-quarters were women [22]. The median length of stay for residents was 511 days for women and 355 days for men. By 2030, the number of nursing home residents is projected to double [23].

Nursing home residents are particularly vulnerable to falls and fall-related injuries. At least half of nursing home residents fall annually and the proportion is higher among certain high-risk populations, such as people with dementia, where the incidence is 70%–80% [24]. Compared to seniors living in the community, people in nursing homes are older, frailer, and have a higher prevalence of cognitive impairment. Nursing home residents also tend to have a greater number and more severe chronic conditions; greater limitations in their basic activities of daily living; and a higher prevalence of gait problems [25]; all factors that are associated with falling [26].

The fall rate among nursing home residents is two to three times the rate for older adults living in the community, with the average incidence 1.5 falls per bed per year [27]. A typical 100-bed nursing home reports between 100 and 200 falls annually, and many falls probably go unreported [28]. Nursing home residents tend to fall repeatedly, which increases their chances of sustaining injuries. In this population, approximately 12% of falls cause severe injuries such as head trauma and serious lacerations and an additional 4% result in fractures. About 35% of fall-related injuries occur among non-ambulatory residents [29].

Hospitals

Fall rates among hospital patients vary by patient population, type of hospital, and reasons for hospitalization. The highest

rates are seen among the oldest patients and, within the geriatric population, rates of 8.9–17.1 falls per 1,000 patient days have been reported for neuroscience, rehabilitation, and psychiatry departments [30,31]. Methods for calculating hospital fall rates differ. The most accurate approach is to report the number of falls per 1,000 patient bed-days, but many studies calculate the fall rate as the number of falls per 100 hospital admissions. These differences make it difficult to compare fall rates among and across institutions.

EPIDEMIOLOGY

Fatal Falls

In 2007, 18,300 older adults died from fall injuries, an average of one death every 35 min [8]. Rates differ by both sex and race. Whites have the highest fall death rates followed by the rates for Asians and blacks [32]. Men are much more likely than women to die from a fall. In 2010, the age-adjusted fall death rate for men (63.1 per 100,000 population) was 55% higher than the rate for women (44.9 per 100,000) [7]. For both men and women, rates increased sharply with age with the greatest rate increase occurring after 80 years of age [7] (Figure 126.2).

It is unclear why men are more likely than women to die from a fall. This disparity may be due to gender differences in the prevalence of underlying chronic conditions at similar ages, such as cardiovascular disease, or it may reflect greater risk-taking behaviors, such as climbing on ladders, among men.

National data show that fall death rates are increasing [7]. From 2000 to 2007, age-adjusted rates increased 45% in men and 55% in women (Figure 126.3). Reasons for this increase are unclear. The number and rate of fatal fall injuries are calculated using vital records data that are compiled by the National Center for Health Statistics. Although comprehensive, the quality of these data depends on the training and/or experience of the physician or medical examiner filling out the death certificate. The number of deaths attributable to falls may be undercounted if a fall did not occur close to the time of death.

Few studies have examined the specific causes of fall-related deaths, although there is evidence that up to half are due to traumatic brain injuries [33]. Complications following fractures, especially hip fractures, also contribute significantly to fall deaths [19].

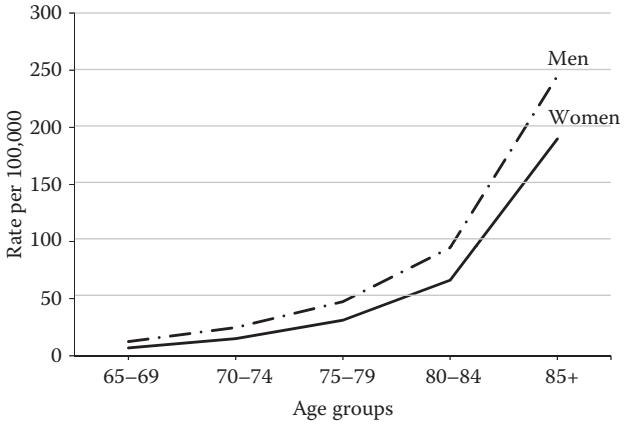


FIGURE 126.2 Fall death rates among men and women aged 65 years or older by age-group, United States, 2007. (Data source from NEISS-AIP, 2000–2010.)

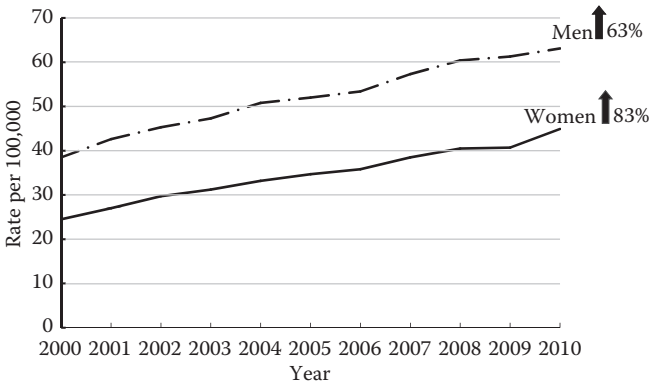


FIGURE 126.3 Trends in age-adjusted fall death rates for men and women aged 65 years or older, United States, 2000–2007 (Data source from NEISS-AIP, 2000–2010).

Nonfatal Falls

In 2009, 2.2 million nonfatal falls among people aged 65 years and older were treated in hospital emergency departments [7]. The majority of fall injuries were mild to moderate; about three-quarters of patients were treated and released, while one quarter were hospitalized. Like fatal fall rates, nonfatal rates have increased, although to a lesser extent. From 2001 to 2009, age-adjusted fall injury rates increased 21.4% in men and 16.4% in women [7].

A recent analysis of the 2006 Current Medicare Beneficiary Survey data found that nearly 7 million community-dwelling Medicare beneficiaries aged 65 years and older reported having fallen in the past year [8], and over 2 million beneficiaries sought medical attention following a fall. Women were significantly more likely than men to seek medical treatment for a fall (37.5% vs. 24.3%) and to talk with a health care provider about preventing future falls (31.2% vs. 24.3%). This is consistent with other studies that have noted women's higher incidence of fall injuries [34,35].

Women are disproportionately affected by nonfatal fall injuries (Figure 126.4). In 2009, after adjusting for age, the fall injury rate for women was 40% higher than for men [8]. In a population-based study, Stevens and Sogolow found that nonfatal fall-related injury rates for women were 40%–60% higher than for men of comparable age [34].

Women also were more likely to sustain serious injuries such as fractures and head injuries that required hospitalization. The most prevalent nonfatal fall injuries were fractures, contusions or abrasions, and lacerations. Compared to men, injury rates for women were 2.2 times higher for fractures, 70% higher for contusions or abrasions, and 10% higher for lacerations [34].

Not surprisingly, the hospitalization rate for women was 1.8 times that for men, and women's hospital admission rates for fractures and lower trunk injuries were more than twice as

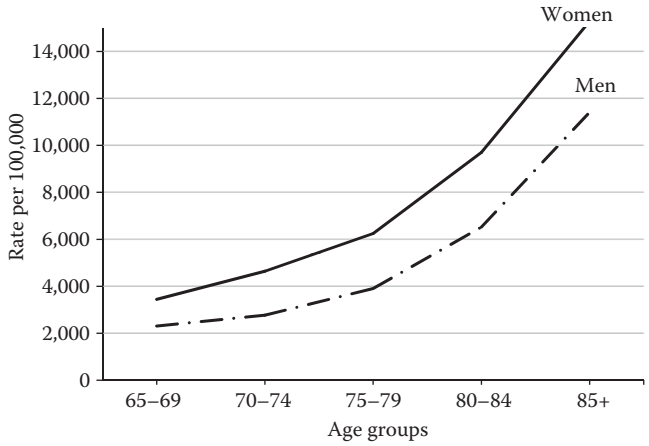


FIGURE 126.4 Nonfatal fall injury rates for men and women aged 65 years or older by age-group, United States, 2009. (Data source from NEISS-AIP, 2010.)

high as men's rates. Similarly, in an analysis of Washington State hospital discharge data, researchers found that fall-related hospitalization rate for women was twice that for men [36]. About 46.7% of all patients who were hospitalized for a fall injury were subsequently transferred to a skilled nursing facility [36].

Much of the gender disparity is due to women's greater susceptibility to hip fracture, an extremely serious fall injury that can result in disability, nursing home admission, and increased mortality [37–39]. White women are much more likely to sustain hip fractures than are African American or Asian women [20]. Treatment typically includes surgery and hospitalization, frequently followed by admission to a nursing home and extensive rehabilitation [40].

Falls are the strongest risk factor for hip fracture [41]. However, a significant contributing factor is osteoporosis, a metabolic disease that affects postmenopausal women and men over 80 years of age. It is characterized by low bone mineral density (BMD) and deterioration of bone structure that make bones porous and susceptible to fracture. The National Osteoporosis Foundation estimates that more than 10 million people over age 50 years in the United States have osteoporosis and 80% of those affected are women. An additional 34 million people have low BMD and are at risk for the disease [42].

FALL RISK FACTORS

Epidemiologic studies have identified numerous fall risk factors and the prevalence of many of these increases with age. Risk factors frequently are classified as either intrinsic (i.e., originating within the body, such as age, female gender, leg weakness, balance disorders, and poor vision) or extrinsic (i.e., originating outside the body, such as environmental hazards). Some researchers have further refined this classification to include biological, behavioral, environmental, and socioeconomic risk factors [43]. The following table lists selected risk factors in each category (Table 126.1).

TABLE 126.1
Selected Fall Risk Factors

Biological	Behavioral	Environmental	Socioeconomic
Advanced age	Multiple medications	Lack of stair handrails	Low income
Previous falls	Psychoactive medications	Poor stair design	Lack of education
Female gender	Inactivity	Lack of bathroom grab bars	Poor living conditions
Muscle weakness	Risk-taking behaviors	Dim lighting or glare	Lack of social support
Poor balance and coordination	Fear of falling	Obstacles and tripping hazards	Living alone
Gait disorders	Improper or inappropriate use of mobility aids	Slippery or uneven surfaces	Illiteracy and/or language barriers
Chronic conditions: Arthritis, diabetes, stroke, Parkinson's disease, incontinence, dementia	Inappropriate footwear	Poor building design and/or maintenance Poorly designed or maintained public spaces	
Poor vision			
Functional limitations			
Acute illness			

Source: Data adapted from Scott, V., *Prevention of Falls and Injuries among the Elderly*, British Columbia-Office of the Provincial Health Officer, Vancouver, British Columbia, Canada, 2004; Rubenstein, L.Z. and Josephson, K.R., *Med. Clin. North Am.*, 90(5), 807, 2006.

Biological Factors

Some biological risk factors are important but cannot be modified, such as older age, being female, and being cognitively impaired. Having certain chronic conditions also increase fall risk through various mechanisms. Conditions such as stroke and Parkinson's disease adversely affect balance, gait, and muscular coordination [44,45]; diabetes can cause loss of vision and peripheral neuropathy leading to decreased sensation in the feet [46]; and arthritis affects flexibility [47] and also may cause chronic pain [48].

Behavioral Factors

Behavioral factors are the focus of public health efforts because they are generally considered modifiable. Risky behaviors include climbing on ladders or chairs [17]; being inactive, which leads to poor physical conditioning and muscle weakness [49]; taking four or more medications; and taking medications that affect the central nervous system.

Psychoactive medications such as tranquilizers, sedatives, and antidepressants have been most strongly associated with falls [50], but diuretics, antihypertensive medications, and narcotic analgesics also increase fall risk [51].

Although all these factors are potentially modifiable through science-based interventions, it is well documented that human behavior is very difficult to change, especially for sustained periods of time. Changing older adults' behaviors to prevent falls is no exception [52].

Environmental Factors

Some environmental factors, such as uneven pavement and poorly designed public spaces, such as street crossings and parking lots, are difficult or impossible to change. Fortunately, there are environmental risk factors in the home that can be modified. Examples include clutter in walkways, tripping hazards, dim lighting, and lack of stair railings or grab bars in the bathroom [53].

Socioeconomic Factors

Although evidence is limited, some research suggests that a number of risk and protective factors are related to socioeconomic conditions. For example, low income is highly associated with poor health status and disability that, in turn, are associated with increased fall risk [54,55]. Some psychosocial conditions such as depression also increase the risk of falls and fall-related injuries [56–58]. Conversely, social integration, as measured by the size and quality of family and friendship networks, has been shown to protect against falls [59] and fall-related fractures [56]. Fear of falling has been identified as a fall risk factor, particularly when it causes a reduction in physical activity, which may be protective [60].

Risk Factor Interactions

Most falls are the result of interactions among multiple risk factors [44]. In an early study of community-dwelling older adults, Tinetti et al. found that the likelihood of falling increased with the number of risk factors present [61]. The proportion of people who fell increased from 27% for those with up to one risk factor to 78% for those with four or more risk factors.

Fall prevention efforts have focused on a number of potentially modifiable risk factors. These include muscle weakness in the legs, gait and balance problems, poor vision, and environmental hazards [5]. In addition, identifying and treating the symptoms of chronic conditions may reduce fall risk [62].

FALL INTERVENTIONS

The frequency of falls among older adults, combined with a high susceptibility to injury due to age-related physiological changes (e.g., decreased muscle strength and endurance, delayed reaction times) and a high prevalence of chronic conditions, makes all fall outcomes potentially serious. Unfortunately, many older people are not aware of their risk of falling or avoid discussing these issues with their health care providers [52]. Consequently, opportunities to implement prevention strategies are often missed.

Clinical Assessment and Risk Factor Reduction

In a meta-analysis of randomized controlled trials (RCTs) of fall interventions, Gillespie et al. concluded that the most effective multifactorial fall intervention was a clinical assessment by a health care provider combined with individualized fall risk factor reduction, referral, and patient follow-up [63].

The American Geriatrics Society (AGS) published clinical fall assessment guideline in 2001 [64] and updated them in 2010 [62]. The AGS recommends that a health care provider ask all older adults if they have fallen in the past year. People who have fallen two or more times, or who are experiencing difficulties with walking or balance, should receive a multifactorial fall risk assessment followed by individualized interventions including treatment and/or referrals.

A multifactorial fall risk assessment includes taking a fall history; reviewing all medications; testing gait, balance, neurological function, lower extremity muscle strength, cardiovascular status, and visual acuity; assessing activities of daily living including the use of mobility aids and fear of falling; and evaluating the condition of the feet and usual footwear. Intervention strategies would include medical management tailored to the identified risk factors, including referrals to specialists, such as neurologists and ophthalmologists, coupled with an appropriate exercise program [62].

Primary care physicians have been slow to put the AGS recommendations into clinical practice because many feel they do not have adequate knowledge about methods of risk assessment and/or fall prevention [65–67].

Exercise

After clinical assessment with targeted risk factor reduction, the most effective single intervention is exercise, which can reduce fall risk by 24% on average [68]. However, recruiting participants and maintaining long-term compliance with an exercise program can be problematic.

The Cochrane group conducted a meta-analysis of 43 RCTs of fall interventions that included exercise [63]. They concluded that multiple component exercise interventions were effective in reducing the rate and risk of falling. The evidence supported three different approaches: multiple component group exercise programs, individually prescribed multiple component exercise carried out at home, and Tai chi as a group exercise.

In an RCT of a Tai chi intervention, Li et al. found the risk of falling was decreased 55% among participants in the Tai chi group compared to the control group [69]. In another RCT, Voukelatos et al. studied the effectiveness of a community-based Tai chi program and found that the fall rate in the Tai chi group was 28% lower than in the control group after 16 weeks and 33% lower after 24 weeks [70].

Sherrington et al. carried out a meta-analysis of 44 fall intervention studies that devoted at least 25% of the time to exercise [71]. They found that challenging balance, making exercises progressively more difficult, and having at least 50 h of exercise were the key factors associated with program effectiveness. Including a walking program did not contribute to reducing fall rates, possibly because the time spent walking took the place of time spent improving balance [71]. However, walking programs have other health benefits including improved fitness, weight loss, and lowered blood pressure [72]. Research is needed to better understanding the effect of walking programs on fall risk.

Medication Management

Studies have demonstrated clearly that psychoactive medications—specifically benzodiazepines, antidepressants, and sedatives/hypnotics—increase fall risk [50,73–75]. Medication management involves a doctor or pharmacist first reviewing all prescription and the over-the-counter medications an older adult is taking and then reducing the number of medications, finding alternative drugs, and/or adjusting dosages so as to reduce side effects and interactions that may lead to falls [50,73]. A relatively small study by Campbell et al. found that eliminating psychoactive medication use among community-dwelling older adults reduced fall rates by 66% [76]. However, 6 months after the study ended, almost half the participants had resumed taking psychoactive medications.

Vision Enhancement

Impaired vision, which encompasses poor visual acuity, reduced contrast sensitivity and depth perception, and visual field loss, increases the risk of falling [77,78]. Eye examinations and vision correction would be expected to help reduce this risk. However, fall interventions employing vision correction have been disappointing [79]. Evidence that cataract surgery reduces falls has been inconclusive [80–82].

Many older adults use glasses with multifocal lenses that can reduce edge contrast and depth perception, creating a fall hazard [83]; single vision lenses may be a better choice for activities, such as walking, that require good depth perception. A recent Australian study concluded that providing glasses with single vision lenses to older adults who usually wear multifocal glasses is an effective fall prevention strategy, but only for those people who are fairly active and take part in regular outdoor activities [84].

Home Modification

More than half of falls in community-dwelling older adults occur in or around the home [18,21], so modifying the home environment is a popular fall prevention strategy. However, simply reducing household environmental risks, such as improving lighting and removing tripping hazards, has not been shown to reduce falls among the older community population [85,86]. Day et al. conducted a factorial trial of three fall interventions: exercise, vision enhancement, and home hazard reduction [53]. Individually, only the exercise program was effective; this intervention reduced falls by 18%. However, when home hazard reduction was combined with the exercise program, falls were reduced by 24%, and when the intervention included all three components, falls were reduced by 33%.

Three randomized controlled intervention studies for community-dwelling older adults that focused on home modification were effective in reducing falls [87–89]. These individualized interventions involved home visits by occupational therapists who discussed behavioral changes with each client, tailored environmental changes to the client's specific needs, and facilitated recommended home modifications.

Results of interventions to reduce falls among nursing home residents have been inconsistent. Some multifactorial interventions that included environmental modification, staff education and training, and other factors (e.g., exercise programs, hip protectors, medication modification), have been effective in reducing falls [90–92]. However, other interventions for this population have been ineffective [93,94].

Vitamin D

Vitamin D has a direct effect on muscle strength, calcium absorption, and bone growth, and vitamin D with calcium may help decrease the risks of falls and fractures in older adults [95]. Sources of vitamin D include food (such as fish, eggs, and fortified milk), sun exposure, and dietary supplements.

After conducting a meta-analysis of eight randomized clinical trials, Bischoff-Ferrari et al. concluded that vitamin D supplementation in a dose of 700–1000 IU a day reduced the risk of falls among older adults by 19% [96], while a Cochrane review reported that vitamin D supplements reduced falls only in community-dwelling older adults with initially low 25-hydroxyvitamin D levels [97]. A systematic review by the Agency for Healthcare Research and Quality concluded that the evidence that vitamin D reduced falls and fractures was inconclusive [98], while a recent report by the U.S. Preventive Services Task Force concluded that vitamin D with or without calcium was associated with a 17% reduced risk of falling during 6–36 months of follow-up [99].

Vitamin D as a fall prevention strategy is appealing because it is inexpensive and would be acceptable to high-risk older adults [100].

Multifactorial Interventions

Falls often are caused by a complex interaction between the individual and their environment. In 1994, Tinetti et al. published the results of a landmark fall intervention study that focused on a number of risk factors: balance, gait, impaired arm or leg strength or range of motion, use of sedatives, use of four or more prescription medications, postural hypotension, and ability to transfer safely (i.e., move from the bed to a chair) [101]. This study demonstrated that an intervention

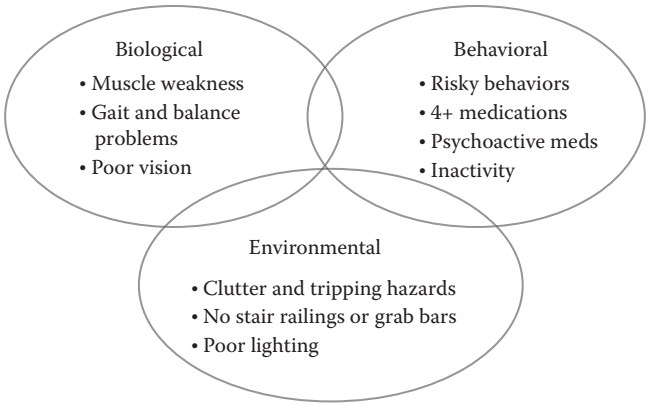


FIGURE 126.5 Risk factors addressed by multifactorial fall interventions.

that addressed multiple risk factors could significantly reduce falls among community-dwelling older adults.

The majority of effective interventions include multiple components that address a variety of risk factors (Figure 126.5). These may incorporate risk factor screening and treatment or referrals to specialists to reduce fall risk; exercise programs or physical therapy to improve gait, balance, and strength; medication management; environmental modification; and other elements such as education about fall risk factors and vision assessment and correction [53,102–104].

PERCEPTIONS OF RISK

Many older people are not aware of their fall risk or avoid discussing these issues with their health care providers [52]. Consequently, opportunities to implement prevention strategies are often missed. Effective fall prevention approaches require older adults to adopt new behaviors and such changes are unlikely if older adults do not perceive fall prevention advice to be relevant or personally meaningful.

Some people believe falls are an inevitable part of aging and cannot be prevented; others do recognize preventable fall risks in the general older population or among their peers but do not see themselves as personally vulnerable. Others attribute falls simply to unavoidable bad luck [105,106].

Because many older adults reject the idea that they are at risk of falling, messages promoting fall prevention programs should focus on the positive health and social benefits, such as improving balance and maintaining independence, rather than emphasizing negative information about falls and fall injuries [52,106]. Formative research with target audiences will increase the likelihood that messages will be well received.

The Centers for Disease Control and Prevention Injury Center has developed educational materials about falls for older adults, caregivers, and health care providers. Links to selected resources are provided in Table 126.2.

TABLE 126.2
Selected Resources on Falls and Fall Prevention

Articles	Self-Reported Falls and Fall-Related Injuries among Persons Aged ≥65 Years—United States, 2006
	http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5709a1.htm
CDC publications	Preventing Falls: What Works—A CDC Compendium of Effective Community-based Interventions
	http://www.cdc.gov/HomeandRecreationalSafety/Falls/compendium.html
	Preventing Falls: How to Develop Community-based Fall Prevention Programs
	http://www.cdc.gov/HomeandRecreationalSafety/Falls/community_preventfalls.html
	Fact sheets: CDC—Falls Among Older Adults: An Overview
	http://www.cdc.gov/HomeandRecreationalSafety/Falls/adultfalls.html
	Costs of Falls among Older Adults
	http://www.cdc.gov/HomeandRecreationalSafety/Falls/fallcost.html
	Hip Fractures among Older Adults
	http://www.cdc.gov/HomeandRecreationalSafety/Falls/adulthipfx.html
	Falls in Nursing Homes
	http://www.cdc.gov/HomeandRecreationalSafety/Falls/nursing.html
Podcasts	Adult Falls—Date released: June 8, 2007. Series: A Cup of Health with CDC
	http://www2c.cdc.gov/podcasts/player.asp?f=5812
	Falls Among Older Adults—Date released: March 13, 2008. Series: A Cup of Health with CDC
	http://www2c.cdc.gov/podcasts/player.asp?f=8521
	Preventing Older Adult Falls and TBI—Date released: March 7, 2008. Series: CDC Featured Podcasts
	http://www2c.cdc.gov/podcasts/player.asp?f=6052658

RESEARCH GAPS

Research has identified effective interventions for community-dwelling older adults [107], but fall interventions for nursing home residents and hospital patients are more limited. There is evidence that multifactorial interventions including risk assessment, staff education, and supervised exercise can reduce falls and fall risk in hospital patients and that vitamin D supplementation can reduce fall in nursing home residents [108].

Further research is needed now to study the effectiveness of walking programs to reduce fall risk; to tailor interventions for subgroups with differing characteristics and risk factors, such as people with chronic conditions or differing levels of functional impairment; to determine the relative contribution of selected risk factors to fall events; to determine the underlying causes and/or circumstances of falls; and to understand how these factors differ for men and women. Clarifying these differences as well as collecting information about the location and events preceding a fall or fall-related injury is vital to identifying high-risk behaviors and situations, and for developing and implementing targeted fall prevention strategies.

Future Directions

Much is known about effective fall prevention strategies [107]. We now need to refine these proven interventions to broaden their use across diverse populations; create an infrastructure to train implementers how to use proven strategies; disseminate effective fall prevention programs; and support widespread adoption at the local level. We also must enhance provider training to incorporate fall risk assessment and interventions into clinical settings, as well as linking clinicians to community-based interventions. Such a multifaceted approach would support broad implementation of effective fall interventions and would reduce the personal and societal burden associated with older adult falls.

CONCLUSION

Falls and fall-related injuries are age-related problems, and the U.S. population is aging rapidly. People older than 85 years are the fastest growing segment of the older population [109] and have the highest fall injury rate [8]. In future, a greater number of older adults will be affected by fall injuries unless we take preventive action—including educating older adults, health care providers, and senior services providers about fall risk factors and effective prevention strategies, incorporating fall prevention into clinical care, and disseminating and implementing effective fall prevention programs in our communities. Such a comprehensive approach will reduce the societal burden of fall injuries and will improve the health and quality of life of older adults.

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127 Preventing Repeat Intimate Partner Violence

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CONTENTS

Introduction 1507
IPV in the United States 1507
Epidemiology of IPV 1507
Health Consequences of IPV 1508
Need for Interventions 1508
Universal Screening for IPV 1508
Validated Screening Tools 1509
Acceptability of Screening to Patients and Providers 1509
Effectiveness of Screening for IPV 1510
The U.S. Preventative Services Task Force Evaluation of IPV Screening 1510
Recent RCT for Screening for IPV in Health care Settings 1511
Interventions to Address IPV 1512
Interventions in the Health care Setting 1512
Interventions Outside of the Health care Setting 1513
Role of the Health care Provider in the Prevention of IPV 1514
Screening for IPV 1514
Implementing Interventions 1514
Collecting Data to Inform Intervention Development and Policy 1514
Act as Policy Advocates 1515
Conclusions 1515
References 1515

INTRODUCTION

Over the past 25 years, intimate partner violence (IPV) has gained increased recognition in the medical and public health fields as a significant problem affecting women in the United States and globally. IPV is perpetrated by one partner in a relationship (either current or former spouses or dating partners) against the other and can include physical violence, sexual violence, threats of violence, or emotional abuse [1]. The consequences of IPV are broad, ranging from physical injuries, chronic conditions, mental health outcomes, and death and costing billions of dollars a year in medical expenditures and lost productivity. Therefore, preventing repeat IPV should be a priority for medical and public health practitioners.

This chapter provides the necessary background to facilitate action by health care and public health practitioners. Following an overview of the epidemiology and health consequences of IPV in the United States, the chapter will discuss the current state of the science on screening for IPV in the clinical setting and present existing interventions to address IPV. Finally, this chapter will summarize the role of the health care and public health practitioner in addressing IPV in order to prevent repeat violence among women.

IPV IN THE UNITED STATES

Epidemiology of IPV

One of five women experience physical assault by an intimate partner in their lifetime, and an estimated 1.3 million women are victimized by 4.5 million physical assaults in their intimate relationships annually [2]. Among clinical samples, the prevalence rates range from 4% to 44% of women experiencing IPV in the past year [3–6]. Both men and women are victims as well as perpetrators of violence in their intimate relationships. However, women are more often the victims of IPV, are more likely to sustain more severe physical injury, and are more likely to be killed by an intimate partner as compared to men [7–10].

While women of all ages, race/ethnicities, and sociodemographic statuses experience violence in their intimate

relationships, the prevalence of IPV varies between different groups. Findings from the National Violence Against Women Survey indicated that American Indian/Alaska Native women experience higher rates of IPV compared to women of other racial backgrounds, while Asian/Pacific Islander women report lower rates of IPV [9]. The National Violence Against Women (NVAW) survey and other research indicates that African American women report experiencing significantly higher rates of lifetime abuse and intimate partner homicide compared to women overall, and higher rates of severe violence than white women [2,11–13]. For example, in one large sample of African American women in Baltimore, 62% of women reported past year abuse from an intimate partner, a rate that is significantly higher than most estimates of IPV in the general population [14]. Women of mid-level socioeconomic status and those with higher levels of education have a lower prevalence of IPV than their low-income counterparts [15]. Low-income women, regardless of race and ethnicity, may be doubly disadvantaged because they not only have fewer resources for leaving an abusive relationship but their health status may already be compromised due to their impoverished circumstances. These factors make IPV and its associated health consequences a central concern as a health disparities problem in need of attention.

Health Consequences of IPV

IPV is the largest cause of injury for women who are treated in emergency departments (EDs) as well as the most prevalent cause of homicides in women [15]. Approximately 42% of women who are physically assaulted by their partner sustain injuries, [1,9] and between 40% and 60% of murders of women are committed by their intimate partners [15]. Women who have experienced IPV are more likely than women who are injured through other causes to sustain injuries to their face, neck, throat, breast, and abdomen and often experience chronic pain and gastrointestinal (GI) disorders. The chronic pain and GI disorders can result not only from the injuries themselves but from the fear and stress associated with experiencing abuse as well. Moreover, psychological IPV itself has been associated with several physical health outcomes such as arthritis, chronic pain, migraine, stomach ulcers, and chronic pelvic pain [16].

Numerous reproductive health consequences can result from IPV. Women who experience IPV are more likely to have gynecological health issues, such as sexually transmitted infection (including HIV), vaginal bleeding or infection, fibroids, pelvic pain, and urinary tract infections, and other reproductive health outcomes such as unintended pregnancy [15]. IPV experienced during pregnancy can have additional health impacts such as delayed entry into prenatal care, premature labor, poor weight gain, anemia, first or second trimester bleeding, as well as negative health consequences for the infant, such as low birthweight or fetal trauma resulting in miscarriage or spontaneous abortion [17].

In addition to experiencing physical and reproductive health consequences, abused women also suffer from numerous mental health sequelae of IPV. Depression, anxiety, and posttraumatic stress disorder (PTSD) are the most common mental health outcomes associated with IPV, and suicidality has also been associated with the experience of violence in intimate relationships [18]. Several studies have described the increased risk of depressive and PTSD symptoms associated with living with IPV [18–29]. A meta-analysis of 11 studies indicated that between 31% and 84.4% of women who had experienced IPV subsequently met the criteria for PTSD [30]. Furthermore, qualitative inquiries into the lives of women who have experienced IPV have indicated that these women describe violence, substance use, and depression as intricately related and overlapping problems [31].

Need for Interventions

Given the significant impact of IPV on women's physical, reproductive, and mental health, it is not surprising that women who experience IPV consume more medical care than their non-abused counterparts. Not only do they seek more medical care for their injuries associated with the violence they experience but they also use more of other types of health care services and more prescriptions [15,32]. Evaluations of women's health care utilization and costs indicate that women who experience IPV use more health care services, including increased hospitalization, more use of general clinics and mental health services, and more out-of-plan referrals, which result in increased costs as compared to their non-abused counterparts [33]. A study of female Health Maintenance Organization (HMO) enrollees indicated that the average health care cost of women who experienced IPV was $1700 more over a 3 year span than matched women who were never abused [34].

Thus, the medical care setting provides an ideal, albeit usually missed, opportunity to address this important women's health issue. Addressing IPV in the health care setting could help to prevent injury and numerous other health-related sequelae. However, in order to provide treatment or intervene to prevent repeat IPV, it is necessary to first identify the women who are experiencing it. Screening for IPV is the obvious choice as a means to accomplish this in the health care setting.

UNIVERSAL SCREENING FOR IPV

A feasible low-cost, high impact policy to address IPV is the universal screening of women for IPV in the medical care setting. Universal screening has been defined as "universal routine inquiry" [35] or "a standardized assessment of patients, regardless of their reasons for seeking medical attention" [36]. Therefore, a policy of universal screening would require that every woman would be asked questions, regardless of the nature of her visit to the health care setting, that could identify her as being exposed to violence in her intimate relationship. Universal screening could identify women who are experiencing IPV, but do not present with outward clinical signs such as injury, and assist with

the primary prevention of serious health-related outcomes of IPV. Screening for IPV would also allow for the identification of women who are at high risk of serious or fatal violence. By identifying women who are experiencing IPV, especially those who are particularly vulnerable or at risk for severe abuse, clinical providers can provide counseling and referral to existing social services, such as shelters, legal services, or mental health services and thus reduce women's risk of repeat victimization.

Several issues arise in determining whether universal screening for IPV is an appropriate policy to implement to begin to prevent future IPV. First, are there validated screening tools that can correctly identify women who are experiencing IPV? Second, is universally screening all women who present in health care settings an acceptable practice for patients as well as providers? And lastly, can a policy of universal screening effectively lead to the prevention of subsequent IPV? Each of these questions is addressed in the following sections.

Validated Screening Tools

Several screening tools have been tested and validated as useful in identifying women experiencing IPV or at risk for severe physical harm as a result of IPV. These tools can be used to quickly identify women who present in primary care for regular check-ups or in the ED and are currently experiencing violence, alert clinicians to this issue, and create an opportunity to refer women to existing IPV services in the community such as legal aid, shelters, or specialty health care. The utilization of these tools in a systematic and universal way could identify many at-risk or abused women who would have otherwise gone without intervention.

A few systematic reviews have evaluated IPV screening tools that have been tested in health care settings, and the Centers for Disease Control has published a compilation of more than 30 tools available to clinicians to screen for violence among their patients [37,38]. While the reviewers found that further testing and validation of these scales in more diverse populations is warranted, their work also synthesizes the utility of several scales in the clinical setting. The systematic review focuses on the most studied tools in clinical settings, which include Abuse Assessment Screen (AAS), the Hurt, Insult, Threaten, and Scream (HITS), the Partner Violence Screen (PVS), and the Woman Abuse Screening Tool (WAST), which are summarized in Table 127.1 [37]. The AAS has been tested mostly among low-income and uninsured women and in countries outside the United States and was found to have high sensitivity and positive predictive values but varying specificity. The HITS has been tested among varying populations, including Hispanic and African American women, as well as in Spanish, and was found to have adequate internal consistency (alpha = 0.80) and good validity compared to the Conflict Tactics Scale, which is a previously validated instrument to measure IPV. The PVS has a wide range of sensitivities and specificities when tested among a population with a range of race/ethnicities and socioeconomic status (SES), but all were adequate. The WAST was tested among white, African American and Latina, and Spanish women and was also found to have varying sensitivities and specificities but good internal reliability and discriminant validity in differentiating between abused and non-abused women.

Despite the need for additional testing of some of these tools, they are viable options for clinicians to identify women who are experiencing or at risk for IPV. Women can be screened using very few items that take a small amount of time to administer, making these tools appropriate for a clinical setting where the lack of time with patients might be an issue.

Acceptability of Screening to Patients and Providers

Because IPV is historically not an issue that is dealt with in the health care setting, or typically considered appropriate to mention, discuss, or intervene with, clinicians do not often or routinely screen for IPV. In fact, the rates of IPV screening by health providers are surprisingly low and vary by setting [43]. Women who present to emergency rooms with certain types of injuries are more likely to be screened for IPV than women who present with no visible signs or symptoms of IPV-related health outcomes or women who visit clinicians for other medical issues [44]. Among a nationally representative sample of women, only 7% reported having ever been asked about experiencing violence by a health care professional [45].

In studies of the acceptability of IPV screening, the majority of women have reported that IPV screening in clinical setting is acceptable [46]. The systematic review by Ramsay et al. determined that women's acceptability of IPV screening in a clinical setting ranged from 49% to 75% [46–48]. In one study of 442 abused and non-abused women, high proportions of both groups believed that screening would make it easier for abused women to get help (86%) and that they would be glad someone took interest (96%); moreover, 88% of the non-abused women reported that they would not be insulted if asked about IPV [47].

However, in studies of provider acceptability of screening, two-thirds of physicians and one-half of ED nurses were *not* in favor of screening [48,49]. Some of the barriers to screening for IPV that were cited include a lack of skills or education in screening, a fear of offending or harming women, a lack of known effective interventions, and limited time. Other studies indicate that the acceptability of screening can vary based on provider characteristics. For example, providers who are females, obstetricians/gynecologists, trained within the past 5–10 years, and who work in clinics or hospitals perceive fewer barriers to screening [50].

The limited data that are available suggest that patients would be supportive of universal screening and that more recently trained health care providers would be as well. Thus, the next question concerns whether such screening is effective. The systematic review by Ramsay et al. found that, in general, screening programs resulted in increased rates of identifying women experiencing IPV in various clinical

TABLE 127.1
IPV Screening Tools

Screening Tool	Administration Method	Items	Scoring
Abuse Assessment Screen (AAS) [39]	Clinician administered	1. Have you ever been emotionally or physically abused by your partner or someone important to you? 2. Within the last year, have you been hit, slapped, kicked, or otherwise physically hurt by someone? If yes, by whom? How many times? 3. Have you been hit, slapped, kicked, or otherwise physically hurt by someone? If yes, by whom? How many times and where? 4. In the last year, has anyone forced you to have sexual activities? If so, whom? How many times? 5. Are you afraid of your partner or anyone you listed above?	Abuse indicated by positive response to one or more items
Hurt, Insult, Threaten, and Scream (HITS) [40]	Clinician administered or self-report	How often does your partner: 1. Physically hurt you? 2. Insult you or talk down to you? 3. Threaten you with harm? 4. Scream or curse at you? (Response options on five-point Likert scale: 1 = never, 2 = rarely, 3 = sometimes, 4 = fairly often, and 5 = frequently)	Abuse indicated by score of ≥10.5
Partner Violence Screen (PVS) [41]	Clinician administered	1. Have you ever been hit, kicked, punched, or otherwise hurt by someone in the past year? If so, by whom? 2. Do you feel safe in your current relationship? 3. Is there a partner from a previous relationship who is making you feel unsafe now?	Abuse indicated by positive response to items 1 or 3, or negative response to item 2
Woman Abuse Screening Tool (WAST) [42]	Self-report	1. In general, how would you describe your relationship—a lot of tension, some tension, or no tension? 2. Do you and your partner work out arguments with great difficulty, some difficulty, or no difficulty? 3. Do arguments ever result in you feeling down or bad about yourself? 4. Do arguments ever result in hitting, kicking, or punching? 5. Do you ever feel frightened by what your partner says or does? 6. Has your partner ever abused you physically? 7. Has your partner ever abused you emotionally? 8. Has your partner ever abused you sexually? (Response options for #3–#8: often, sometimes, never)	Cut off for abuse not available

settings, including primary care clinics and EDs [46]. Because the first step toward intervention for IPV is identification of women who are experiencing IPV, universal screening offers a feasible and acceptable means to that end.

Effectiveness of Screening for IPV

There are two related questions that address the effectiveness of screening for IPV. First, does *screening increase identification of IPV* and if so, does *identification reduce repeat victimization?* Several studies have indicated that instituting screening protocols for IPV in health care settings results in a significant increase in identification of IPV with acceptable accuracy [51–54]. Evidence addressing the question as to whether identification of IPV in the health care setting reduces repeat victimization is discussed in the following section.

The U.S. Preventative Services Task Force Evaluation of IPV Screening

In order to assess the effectiveness of IPV screening, the U.S. Preventative Services Task Force (USPSTF) conducted

a systematic review of the existing literature on IPV screening and IPV interventions. A total of 14 studies that met the USPSTF inclusion criteria for screening studies were examined. These studies compared various screening instruments against each other [39–41,55–57], compared screening instruments with a directed interview [54,58], measured inter-rater reliability or internal consistency of screening tools [59–61], and compared methods of administration of screening tools [62–64]. Of these, only four were ranked as having good internal and external validity (the HITS, PVS, AAS, and WAST summarized in "Validated Screening Tools" Section).

A systematic review specifically examining interventions for violence against women was conducted, which included interventions for batterers and couples, and interventions for women outside of the clinical setting, in addition to interventions for women in health care settings. This review found that screening instruments for IPV are available to identify women experiencing abuse but concurred with other reviews and studies that the effectiveness of screening for explicitly reducing violence or improving health outcomes has not been evaluated [65].

However, some critical evidence concerning IPV screening was excluded from the collection of studies in the USPSTF's systematic review, as was identified in a response by the Family Violence Prevention Fund [66]. First, the USPSTF used an analytic framework for screening tools that examines its use only among asymptomatic patients. Many IPV experts believe that a behavioral assessment and counseling tool using a different analytic framework would be more appropriate for a problem like IPV. This distinction is based on the observation that IPV is more of a chronic problem that can escalate over time, making it difficult if not impossible to distinguish "asymptomatic" from "symptomatic" women. Therefore, screening can be beneficial even for women who are already "symptomatic"—i.e., women who present with physical or mental trauma as a result of IPV that they may have been experiencing for years. Even such women have shown improvements in health outcomes and reduced risk for repeat violence after screening. A study by McFarlane et al. was excluded from the review because it was designed to asses an intervention for reducing repeat IPV but found that all women who were assessed using the AAS and subsequently offered a resource card or counseling sessions showed a decrease in threats of abuse, assaults, and danger risk for homicide over time [67]. Therefore, the USPSTF's decision to consider IPV screening as a way to identify asymptomatic patients, as opposed to a way to "diagnose" women with IPV who might have presented with some symptoms, they systematically excluded all research involving patients presenting with any signs of prior trauma or IPV. Given the nature of IPV, this was potentially an inappropriate distinction and could explain the USPSTF's inclusion of only 14 screening studies of 886 identified in the literature search.

Additionally, IPV experts and researchers raised the critique that the USPSTF's emphasis on randomized controlled trials (RCTs) in the evaluation of validity of IPV screening studies is perhaps inappropriate. Because many researchers consider it unethical to conduct studies related to IPV where a control group of women being abused receives no intervention, many IPV-related studies are limited in their ability to use an RCT design. However, the Family Violence Prevention Fund points out that the USPSTF has recommended assessment and counseling services for various other health issues, such as alcohol and drug use among adolescents and unintended pregnancy, even though RCT evidence was lacking in these cases [66]. They further assert that "the public health benefit of identifying a history of victimization within the context of other psychosocial health problems and risk behaviors, giving supportive messages to patients who disclose abuse, and providing appropriate referrals could prevent future injuries, illness and improve overall quality of care" [66, p. 4].

The USPSTF limited its review to studies that examined the outcomes of morbidity, disability, and mortality. However, there are several outcomes that could be considered an indication of a successful result of IPV screening that were not considered. These include referral to support services such as legal or shelter services, the initiation of safety planning behaviors, and the receipt of advocacy services at the health care setting itself. Several studies exist in the literature that indicate that screening for IPV leads to risk reduction and public health benefits, but do not directly link screening to morbidity or mortality outcomes, and these were not included in the USPSTF's review [68–72]. For example, an intervention in an ED that implemented universal screening, on-site IPV advocacy, and telephone-based counseling by a case manager found that more than half of women identified as IPV victims were able to receive ongoing community-based services to address their IPV and nearly one-fourth reported a reduction in perceived risk of IPV by their abusive partner. While this study was not randomized and does not show clinical outcomes associated with IPV screening, it does suggest that IPV screening could be effective in helping women stay safe [68].

The USPSTF admittedly takes a "conservative evidence-based approach to this process, making recommendations that reflect primarily the state of the evidence and refraining from making recommendations when they cannot be supported by evidence" [73, p. 31]. The panel acknowledges that clinicians and policymakers might consider other issues, such as cost-effectiveness, resource priorities, ethics, and legal concerns, when deciding whether or not to accept their recommendations [73].

Recent RCT for Screening for IPV in Health care Settings

More recently, an RCT to investigate the effectiveness of universal IPV screening in health care settings was conducted in Canada [35]. This study recruited participants from 12 family practices and community health centers, 11 EDs, and 3 obstetrics/gynecology clinics and randomized them

by day or work shift. Women who had a male partner in the past 12 months and presented to the health care setting on a randomly assigned screening day or shift were given the eight-item WAST and asked additional questions about their socioeconomic characteristics. The WAST was included in the patient charts of women who screened positive for IPV before they saw their clinician. Women with male partners in the past 12 months who presented for health care visits on the assigned non-screening control days or shifts were asked about their socioeconomic characteristics only before seeing their clinician. After their visit, they were given the WAST to screen for IPV. Both groups of women were given an information card containing contact information for services available for women experiencing violence, and all women were followed up at 14 days, 6 months, 12 months, and 18 months.

Results from this study indicated that while women in both groups overall reported a reduction in the experience of IPV, there were no statistically significant differences in IPV recurrence over time between women who were screened for IPV before their clinical appointment and those who were not. The study concluded that there is not sufficient evidence indicating that universal IPV screening in clinical settings prevents or reduces women's experience of IPV. However, a critical point of importance is that this study tested the effectiveness of screening alone, not the effectiveness of screening followed by any type of referrals, intervention, or treatment. The clinicians were simply provided the positive screening tools in their patients' charts, and any subsequent referrals or discussion of violence during the clinical visit was left to the discretion of the clinicians. In fact, only 44% of women who were screened for IPV prior to their visit reported discussing the violence with their clinician during their visit.

Therefore, while this study agrees with the findings of the USPSTF and suggests that there is insufficient evidence to support universal screening for IPV, it does not adequately test the effectiveness of screening when accompanied by referrals to IPV services or interventions. As is the case with numerous other health issues, screening alone is not preventative, and it is the quality and effectiveness of the treatment or intervention made available to patients who are screened that can actually prevent a health issue or result in secondary prevention. The authors of this study suggest that a lack of evidence for effective IPV treatment and services exists, and therefore, no effort was made to control whether clinicians actually implemented any sort of treatment or intervention after a women screened positive for IPV. However, several studies of interventions in the health care setting to address IPV have shown promising results in the reduction of repeat IPV among women.

INTERVENTIONS TO ADDRESS IPV

Interventions in the Health care Setting

Despite the substantial impact of IPV on women health and their use of health care, there is a dearth of knowledge about what services would help women in this setting. The few intervention trials that have been reported are reviewed briefly here.

Parker et al. [74] tested the effectiveness of an intervention for pregnant women who were experiencing IPV in a clinical setting. The intervention was based on a model of empowerment to increase women's independence and control and was administered by masters or doctorate level nurses in prenatal clinics during scheduled clinical visits. The three 30 min intervention sessions focused on creating a safety plan, providing information about the cycle of IPV, offering phone numbers for community resources, and providing information on protective orders and filing criminal charges. Women were also provided a printed brochure with information covered in the intervention sessions. Half of the women who completed the intervention were also invited to attend group counseling and information sessions. Women in the comparison group were given a card with information about resources available in the community to address IPV. The findings from this study indicated that at 6 and 12 months after the intervention, women who received the intervention reported experiencing significantly less violence. However, women were not randomized into the intervention and control groups.

The effectiveness of three types of interventions to decrease IPV among pregnant women was examined in a study that implemented a randomized design. This study by McFarlane et al. [75] compared a brief intervention, a counseling intervention, and a counseling plus outreach intervention by randomly assigning pregnant women who reported IPV in the previous year or during their current pregnancy to each group. Women in the brief intervention group were given a resource card with the phone numbers of available community resources to address IPV, as well as a brochure. Women in the counseling intervention group were provided access to counseling services located in the clinic, which they could use at their own discretion. Professional counselors were available to provide counseling and education on IPV, referrals to services, and assistance with accessing these services. The final treatment group included the services available in the counseling intervention group as well as the availability of a nonprofessional mentor who offered education and support services and assistance with referrals and access to resources. These mentors were available to women in this treatment group through in-person and telephone contact. At 2, 6, 12, and 18 months after the interventions were delivered, women in all groups reported decreased threats of violence and physical violence. However, there were no significant differences in the experience of violence between the three intervention groups. The decrease in violence for all women, even those who were simply given a resource card, indicates that the IPV screening itself could have acted as an intervention. The authors note that by simply completing an IPV screen in a clinical setting and being offered resources, women might be alerted to the fact that their experience of IPV is serious and that their provider is available to assist them.

Similar interventions were also tested by McFarlane et al. in an RCT of women (not limited to pregnant women) who presented at public health care clinics and screened positive

for IPV in the past year using the AAS [67]. Women were randomized by weeks into two study groups. Those in the first group were screened for IPV and then given a resource card that contained information about creating a safety plan and resources available to address IPV. Women in the second group were screened for IPV and then provided nurse case management during the visit, which included supportive care, provision of referrals, and guidance in accessing resources. Findings from this randomized study showed that all women, regardless of the type of intervention they received, reported experiencing a reduction in threats of physical IPV, actual physical IPV, and risks for homicide. Additionally, the adoption of safety behaviors increased for women in both groups. Therefore, this study indicates that screening for IPV and referring women to available services, even by simply providing them with printed information, can reduce their experience of IPV.

A more recent study by Kiely et al. [76] evaluated the impact of an intervention for IPV that was integrated into a broader intervention to reduce cigarette smoking, environmental smoke exposure, depression, and IPV among pregnant women. This IPV intervention was based on the previously tested intervention by Parker et al. [74] and provided information on IPV, available resources, and assistance in developing a safety plan over a minimum of four sessions in prenatal clinics. Women were randomized to receive this integrated intervention or to receive usual care as was standard in the prenatal clinics. After completing the interventions sessions, women in the treatment group who experienced minor physical IPV were significantly less likely to experience IPV during the follow-up period of 8–10 weeks postpartum. However, this intervention did not show significant effects on the experience of more severe physical IPV and sexual IPV.

The studies described earlier have been generally grounded in an empowerment theory approach to IPV, which has been most prominent in the IPV advocacy movement from its inception. An alternative yet complementary approach that has been proposed is the application of a stages-of-change model [77]. The stages-of-change, more properly called the Transtheoretical Model (TM), was created by Prochaska and DiClemente and it describes behavior change as a dynamic, stage-based process [78,79]. The TM may be particularly appropriate for IPV interventions delivered in the health care setting because it provides a systematic approach to assessing an individual's readiness to change and tailoring patient counseling accordingly, and it has demonstrated its utility for changing a number of other health-related behaviors. Work by Brown [80] and Burke et al. [81,82] found that women describe their experiences living in and surviving abusive relationships in ways that are consistent with the stages of the model. Qualitative interviews with 78 IPV survivors followed by quantitative surveys of 96 IPV survivors led Burke et al. [82,83] to conclude that the TM model fits women's lived experiences and that women can be staged according to their readiness to end the relationship: (1) *Pre-contemplation—Does not want to end the violent relationship or is unsure;* (2) *Contemplation—Wants to end the violent relationship, but has not done anything to get ready to do so;* (3) *Preparation—Wants to end the violent relationship and has started taking actions, getting prepared;* (4) *Action—Has ended the violent relationship less than six months ago; and* (5) *Maintenance—Has ended the violent relationship at least six months ago.* The TM also incorporates influencing factors—i.e., 10 processes of change that describe how individuals move from one stage to the next, decisional balance (weighing the pros and cons of change), and self-efficacy (confidence on one's ability to change). This feature of the model is particularly useful from an intervention perspective because these factors can be "activated" through specifically designed counseling activities.

An eight-session, individually tailored counseling intervention based on the TM, using the stages and processes identified in the work by Burke et al. [81–83] was recently pilot tested with a small sample of 12 abused women recruited from a primary care clinic serving HIV-positive patients [84]. The curriculum focuses on goal setting, danger assessment, and safety planning as well as specific stage-based counseling activities to help women make informed decisions about their situation. Data from the six women who completed all the counseling sessions and a follow-up interview 2 weeks later found significant improvements in perceived control, perceived empowerment, and social support. The number of types of IPV events experienced decreased from 3.08 during the 3 months prior to the intervention to 0.50 during the 3 month intervention period. No adverse events occurred, and women's qualitative feedback on the counseling sessions was extremely positive. Although this is a small-scale test of the program, it shows promise and represents an innovation in individually focused interventions for IPV. If found to be effective on a larger scale, such a program could be implemented in a wide array of settings, both in and outside of the health care setting.

Interventions Outside of the Health care Setting

While screening and intervention for IPV in the clinical setting has the potential to prevent repeat IPV for many women, there are numerous activities and interventions taking place outside of realm of health care [85,86]. Decades of work by advocates and the criminal justice system has resulted in the creation of shelters, legal and counseling advocacy programs, national and local hotlines, community campaigns, and a plethora of laws designed to protect women and reduce IPV, including the Violence Against Women's Act enacted by Congress in 1993 [87]. Today, we have organizations such as the Family Violence Prevention Fund (endabuse.org), the National Coalition Against Domestic Violence (www.ncadv.org), and the National Domestic Violence Hotline (www.thehotline.org) that provide information and resources to both professionals and the public. The National Network to End Domestic Violence (www.nnedv.org/resources/coalitions.html) coordinates coalitions in every state and territory. Service programs at the local level, such as shelters, hotlines, legal advocacy programs, and counseling advocacy programs, have been

found to have varying levels of success, and their effectiveness is heavily dependent on their availability and accessibility to women who need them [86,88]. Wathen and MacMillian systematically reviewed the literature on interventions for women and concluded that there were no high quality evaluations of shelter stays, although they found fair evidence that a specific program of advocacy and counseling among women who spent at least one night in a shelter reduced their reported violence and improved their quality of life [65].

In the area of criminal justice interventions, several policies and protocols are thought to impact the prevention of repeat IPV among women. For example, implementing a policy of mandatory arrest for perpetrators of any misdemeanor intimate partner assault was found to result in a reduction in any repeat assault of 25% and a reduction in the number of assaults of 30% [89]. Webster notes the potential promise of special domestic violence courts that can both take into account the sensitive and complicated nature of the relationship between an IPV perpetrator and his victim as well as bring together and integrate additional resources to address IPV [88]. A court order of protection is a measure that a victim of IPV can pursue as well that has been found to lower the risk of repeat violence in some studies [90,91]. Policies that separate perpetrators of IPV from firearms have the potential of preventing severe IPV-related injury and intimate partner homicide. The odds of a woman being killed by her abusive partner has been found to be five times higher if her abusive owns a firearm [92]. Some research has indicated that the implementation of laws that require the removal of firearms from IPV perpetrators does result in a reduction in the IPV-related homicide rate, but the effectiveness of these laws are also impacted by whether judges and law enforcement actually implements them [93,94]. Bell calls for additional research on criminal justice interventions [95]. She emphasizes the need to strengthen the methodology used to include larger samples and longer follow-up periods and, importantly, to incorporate a broader array of outcomes that are informed by listening to victims' stories of the impact of the criminal justice system on their lives.

Finally, research has been conducted to evaluate the effectiveness of interventions targeted at the abuser. Many of these abuser intervention programs are mandated by the courts, although some are voluntary. While the evidence on the effectiveness of these programs does not seem particularly promising, many of the studies were quasi-experimental and were affected by high dropout rates. Webster notes that many programs might not be successful due to their inability to address underlying issues related to the perpetration of violence, such as mental illness and drug and alcohol abuse [88].

ROLE OF THE HEALTH CARE PROVIDER IN THE PREVENTION OF IPV

There are numerous roles for health care providers to play in helping to reduce the impact of IPV on women's health. Because IPV is associated with medical problems that span the spectrum from acute injuries to reproductive health to chronic diseases, all health care providers can contribute [15,22,32]. The evidence that abused women would welcome help from their health providers is clear [46–48].

Screening for IPV

The American Medical Association, American College of Obstetricians and Gynecologists, American Academy of Family Physicians, American Academy of Pediatrics, and American Nurses Association are among numerous medical organizations that recommend IPV screening as part of routine patient care [86,96–98]. Health care providers can play a crucial role in identifying women who are experiencing IPV and thereby take the first step in preventing repeat violence and reducing the negative health outcomes that can result. By integrating a universal screening policy into their standard clinical visit, providers can quickly assess whether their patients are safe in their current relationship or are at risk for repeat IPV. While a gold standard for IPV screening does not exist, numerous screening tools with relatively high validity, sensitivity, and specificity are available that can be implemented in a clinical encounter in a very short amount of time, and these screening procedures have been shown to be acceptable to women patients [46–48].

Implementing Interventions

Providers can also play a role in preventing IPV by implementing interventions in the clinical settings. As several studies have demonstrated, even a simple intervention of providing a referral card with available IPV resources may well decrease repeat IPV [67,74,99], and more intensive interventions could potentially result in an even greater IPV reduction [76]. Newer program models, such as those that integrate IPV within the context of other health-related issues and those that apply behavior change theory should be supported. The paucity of evaluated interventions demands attention, and health care providers should partner with academic researchers to address this gap.

Collecting Data to Inform Intervention Development and Policy

Much of the criticism of implementing universal screening policies has focused on the lack of evidence that universal screening along with effective interventions can result in the reduction of IPV over time [35,65]. In order to improve the body of research to support universal screening policies by agencies such as the USPSTF, health care providers can assist in collecting data on IPV and the impact of screening and interventions in their clinical practice. Future studies showing the potential success of screening paired with effective interventions could bolster the body of data used in systematic reviews and by the USPSTF in making their recommendations.

Act as Policy Advocates

In addition to improving services to individual patients, there are numerous opportunities at the policy level to strengthen domestic violence laws at local, state, and national levels. For instance, a quick search of the National Conference of State Legislatures database found that four states had introduced teen dating violence legislation in a single month, including one bill in Maryland that would change the definition of domestic violence [100]. By partnering with advocates, health care providers can add their influential voice to the policy discussion. Health care providers can also be advocates within their own professional societies. Policy statements by organizations such as the American Medical Association and others can carry considerable weight in policy debates.

CONCLUSIONS

This chapter has focused on ways in which IPV should be a critical concern for those interested in healthy lifestyles. The prevalence of IPV and its consequences makes it one of the most pressing women's health issues, yet it is rarely discussed in the context of healthy lifestyles and it is often ignored in the delivery of health care services. As described in this chapter, ways to improve the quality of women's lives by reducing their experience of violence do exist. Several validated screening tools can be used to identify women who are experiencing IPV. Women support such screening in the context of their health care. There are promising, if not yet widely available, programs that can be delivered to women who are found to be living in abusive relationships. There is an urgent need for additional resources for such programs and careful evaluations of their impacts. However, the health care setting cannot be expected to solve the problem of IPV alone. Indeed, the evidence suggests that strong policies, particularly those focused on holding abusers responsible and improving access to advocacy and counseling services for women, must be implemented as well. Health care providers can be strong advocates both within their organizations to ensure that women are being adequately and appropriately served as well as within their larger community to ensure effective policy solutions are implemented.

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128 Sports and Recreation-Related Traumatic Brain Injury

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CONTENTS

Participation in Sport and Recreational Activity in the United States 1519
Pathophysiology of TBI 1520
TBI Severity and Diagnosis 1520
Determining Severity 1520
Mild TBI and Diagnostic Issues 1521
Mild TBI and Concussion: Diagnostic Issues 1521
Repeat Impact Syndrome 1521
Sports-Related TBI Epidemiology and Surveillance 1522
Limitations of Sports-Related TBI Surveillance 1522
TBI Epidemiology by Sport 1524
Soccer 1524
Football 1524
Boxing 1524
Prevention 1525
Sports Injury Prevention and the Haddon Matrix 1525
Personal Protective Equipment Use 1525
Prevention Education 1526
Return-to-Play Guidelines 1526
Return-to-Play Legislation 1527
Conclusions and Future Directions 1527
References 1527

Because of its magnitude, economic and human impact, and preventability, traumatic brain injury (TBI) is a priority in public health. The Centers for Disease Control and Prevention (CDC) estimated that at least 1.7 million people sustain a TBI annually and there at least 1.4 million annual TBI-related emergency department (ED) visits [1]. With the increasing numbers of people engaged in sport and recreation (SR) activities in the United States, more people are at risk for SR-related injuries, including TBI. From 2001 to 2009, the CDC estimated that the number of TBI-related ED visits for those ≤19 years old from SR activities increased 62% from 153,375 to 248,418 [2].

PARTICIPATION IN SPORT AND RECREATIONAL ACTIVITY IN THE UNITED STATES

According to data from the 2009 United States Department of Labor, Bureau of Labor Statistics' American Time Use Survey, it was estimated that approximately 18.9% (57 million) of the United States population is engaged in sports, exercise, and leisure activities every day with more males (21.7%) than females (16.3%) regularly participating in those activities [3]. However, current estimates of participation in different activities are lacking making the calculation of rates of injury problematic. Often, rates are described using the population of that group; but not every member of a demographic group (e.g., age group, gender) participates in every SR activity. Participation-based injury rates are possible using data from organized activities. The High School Sports Injury Surveillance System collects information on participation (i.e., exposure) and injuries in organized high school activities [4]; similarly, the National Collegiate Athletic Association Injury Surveillance System collects participation and injury information at the collegiate level (www.ncaa.org). However, risks of injury in these organized activities may differ from participation in other less formal, structured, or regulated settings (e.g., recreation leagues, pickup or backyard games). Many recreational activities do not have comparable competitive organizations from which to estimate risk.

PATHOPHYSIOLOGY OF TBI

A TBI is an alteration in brain function, or other evidence of brain pathology, caused by external forces [5]. TBIs in SR activities can result from blunt (e.g., when the head strikes or is struck by something) or penetrating trauma (e.g., when something pierces the skull and breaches the duramater) to the head, or indirect acceleration and deceleration forces (e.g., a blow to the body moving the head violently without itself being subject to blunt trauma). These direct or indirect forces temporarily or permanently disrupt the functioning of the brain [6,7]. The extent and severity of a brain injury after an initial mechanical event depends on many factors including the magnitude of accelerating and decelerating forces applied to the head, the direction of the force, and the subsequent direction, duration, and amplitude of angular accelerations to which the brain is subjected [8–10]; other factors may include age, body size, and weight [11].

Even TBIs that are more mild on the continuum of injury severity can alter the brain's physiology for minutes, weeks, months and even indefinitely setting into motion a variety of pathophysiological processes [12] that seem to reverse in a large majority of people who sustain milder forms of TBI [13,14]. Conversely, sequelae observed in some persons with these mild forms of TBI, and in some animal studies, may reflect a degree of cell death after the injury [15,16].

After the initial mechanical event, depending on the injury severity, there may be direct or primary mechanical alterations of the brain tissue such as laceration of the brain or diffuse axonal injury. These primary mechanical alterations are generally followed by secondary brain injuries that can include brain edema or elevated intracranial pressure. Secondary brain injuries arise from complications initiated by the primary injury itself and/or via other mechanisms, including inflammation, cell receptor-mediated dysfunction, free radical and oxidative damage, and calcium or other ion-mediated cell damage [17]. In turn, these secondary processes modulate gene expression and/or protein regulation that lead either to cell death or repair [17,18]. Additionally, there is epidemiological evidence indicating that synergy exists between permanent neurodegeneration after a TBI and the possession of apolipoprotein Eε4 allele, a risk factor for Alzheimer's-like neurodegeneration [17–20] and poorer outcomes [21]. These processes and their consequences are beyond the scope of this chapter.

Although the current understanding of the underlying pathology of concussion, a form of a potentially less severe TBI, involves a paradigm shift away from a focus on anatomic damage to an emphasis on neuronal dysfunction involving a complex cascade of ionic, metabolic, and physiologic events [22,23], some of these events may involve physical disruption in the neuronal synapses [23] and even cell death [15,16]. However, while changes in metabolic processes and gene expression have been reported in more severe TBIs, more research is needed in the area with respect to milder forms of TBI [22].

In SR activities, the external forces may cause linear, rotational, or angular movement of the brain or a combination of these motions. In rotational forces, for example, the magnitude of this force may be an important factor to cause a concussion [24] and may even contribute to its severity [13]. It has been estimated that angular accelerations ranging from 4600 to 7900 rad/s^2 may increase the risk of developing a mild TBI from 25% to 80% [25]. Although many areas of the brain can be affected by rotational forces, these may primarily affect the midbrain and the diencephalon [26,27] disrupting parts of reticular activating system, which in turn, may result in loss of consciousness (LOC) [27]. It is thought that concussion results from a diffuse brain injury affecting mainly axons distributed over a widespread area of the brain [13,26,28] or inadequate blood flow to the brain due to other concurrent injuries [29].

Acute and chronic neuronal and glial cell lesions have been documented in boxing and football-related literature. Boxers may present with acute elevations of the tau protein, neurofilament light protein, and glial fibrillary acidic protein in the cerebrospinal fluid [30], with sustained release of neuron-specific enolases detectable in serum for up to 2 months [31]. Chronic traumatic encephalopathy manifests primarily by increased tau phosphorylation and patchy distribution of neurofibrillary tangles especially in the frontal and temporal lobes [32]. More recently, findings from studies of the brains of deceased National Football League (NFL) athletes with history of concussion or TBI suggested there was lasting damage to the brain after experiencing at least one concussion leading to a variety of other health outcomes [32,33]. The scope, complexity, and heterogeneity of the pathophysiology of TBI, including mild TBI, present challenges for developing precise, sensitive, and accurate diagnostic tools, severity classification, surveillance tools, and effective medical and health interventions.

TBI SEVERITY AND DIAGNOSIS

TBI results in a constellation of clinical manifestations that range in severity from mild physical, cognitive, emotional, or sleep-related symptoms that may or may not involve a LOC to coma and, in some cases, even death. Survivors present with symptoms that may last from several seconds to days or persist for weeks or months or may continue indefinitely [34,35]. This section will address issues related to TBI severity, diagnosis, and reinjury.

Determining Severity

Based on the clinical manifestations and injury severity scoring systems, TBI is classified as mild, moderate, and severe. The Glasgow Coma Scale (GCS) [36], a clinical tool originally designed to assess coma and impaired consciousness, is one of the most commonly used severity scoring systems. Persons with GCS scores of 3–8 are classified with a severe TBI, those with scores of 9–12 are classified with a moderate TBI, and those with scores of 13–15 are classified with a mild TBI. Other classification systems include the Abbreviated Injury Scale (AIS), the Trauma Score, and

the Abbreviated Trauma Score. Despite their limitations [37], these systems are crucial to understanding the clinical management and the likely outcomes of this injury because the prognosis for milder forms of TBIs is better than for moderate or severe TBIs [34,38,39]. Although mild TBI historically has been considered trivial, studies have demonstrated that its consequences can be devastating in some patients [35].

Mild TBI and Diagnostic Issues

Although mild TBI is one of the most common neurological disorders, there is no single definition for this condition that is universally accepted [35]. The CDC defines mild TBI as an injury to the head resulting from blunt trauma or acceleration or deceleration forces with one or more of the following conditions: any period of observed or self-reported transient confusion, disorientation, or impaired consciousness, dysfunction of memory (amnesia) around the time of injury; LOC lasting ≤30 min; posttraumatic amnesia lasting up to 24 h; GCS scores ranging from 13 to 15; and an AIS Scale score of 2 for the head region [35]. Cases of TBI with intracranial lesions demonstrated by neuroimaging or with selected focal neurological deficits may also be considered as mild if there is no penetrating craniocerebral injury, posttraumatic amnesia lasting longer than 24 h, or LOC lasting longer than 30 min; CDC recommends that these cases of mild TBI with intracranial lesions or focal deficits be analyzed separately to predict outcome [35]. Symptoms among older children and adults, such as headaches, dizziness, irritability, fatigue, and poor concentration, when identified soon after injury, can be used to support the diagnosis of mild TBI but cannot be used to make the diagnosis in the absence of LOC or altered consciousness [35]. Due to advances in the field, this definition should be periodically evaluated and revised as appropriate.

There are, however, recognized issues with the combination of clinical indicators used to measure severity and to predict outcome among those with mild TBI. For example, persons with GCS scores of 13–15 who also present with focal brain lesions and/or even depressed skull fractures may have comparable outcomes as patients with more severe TBI [39]. To overcome the challenge of discharging patients with clinically diagnosed mild TBI, the American College of Emergency Physicians and CDC produced neuroimaging and decision-making guidelines for adults with mild TBI in the acute setting [40]. These guidelines, however, apply to persons aged ≥16 years old who have a nonpenetrating brain injury and a GCS score between 14 and 15 [40].

In most cases, mild TBI is characterized by acute physiological changes that result in at least some acute cognitive difficulties that typically resolve within 3 months post injury [35]. The course of cognitive recovery remains controversial as 7%–33% [35,41–43] may have persistent problems even 1 year after the injury. A "post-concussion syndrome" has been described based on a group of disparate somatic (e.g., headache, dizziness), psychological (e.g., depression, anxiety), and cognitive (e.g., decreased concentration, forgetfulness) signs and symptoms [16]. Long-term consequences of mild TBI may present with neuropsychological dysfunction [44,45] or structural [32,33,46,47] changes to the brain. Recent data from high school athletes who were concussed or sustained a TBI suggested that symptom complexes differed between males and females [48]. Males reported more cognitive symptoms, whereas females reported more neurobehavioral and somatic symptoms. Symptom resolution time and time to return-to-play did not differ between sexes.

Mild TBI and Concussion: Diagnostic Issues

There is confusion among practitioners in the use of the terms mild TBI and concussion. Some definitions for mild TBI, for example, the CDC definition, allow the inclusion of selected nonpenetrating intracranial injuries [13,35,49]; these intracranial injuries do not constitute part of the classical definition for concussion [22,50,51]. The Concussion in Sport Group [22,52], a group of researchers organized by the Ice Hockey Federation, the Federation of Internationale de Football Association Medical Assessment and Research, and the International Olympic Committee Medical Commission, defined concussion as a "complex pathophysiologic process affecting the brain, induced by traumatic biomechanical forces secondary to direct or indirect forces to the head." According to this group [22,52],

1. Concussion may be caused either by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head.
2. Concussion typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously.
3. Concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury.
4. Concussion results in a graded set of clinical symptoms that may or may not involve LOC. Resolution of the clinical and cognitive symptoms typically follows a sequential course; however, it is important to note that, in a small percentage of cases, postconcussive symptoms may be prolonged.
5. No abnormality on standard structural neuroimaging studies is seen in concussion [22,52].

To improve medical management and follow-up, reporting, and study comparisons, public health practitioners, clinicians, researchers, and stakeholders need to reach consensus to standardize these terms and their definitions.

Repeat Impact Syndrome

Repeat impact syndrome, also known as second-impact syndrome, is a rarely reported condition, in which the brain is thought to swell catastrophically after a person suffers a repeat concussion before symptoms from an earlier

concussion have resolved [53]. This condition may lead to permanent brain damage or even death [53–56]. The second brain injury may occur minutes, days, or weeks after an initial concussion of any severity [54–56]. While its cause is unknown, it is thought that the arterioles in the brain lose their ability to regulate their diameters and lose control over cerebral blood flow, causing cerebral edema [55]. Young athletes are thought to be especially vulnerable [57] as are people with a history of multiple head injuries [58]. Although controversy exists about whether this condition is a valid diagnosis, it is recognized by physicians [59]. To reduce the likelihood of this condition, CDC and other organizations have established return-to-play guidelines that will be discussed later in the chapter.

SPORTS-RELATED TBI EPIDEMIOLOGY AND SURVEILLANCE

Traumatic brain injuries in SR activities are a major public health problem. An estimated 44 million boys and girls participate in an organized sport each year [60] and every day close to 19% of all persons aged 15 years old or older in the United States participate in some type of non-work-related physical activity [3]. In the 1990s, it was estimated that 300,000 sports-related TBIs occur annually [61]; this statistic, however, only included TBIs that involved a LOC. Recent reviews have estimated the annual number of SR-related TBIs in the United States as 1.6–3.8 million, which includes those who did not seek medical assistance [62,63]. From 2001–2009, approximately 179,285 patients were seen and treated in EDs for SR-related TBI annually, the highest population-based rate for either sex was found in those aged ≤4 years old closely followed by those aged 15–19 years old [2].

CDC estimated that approximately 80% of all TBIs reported in the United States were mild, 10% were moderate, and 10% were severe [34,35]. In sports, these statistics are similar [34,64,65]. Concussions are considered to be the most common athletic head injury [66] and can occur in any SR activity in the United States [67]. A study of high school and collegiate athletes found that concussions accounted for approximately 8.9% of all high school athletic injuries and 5.8% of injuries in college [68]. Some researchers reported that, among high school soccer players, boys had higher concussion rates than girls [69]; while others suggested girls sustained higher concussion rates than boys while playing comparable sports (basketball, soccer, and baseball/softball) at the high school and collegiate levels [68].

Although increased media attention has highlighted the issue of concussions among the collegiate and professional ranks, high school athletes may be most at risk both due their high degree of sport participation and level of brain maturity. Estimates of high school sports participation in 2009–2010 by the National Federation of State High School Associations suggests that approximately 7.6 million students participated [70] with 11-man football (N=1,109,278), basketball (N=540,207), and baseball (N=472,644) as the top three. Although these estimates may include limitations such as double counting, they provide vital information on the potential levels of exposure for youth athletes.

CDC estimated that annually 6.5% of all SR-related ED-visits are for those ≤19 years old who sustained a TBI. For those ≤19 years old between 2001 and 2009, football-related TBI ED visits (N=25,376) ranked highest among all organized sports followed by basketball (N=13,987) and soccer (N=10,436; Table 128.1) [2]. Additionally, non-contact SR activities, such as bicycling (N=26,212) and playground (N=16,706), are also associated with large numbers of TBI-related visits to EDs (Table 128.1). TBI comprised 15.3% of all injuries seen in an ED related to horseback riding, which was the highest ratio to all injuries among the reported activities [2]. Bicycling, however, ranked highest in the number of TBIs seen in an ED at 26,212 annually, or 7.7% of all injuries seen for that activity (Table 128.1). Approximately, 17.1% of patients with SR-related TBI ED-visits result in hospitalization.

Children and teens may be more likely to be injured in SR participation [71]. Children have a larger surface area to mass ratio with larger heads compared with the rest of their bodies [71]. Additionally, complex motor skills needed for certain skills may not be fully developed in children [71]. Finally, proper management of a SR-related TBI among youth is vital because the brain is still developing [62].

LIMITATIONS OF SPORTS-RELATED TBI SURVEILLANCE

The burden of TBI might be vastly underestimated because medical data sources are limited and many people do not seek care for their symptoms. Lack of appropriate diagnosis is concerning as those who are involved in SR activities may not understand the potential dangers of a TBI. Although the national databases used by CDC and others to estimate the burden of TBI in the United States have relatively good reliability for moderate and severe TBIs [72], they are less effective in capturing milder cases as they rely on an interpretation of information documented by health care providers in the medical records. Bazarian et al. found that cases of mild TBI that were clinically apparent to the health care providers often were not coded as such because of poor medical record documentation [73].

Additionally, information about the activities resulting in TBI, as with other diagnoses, rely on external cause of injury codes in the International Classification of Diseases (ICD); these, for sports, are very generic and not to be improved. When specific SR activities are available in ICD external cause codes, they are often not reliably used by coders to appropriately describe the circumstances of injury [74,75]. To improve TBI surveillance, CDC has recommended steps to enhance external cause coding such as evaluation of the completeness, accuracy, and specificity of coding; and training hospital admissions staff, health care providers, and coders on the importance of documenting circumstances of injury [76].

TABLE 128.1
Estimated Annual Number of Emergency Department Visits for All Nonfatal Injuries and Nonfatal Traumatic Brain Injuries (TBIs) Related to Sports and Recreation Activities among Persons Aged ≤19 years, by Type of Activity—National Electronic Injury Surveillance System—All Injury Program, United States, 2001–2009

	All Ages		All Visits for Sports and Recreation–Related Injuries		% of All Visits for Injuries that were TBIs
Activity	No.*	95% CI (±)	No.*	95% CI (±)	
Bicycling	26,212	(6,809)	323,571	(48,566)	8.1
Football	25,376	(4,845)	351,562	(47,448)	7.2
Playground	16,706	(5,198)	210,979	(37,050)	7.9
Basketball	13,987	(3,077)	375,601	(47,607)	3.7
Soccer	10,436	(3,736)	135,988	(39,167)	7.7
Baseball	9,634	(2,401)	121,309	(22,175)	7.9
All-terrain vehicle riding	6,337	(3,481)	59,533	(14,061)	10.6
Skateboarding	6,004	(2,455)	101,577	(31,907)	5.9
Swimming	4,557	(1,699)	62,745	(14,500)	7.3
Hockey†	4,427	(2,749)	45,450	(24,405)	9.7
Miscellaneous ball games§	4,065	(1,477)	66,543	(15,306)	6.1
Horseback riding	3,638	(1,266)	23,842	(5,169)	15.3
Moped/Dirt bike riding¶	3,370	(978)	39,363	(9,209)	8.6
Scooter riding	3,336	(779)	54,561	(11,784)	6.1
Gymnastics**	3,319	(948)	71,248	(13,881)	4.7
Combative sports††	2,981	(786)	50,639	(10,941)	5.9
Softball	2,735	(756)	49,345	(10,002)	5.5
Exercising	2,406	(825)	77,069	(11,731)	3.1
Tobogganing/Sledding	2,377	(948)	23,306	(8,383)	10.2
Trampolining	2,323	(823)	86,584	(17,540)	2.7
Golf§§	1,887	(609)	17,078	(3,510)	11.0
Ice skating	1,673	(631)	14,608	(4,241)	11.4
Volleyball	1,396	(483)	34,513	(7,568)	4.0
Amusement attractions¶¶	1,266	(470)	15,781	(3,844)	8.0
Roller skating/Unspecified skating	1,126	(316)	34,717	(8,280)	3.2
Go-cart riding	875	(308)	11,078	(2,280)	7.9
In-line skating	853	(335)	25,350	(7,515)	3.4
Track and field	449	(171)	15,553	(3,003)	2.9
Racquet sports***	323	(125)	9,306	(1,984)	3.5
Bowling	153	(74)	6,574	(1,524)	2.3
Other specified†††	9,059	(4,630)	136,210	(44,511)	6.7
Total	173,285	(40,284)	2,651,581	(403,378)	6.5

Source: Centers for Disease Control and Prevention, *MMWR Morb. Mortal. Wkly Rep*., 60(39), 1337, 2011.

Abbreviation: CI = confidence interval.

*Estimates might not sum to totals because of rounding.

†Includes ice hockey, field hockey, roller hockey, and street hockey.

§Includes lacrosse, rugby, handball, and tetherball.

¶Includes other two-wheeled, powered, off-road vehicles and dune buggies.

**Includes cheerleading and dancing.

††Includes boxing, wrestling, martial arts, and fencing.

§§Includes injuries related to golf carts.

¶¶Includes rides and water slides (not swimming pool slides).

***Includes tennis, badminton, and squash.

†††Includes water skiing, surfing, personal watercraft, snow skiing, snowmobiling, snowboarding, camping, fishing, archery, darts, table tennis, nonpowder/BB guns, and billiards.

Additionally, as electronic medical record systems are implemented by health care providers in the United States, the electronic algorithms that accurately automate physician documentation as well as ICD diagnoses, mechanisms of injury, and injury locale is needed.

TBI EPIDEMIOLOGY BY SPORT

This section will focus on three sports that receive intense media coverage worldwide—soccer, football, and boxing, a combat sport.

Soccer

Worldwide, approximately 200 million persons actively play soccer; 20% are women [77]. In the United States, 13.6 million people aged 7 years old and older [78], 43% of whom are female [79], participated in soccer more than once in 2009 [78]. Although most of the soccer-related injuries affect the lower extremities [80,81], head injuries may account for 4%–22% of all soccer-related injuries [82] with goalkeepers tending to have more head, face, neck, and upper extremity injuries [83]. Among high school players in the 2005–2006 school year, an estimated 20,929 concussions occurred among males and 29,167 among females with rates of 0.22 and 0.36 per 1000 athlete exposures, respectively [68]. Among collegiate players from 1988 through the 2003–2004 school year, concussion represented 3.9% of soccer injuries among males and 5.3% among females with rates of 0.28 and 0.41 per 1000 athlete exposures, respectively [84]. It has been estimated that approximately one concussion occurs per team per season [85,86]. In the United States, an estimated 10,436 soccer-related TBI ED visits were reported annually between 2001 and 2009 for those ≤19 years old [2]. These TBI ED visits accounted for approximately 7.7% of all soccer-related visits to EDs in the United States (Table 128.1) [2].

Although brain injuries in soccer may arise from the head contacting other body parts, goalpost, ground, or ball [86], most of the concussions reported in this sport derive from head-to-head contacts, head-to-elbow contact, hit in the head by full force kicked balls at close ranges, and less frequently from head-to-knee and head-to-foot contacts [86,87]. A study of elite Division I college soccer players found that approximately 76% of concussions in males occurred in forward or midfield positions; whereas in women, 67% of concussions occurred in defensive positions [86]. In a study of collegiate athletes from 1998, headaches, that in some cases persisted up to 4 days, were the most frequent TBI-related manifestation reported (93%); others included, confusion or disorientation for up to 30 min (76%), inability to concentrate (62%), nausea (52%), posttraumatic and retrograde amnesia (28%), and LOC (28%) [86].

Data on the impact of "heading," a player purposely redirecting a ball with their head, in producing concussion and cognitive impairment are inconclusive. Neuropsychological studies of chronic TBI among professional and highly competitive amateur adult soccer players conducted in the 1990s reported that impairments in selected aspects of cognitive functioning was inversely related to the number of concussions and to the frequency of ball heading [87,88]. Prospective controlled studies among collegiate and elite soccer players that included clinical examination, imaging, or neuropsychological tests found no evidence of cognitive impairment in soccer players associated with heading [89–91]. While the evidence suggests that the actual act of heading the ball may not be injurious, the situation of heading may put athletes at risk of their heads striking body parts and objects other than the ball, which may lead to concussions and other bodily injuries [92].

Football

During 2009–2010, an estimated 1.11 million preadolescent and adolescent boys and 1249 girls participated in high school football [70]. Among those ≤19 years old, injuries sustained while playing football are the second leading cause of SR-related visits to EDs in the United States ($N = 351,562$) after basketball ($N = 375,601$; Table 128.1) [2]. Of the football-related ED visits, 7.2% ($N = 25,376$) were TBI-related (Table 128.1) [2]. Additionally, for males 10–19 years old, football was the highest ranked SR activity associated with TBI-related visits to EDs [2]. Severe and fatal injuries do rarely occur; in 2010, the death rate was 0.27 per 100,000 participants [93], and the rate of severe neurologic disability was 1.65 per 100,000 [56].

A three-season study that included 693 different high school football players with a mild TBI examined reinjury of athletes. Seventy-two were reinjured; 65 sustained two mild TBIs, 6 had three mild TBIs, and 1 had four mild TBIs. Most (47/72) injuries occurred during the same season as the first injury; 14 occurred in the next season, and two persons had three and four mild TBIs each in the same season [94]. The authors also reported four cases of subdural hematoma and two of intracerebral hemorrhage; of these six players, three returned to play the following season and three changed to other SR activities [94].

In football, as from other causes, even milder brain injuries have the potential for negative consequences [35]. A large scale case-control study of 2300 football players with history of mild TBI without LOC that involved preseason baseline and serial post-injury assessments showed that players with mild TBI had subjective complaints of dizziness, headache, memory dysfunction, and mild deficits in the areas of sustained attention and visuomotor speed that tended to resolve within 5–10 days after the injury [95]; while the effects of concussion may resolve, some individuals have persistent symptoms and cognitive deficits [96]. Similar to results observed in boxing, the severity of cognitive outcomes after football-related TBIs is associated with the number, frequency, and recurrence of head injuries.

Boxing

The objective of boxing and other combat-related sports is rendering an opponent unable to defend themselves, which in

some instances may lead to TBIs that can range in severity from mild to severe or even death. Depending on the weight category of the opponents, impact speeds of at least 10 m/s generating forces of up to 5000 N impact to the opponent's head resulting in translational acceleration forces to the brain of more than 50 g [97,98]. The shearing and acceleration forces may result in lesions affecting the central pathways in the upper brainstem or produce *coup* and *contrecoup*-related lesions [11,99]; the latter lesions are injuries that occur under the site of the impact (*coup*) or in the site opposite to the impacted area (*contrecoup*). Besides presenting acute signs and symptoms of brain injury in a knockout situation, up to 10% of boxers may present with persistent forgetfulness, headaches, and other symptoms [11,100]. Chronic manifestations of repeated brain injury in professional boxers include declines in cognitive performance, tremor, dysarthria, Parkinson's disease, memory disorders, dementia, depression, irritability, aggression, criminality, and addiction [19,32,101,102]. A condition termed dementia pugilistica or chronic boxer's encephalopathy has been reported among boxers with a history of fighting for 12–16 years [103,104]. This condition is considered a variant of chronic traumatic encephalopathy. Symptoms include gait ataxia, speech and hearing problems, tremors, progressive dementia, and multiple neurobehavioral problems [103,104].

In addition to lasting and substantial brain dysfunction due to participation in boxing, boxers may face increased risk of death. In a recent and comprehensive review of the boxing-related literature, Förstl et al. found that on average worldwide, approximately 10 boxing-related deaths occur annually; the absolute figures may also be higher. Two-thirds of those who died were professional boxers, and three-quarters of the boxers died in the boxing ring. More than 80% of the deaths were caused by injuries to the head and neck, such as ruptures or thromboses in larger brain vessels, epidural hemorrhages, or subdural hematomas. Other causes of death can include cardiac complications and tears to the liver or spleen [11]. Risk factors that may be associated with boxing-related death include age, comorbid conditions (e.g., hypertension, diabetes, bleeding disorders), medication (e.g., anticoagulants, steroids, erythropoietin), dehydration, weight loss, large number of punches striking the head during the match, and repeat impact syndrome [11].

PREVENTION

Sports and recreation-related TBI can be prevented using a variety of approaches. For instance, the Haddon matrix, an analytic tool, is demonstrated in this section. Additionally, this section presents information on primary prevention, personal protective equipment, available educational materials, return-to-play guidelines, and legislation.

Sports Injury Prevention and the Haddon Matrix

The Haddon matrix is considered a powerful analytical tool for injury prevention. The matrix clarifies that the event leading to the injury can be separated from the injury itself and from the emergency response to it. The matrix can help identify (1) factors that can prevent the event from occurring in the first place, (2) factors that can mitigate or minimize the injury once the event occurs, and (3) factors that can contribute to immediate and effective care after the injury. [105–107]. Haddon applied the elements of disease causation to injury agent or vector (e.g., a tackle to the head), host (e.g., the player who was tackled in the head), and environment (e.g., a football field with poor officiating and poor ground surface). The matrix also helps to visualize the previous three phases to help formulate the steps that should be considered for preventing the event, reducing injury damage when an event occurs, and minimizing further damage to decrease morbidity and disability [105–107]. Prior to an injury (the *pre-event phase*), the physical and medical condition of an athlete and his or her knowledge of the activity, skill level, appropriate use of equipment, as well as consistent practice of good sportsmanship all influence risk of injury before it occurs. The presence of effective coaches, referees, and other professionals, in addition to community medical resources, all contribute to the level of safety. Examination of pre-event factors can help determine what can be done to reduce the likelihood of injury. Examples may include remediation of playing surfaces, securing equipment, enhancing training techniques, or enforcing use of protective gear. If an injury event does occur (the *event phase*), the preexisting physical condition of the individual and the circumstances of the event, such as protective equipment use, help to determine the extent and severity of the injury. Following the event (*postevent phase*), the emergency response, quality of care, and any environmental factors that may slow the treatment and rehabilitation affect the potential consequences of the injury. Use of this matrix by SR organizations and policy makers, in conjunction with public health practitioners and health care providers, can provide a framework for prevention efforts (Table 128.2) [108].

Personal Protective Equipment Use

One of the best prevention strategies to reduce the potential for a SR-related TBI is the proper use of personal protective equipment [67]. However, sports helmets are designed to prevent severe and fatal injuries (e.g., skull fracture, penetrating injuries, and severe brain injuries) rather than preventing all concussions [92]. Sports helmets may reduce the incidence or severity of SR-related head injuries [62] by reducing potential impact forces [109]. Helmets and other protective equipment should fit properly, be appropriate for the position or activity, be well maintained, and be consistently and correctly used [108].

Among skiers and snowboarders, wearing protective equipment, like helmets, has effectively diminished the potential head injuries [110]. Studies focusing on newer football helmet technologies have found decreases in absolute and relative risk for sustaining concussions [111] and a potential 10%–20% reduction in risk of concussion in recreated collisions from the NFL [112]. Despite advancements

TABLE 128.2
Examples of the Haddon Matrix Applied to Sport-Related TBI

	Agent (Sport)	Host (Athlete)	Physical Environment	Social Environment
Pre-event phase	Institute rules preventing dangerous physical contact	Teach appropriate skills training and conditioning	Ensure playing surface is in good condition	Support parents, coaches to encourage good sportsmanship
Event phase	Require use of appropriate protective equipment	Minimize impacts through physical characteristics (e.g., reaction time and strength)	Ensure that goalposts, backboards, and other obstacles are padded	Support athletic trainers to monitor athletes
Postevent phase	Train coaches to recognize concussion	Follow appropriate rehabilitation and return-to-play	Ensure access to emergency services	Teach parents, coaches to support appropriate return-to-play

in protective equipment, those who engage in SR activities are still vulnerable to injuries. The use of effective protective equipment is not always mandatory or available in non- or partial-contact sports such as lacrosse or field hockey. Some of the difficulties in the prevention of concussion and TBI in SR activities may stem from the lack of a universal definition and a common belief that they are "part of the game" [113].

Prevention Education

CDC, along with partner organizations, has developed guidelines and management techniques to help prevent SR-related TBI. Education is essential as many people do not understand the signs/symptoms and potential consequences of this injury. For example, in one study, only 61% of youth coaches correctly identified concussion signs and symptoms and 26% of coaches returned athletes to competition before symptoms resolved [114].

CDC created the "Heads Up" initiative with a series of products designed to specifically address sports concussions by providing coaches, school and health professionals, parents, and athletes information on prevention, recognition, and proper response [67]. In particular, the "Heads Up" initiative focuses on (1) providing prevention strategies to help reduce the risk for concussion and other injuries, (2) stopping an activity if a TBI is suspected and seeking medical evaluation and approval before returning to play, and (3) learning TBI signs and symptoms and encouraging athletes and others to report a suspected TBI. To assist with concussion management, the CDC has also developed educational materials for those who may encounter injured athletes including one for physicians "Heads Up: Brain Injury in your Practice" and for school nurses, counselors, and teachers "Heads Up: Know your concussion ABCs" (www.cdc.gov/concussion). These free materials may help with clinical diagnosis of mild TBI, including concussions, and may improve outcomes through early diagnosis and appropriate management of injured participants (http://www.cdc.gov/concussion/sports/index.html).

CDC's "Heads Up" initiative and other educational resources are helping to create momentum on this issue. National evaluation studies of the CDC coaches' resources have demonstrated a positive impact on coaches' knowledge, attitude, and behavior toward concussion [115]. After use of CDC's educational materials, 50% of high school coaches reported viewing concussions more seriously and 38% reported changing their management of concussion [115]. Moreover, a study of CDC's materials for youth sports demonstrated that 77% of coaches reported being able to more easily identify athletes with a suspected concussion and 72% of coaches reported educating others about preventing and managing concussions [116].

Return-to-Play Guidelines

Implementation of return-to-play decisions can depend on a multitude of factors such as the level of sufficient resources including team physicians or staff members who are experienced in concussion management [52]. In some instances, return could be a quick process, but many cases should follow a graduated return-to-play protocol. Each step is designed to allow ample time for full physical and cognitive recovery; the athlete can progress as long as the athlete remains asymptomatic [52]. A 6 day gradual return-to-play protocol after the athlete is symptom-free at rest is suggested [52]. If any concussion symptom returns during any of the activities, the athlete should rest for 24 h then return to the previous level [52]:

- Day 1: no activity; complete physical and cognitive rest
- Day 2: light aerobic exercise (walking, swimming, or stationary cycling). No resistance training
- Day 3: sport-specific exercise. No head impact activities
- Day 4: non-contact training drills
- Day 5: full-contact practice; participate in normal practice activities
- Day 6: return to competition; normal game play

Return-to-Play Legislation

Multiple states across the United States have taken action to address the issue of return-to-play through legislation. As of July 2012, approximately 42 states have enacted laws regarding sports concussion among school-aged athletes. One of the first and most comprehensive laws, Washington State's *Zackery Lystedt Law*, requires the immediate removal of any athlete who is suspected of sustaining a concussion with return to participation only after evaluation and clearance by an appropriate medical professional [117]. Of the 42 current laws, 39 include similar language as the Lystedt law which includes requirements for concussion education materials for coaches, parents, and student athletes, removal from play, and return-to-play. Sustaining a repeat TBI before the brain recovers could potentially slow recovery and increase the risk of long-term consequences [67]. The results, both intended and unintended, of these legislative efforts in protecting athletes are yet to be determined.

CONCLUSIONS AND FUTURE DIRECTIONS

TBI is a major public health issue affecting millions of Americans participating in sports and recreational activities annually. Studies have shown SR-related TBI to be a fairly common yet underreported injury affecting primarily young participants. Proper use of appropriate protective equipment for specific sports or activities, following the rules of the game, appropriate training in the skills of the sport, and portraying good sportsmanship can be simple prevention strategies. While not all TBIs can be prevented, accurate and consistent case ascertainment and medical management have the potential to minimize reinjury and reduce TBI-related impairment and disability. Additionally, continued education of medical professionals, coaches, trainers, parents, athletes, and other stakeholders, could help reduce the risk of long-term consequences and potential catastrophic injuries. Further research, however, is needed to identify primary prevention strategies to decrease TBI and associated morbidity and mortality.

Currently, the definitions of concussion or TBI utilized are not consistent and a national injury surveillance system in the United States that covers SR activities, resulting in a poor understanding of the epidemiology of SR-related TBI especially among younger participants. To fully understand SR-related TBI in the United States and globally, strategies for improved surveillance and reporting are needed. These data could inform the incidence, severity, risk factors, mechanisms, and outcomes of TBIs. There is also the need to translate research findings into usable knowledge and evidence-based prevention interventions so coaches, trainers, team physicians, and clinical and public health practitioners can counsel athletes and the public [118]. Additionally, future research should examine not only contact and organized sports such as football and basketball but also recreational activities such as bicycling and horseback riding.

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Part XXIII

Public Policy and Environmental Supports for Lifestyle Medicine

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129 Lifestyle Medicine in an Era of Health care Reform—2011

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CONTENT

References 1536

The Patient Protection and Affordable Care Act, often known as the Affordable Care Act (ACA) of 2010, was signed into law on March 23, 2010. This attempted overhaul of the U.S. health care delivery system is still being implemented and debated within the halls of Congress as well as within state legislatures and halls of justice. However, elements of the ACA will no doubt continue to be implemented. These elements include components within ACA that promise to have an impact on lifestyle medicine and primary prevention through the health care delivery system itself [1]. Such components include increased Medicaid payments in fee-for-service and managed care for primary care services provided by primary care doctors (family medicine, general internal medicine, or pediatric medicine) including a 10% bonus payment to primary care physicians in Medicare from 2011 through 2015 [1]. These actions are intended to provide greater incentives for primary care providers to integrate preventive care services into their practices. Included in ACA is the establishment of a National Prevention, Health Promotion, and Public Health Council to coordinate federal prevention, wellness, and public health activities. This council will develop a national strategy to improve the nation's health, create a Prevention and Public Health Fund to expand and sustain funding for prevention and public health programs, and create working groups associated with the Clinical Preventive Services and Community Preventive Services Task Forces to develop, update, and disseminate evidence-based recommendations on the use of clinical and community prevention services. Further efforts will be made to provide coverage of preventive services that have been shown to be effective and further modification and possible elimination of cost-sharing for preventive services in Medicare and Medicaid. Finally, there will be an increase in Medicare payments for certain preventive services up to 100% of actual charges or fee schedule rates, which are intended to include lifestyle medicine services such as obesity prevention services [1].

The ACA legislation also authorizes the establishment of a Patient-Centered Outcomes Research Institute (PCORI). This non-federal institute is charged with setting research priorities and promoting research that provides a clinical evidence base to help physicians, other primary care providers, and patients make informed decisions about a patient's health care; to assist health care delivery systems in providing evidence-based, efficient, and safe health care; to ensure that evidence is dependent on and applied to racially and ethnically diverse and geographically distributed communities; and to develop broad prevention and screening strategies that promote health across such diverse populations. Much reporting about the PCORI research agenda has focused on the term "comparative effectiveness research" (CER). Although the intellectual underpinning of effectiveness research has existed for over half a century, the legislation lays out a far more expansive and inclusive role for CER. In addition to comparing therapeutic treatments, CER is intended as the rigorous application of science to evaluate and compare health outcomes, clinical effectiveness, and risks and benefits of a much broader set of interventions—from new health care delivery methods to medical procedures and devices, to drugs and biologicals, to integrative health practice strategies, as well as prevention strategies. Moreover, the legislation directs that CER must include broad participation across the nation to create a representative evidence base that could help identify and address health disparities and inform decisions by patients in special population groups. CER is expected to extend beyond academic health centers and teaching hospitals to include research in partnership with community-based care settings and practice-based networks, as well as with community-engaged research, which provides for the engagement with communities as partners in research [2]. Such a focus on CER and similar methods that embody rigorous science to determine what interventions/treatments work best for whom, in what settings, and under what circumstances supports lifestyle medicine by translating preventive care and disease management evidence into changes in practice and behavior at the level of individuals, populations, and health care delivery systems [3].

The reestablishment of primary care as the first line of medical care and preventive care practice is critical to the success of health care reform success [4,5]. The ACA takes important, although modest steps, in addressing critical primary care needs: payment reform, enhancing the training pipeline, transforming practice, and buttressing the primary

care safety net. ACA provisions include establishment of a National Health Care Workforce Commission, increased support for workforce training (Title VII and the Prevention and Public Health Fund), cultural competency training, enhanced payments, expansion of health centers, and piloting of new care models. ACA also provides bonus payments to primary care physicians under Medicare and eliminates differences in payments between Medicaid and Medicare for primary care. It further provides Medicare bonuses to primary care physicians who work in shortage areas, helping to minimize geographically related disparities. These reforms may begin to minimize disparities in resources between primary care practices whose patient populations differ by social disadvantage. These reforms could also conceivably reduce de facto segregation in health care by insurance type (e.g., faculty practices vs. clinics) although federal regulations prohibiting intra-institutional segregation of care by insurance type within systems receiving federal funding may be needed. To be sure, modest increases in payments alone will not be sufficient to address the maldistribution of primary care physicians, much less avert a primary care shortage [6].

Although the recently enacted ACA legislation contains elements that could advance lifestyle medicine and primary prevention, a large segment of the population is clearly opposed to expansion of the government's role in regulation of the health care delivery system and private health plans. Critics have argued that the government mandate for expanded private health plan coverage has already resulted in higher costs and will ultimately lead to unsustainable cost increases that will drive employers to abandon sponsorship of a health plan as an employee benefit. Understanding the role of employers is central to understanding the U.S. health care system. At present, almost two-thirds of American citizens under the age of 65 years are covered by an employer-sponsored health plan. The sudden disappearance of employer-sponsored health insurance would create chaos [7].

The historic linkage of health insurance to employment for over 80 years has presented a problem of access to affordable health care services for unemployed individuals, but the private sector system does promote innovation and value through its influences on competing providers [8,9]. Furthermore, the availability and generosity of health care coverage for Americans ultimately depend on the economic fortunes of private companies. Government-sponsored health insurance relies on individual and corporate taxes, which are directly linked to employment and economic growth. The less tax revenue collected by the federal and state governments, the greater will be the necessity to ration care among the population that relies upon a government-sponsored program [7]. If Medicare and Medicaid costs continue to grow at the current rate, they will consume 20% of the gross domestic product by 2050 [10].

Because businesses currently have a major role in directly financing a large portion of health care services, they have a substantial influence on the overall efficiency and quality of the U.S. health care delivery system. Traditional fee-for-service reimbursement creates an incentive for providers to supply a high volume of expensive services as long as the payment exceeds the cost of the service delivery [11]. Capitation (i.e., prospective payment of a fixed compensation amount for medical management of a case) places a high level of financial risk on providers, which encourages restriction of services as a means to maximize profits [12]. Value-based purchasing and pay-for-performance are terms that have been applied to employer initiatives that hold health care providers accountable for effective and efficient management of the health-related needs of employees and dependents. An example of a strategy for improving the value of health care services is the combination of payment bundling (i.e., aggregation of all fees for services provided to manage a case by multiple providers) and subsequent payment of a bonus that is based on the difference between the total cost of the bundled fee payments and a prospectively developed budget for medical management of the patient's condition. The case budget incorporates a patient-specific severity adjustment and an allowance for potentially avoidable complications. Such a payment model encourages collaboration among providers and it incentivizes both conformity to clinical practice guidelines and efforts to minimize potentially avoidable complications [12].

Value-based purchasing and pay-for-performance represent employer-initiated innovations that Medicare has begun to use on an experimental basis [11]. The Medicare Physician Group Practice (PGP) Demonstration introduced "shared savings" as a mechanism to reduce costs and improve quality of care provided to its beneficiaries. Participating PGPs received regular fee-for-service reimbursements but were also eligible to receive an additional performance payment if a Centers for Medicare and Medicaid (CMS)-specified cost target was achieved (i.e., an 80% share of the difference between the actual cost of services provided and a risk-adjusted spending trend for treatment of the given condition in a given market). The Medicare PGP Demonstration served as the model for a provision of the ACA legislation that establishes the Accountable Care Organization (ACO) as a mechanism for providers to become eligible for participation in the Medicare Shared Savings Program [13,14].

The specifications for ACO certification were not clearly defined in the new law, but Department for Health and Human Services has issued a notice of proposed rule-making that will define the manner in which physicians, hospitals, and other providers can create an affiliation that will be collectively accountable for delivery of high-value services. Although the intent of the ACA legislation is to reduce the cost and improve the quality of health care for all Americans, CMS payment policies have historically resulted in cost-shifting to private payers. An analysis of the PGP Demonstration suggested that most provider groups would experience a financial loss as a result of participation in a similar shared savings program, which poses a risk to the entire value-based purchasing movement initiated by employers [15]. The creation of ACOs by dominant providers through mergers and acquisitions could drive up costs for private payers. Market consolidation can also have an adverse effect on the ability of private payers to obtain the service quality data that are

essential to value-based purchasing [13]. Although the inclusion of a hospital in an ACO is needed for optimal coordination of health care services, a potentially serious conflict of financial interests exists between physician groups and hospitals with regard to the necessity for hospitalization of many patients. Some experts believe that hospital-centric provider organizations adversely affect the potential for physician groups to benefit from a shared savings program [14] and that they will not serve the best interests of the country [12].

Each of three parties—the provider, the payer, and the patient—has a role in determination of the value that is realized from medical services. A major issue affecting the potential for success of the ACO concept in the private sector is the interrelated matter of provider control over the various services needed to manage a patient's condition and the patient's willingness to accept a service delivery system that precludes the option of seeking care from providers outside the organization [16]. Because past managed care cost-containment strategies have not adequately addressed quality of care issues, many consumers have become reluctant to accept restrictions on provider selection. Consumers will need access to cost and quality information to understand the benefits that will be derived from voluntary enrollment in an ACO.

Modification of patient behaviors is central to the practice of lifestyle medicine and primary prevention, but the patient's responsibility to ensure that a high degree of value is derived from clinical medical services has only been emphasized by employer-sponsored health plans. Patient consumerism is promoted by high-deductible health plans that are combined with health savings accounts to incentivize healthy behaviors and through employer-sponsored worksite health management programs. Because impaired glucose metabolism is the primary underlying cause of numerous high-cost conditions, regular physical activity and health dietary behaviors can profoundly influence employers' self-insured health plan costs [17,18]. Because poor employee health decreases corporate profitability through high health plan costs, work absenteeism, and suboptimal productivity, employers have a strong interest in promoting personal responsibility for healthy lifestyle choices and informed utilization of health care services. Unless commercial insurance and government-sponsored health plans incentivize healthy behaviors and health care consumerism, no type of provider payment model is likely to produce long-term control of cost escalation.

Years of fee-for-service reimbursement have produced a provider-centered and process-oriented system for the delivery of clinical services that is highly resistant to change. Both CMS and commercial insurance pay-for-performance initiatives have defined quality of care on the basis of process-of-care measurements (e.g., provider adherence to clinical practice guidelines), rather than patient outcomes [19,11]. Value should be defined as the outcomes achieved per dollar spent. Measuring the total costs over a patient's entire care cycle and relating them to the outcomes realized from the collective set of services could lead to future reallocation of spending among the various types of services. For example, greater frequency of physical activity among obese individuals has been documented to produce greater claims costs related to treatment of musculoskeletal disorders [20]. Primary and preventive care of obese patients might provide greater value (i.e., better long-term outcomes at lower cost) through substantial involvement of a clinician who possesses expertise in exercise prescription for avoidance of musculoskeletal disorders. Different patient populations (e.g., obese children, healthy adults, patients with multiple chronic conditions) will need different bundles of services, which require different types of outcomes measurement. Condition-specific outcomes measurement instruments are needed and no single outcome can fully capture the results of care [19]. The outcomes that are most important to the patient should provide the numerator for the value equation, and the denominator should be the total cost of all services that jointly determine success in meeting the patient's needs [19].

Although the term "patient-centered care" is widely used, the existing provider-centered and disease-oriented health care system often fails to devote sufficient attention to the needs, concerns, and preferences of patients. Patient-centered care involves efforts to inform, educate, and communicate with individual patients, shared decision making, and continuous advocacy of injury and disease prevention. Clinical care is delivered to one patient at a time, but a "population health" perspective is essential for improvement of the quality of care that is provided to individual patients. Identification of the needs of specific patient populations can be achieved through systematic collection and analysis of patient-centered outcomes data, but it is difficult to accomplish without utilization of appropriately designed health information technology (HIT). Unfortunately, the current organizational structure of the health care system and prevailing financial incentives have focused HIT development on systems for documentation of billable events, rather than collection of data to support continuous quality improvement [21]. The HIT for Economic and Clinical Health Act clearly supports development of a mechanism for secure exchange of electronic data between providers, but such a platform is not likely to facilitate meaningful improvements in health care value without financial incentives that reward patient-centered care.

The American health care system faces three interrelated problems of cost, quality, and access to services [7]. The respective roles of government programs, commercial health insurance, and self-funded employer health plans as separate sources of reimbursement for health care services greatly complicates efforts to reorganize the system. The federal government clearly plays the major role in determination of access to services for a large segment of the American population, but universal coverage will not solve the problems of rising costs and quality concerns. Overzealous pursuit of universal access could diminish the private sector's positive influences on the health care delivery system. As the proportion of services financed by government programs grows beyond 50%, a tipping point may be reached. Continued escalation of costs may cause increasing numbers of employers to discontinue sponsorship of a health plan, which would further increase the proportion of people relying on the government for access

to care. Provider cost-shifting to private payers as a means to compensate for lesser reimbursement amounts from government programs would yield progressively lower levels of compensation. Lacking a robust private health care market, providers are unlikely to have a sufficient financial incentive to reorient the system to a patient-centered approach. Lacking outcomes data, the likely result would be a single-payer system that rations care on an irrational basis.

Competitive markets and consumer choice have historically provided value in other sectors of the economy, whereas government programs have historically been plagued by bureaucratic processes and the influences of special political interests. The private sector's flexibility and inventiveness are probably essential for realization of greater health care value [8]. There are clearly many challenges to the achievement of an effective and fair realignment of provider financial incentives. For example, mechanisms are needed to clearly distinguish random variations in patient outcomes and patient mix from variation in practice patterns and avoidable complications [11]. Assuming that providers are compensated fairly for provision of high-value services, and that they are not financially penalized for circumstances beyond their control, the potential for a sudden and dramatic shift toward a patient-centered approach to care might be realized.

Regardless of whether the ACA is repealed, declared unconstitutional, modified, or fully implemented, traditional fee-for-service reimbursements to individual providers are unlikely to continue. If an optimal balance is achieved between government-mandated initiatives and private sector influences on the U.S. health care delivery system, perhaps the cost, quality, and access problems can be collectively resolved. In any case, physicians and other health care practitioners who are committed to delivery of patient-centered clinical care should welcome payment reform that rewards excellence and facilitates realization of optimal patient outcomes.

In keeping with policy reform in support for lifestyle medicine, the CMS in 2004 established obesity as a recognized disease, thus allowing Medicare to consider covering payments for obesity-related treatments [22]. Despite Medicaid being a state administered program, the Medicare decision has stimulated a number of states to extend their Medicaid programs' coverage of services to include both prevention and treatment of obesity. Examples from the states include West Virginia [23] and Tennessee [24] who offer both full and partial reimbursement for Weight Watchers© programs.

Another set of policy supports for lifestyle medicine have occurred through the National Committee for Quality Assurance starting in early 2006 with the approved Healthcare Effectiveness Data and Information Set (HEDIS) measures of health plan performance regarding the measurement of physical activity and body mass index as "vital signs" among adults, children, and adolescents. In addition, nutrition and physical activity assessment and counseling for adults, children, and adolescents were also recommended. Most U.S. health plans use HEDIS measures to monitor provider performance associated with patient care and services and report to providers, purchasers of health care plans, and consumers on the quality of health care throughout the nation [25]. The new chronic disease prevention and obesity-related measures attempt to target improvements in providers' practice behaviors related to chronic disease and obesity prevention, care, and treatment. The launching of such chronic disease/obesity-related HEDIS measures demonstrates the role that a policy intervention can potentially impact preventive care practice behaviors among providers and health behavior change among patients [25].

Current policies and practices supporting the delivery of health care do not provide adequate incentives, both monetary and otherwise, directed toward providers to integrate lifestyle medicine and preventive care into their existing practices [5]. Indeed, one of the highly held ideals among preventive care advocates, the potential cost savings afforded by preventive care to the health care system as a whole, has been questioned by many within the medical community [26,27]. However, these positions often confuse early detection and treatment with primary prevention and public health efforts, where the latter appear to provide the best evidence for cost savings and prevention of premature morbidity and mortality [28–30].

Indeed, those policies and evidence-based interventions outlined within this section of *Lifestyle Medicine* seek to identify primary prevention strategies of active living and healthy eating that hold significant promise in alleviating premature suffering from disease and early death. In addition the practices outlined can also greatly benefit the patient with an existing chronic condition by effectively using lifestyle medicine to manage and control disease.

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130 Policy and Environmental Supports in Promoting Physical Activity and Active Living

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CONTENTS

Schools 1540
Worksites 1541
Community Organizations 1541
Public Recreation Facilities 1542
Promoting the Use of Facilities 1542
Costs/Benefits and Funding 1543
References 1543

Community-based approaches to promoting physical activity were initially assessed systematically for effectiveness by Kahn et al. [1] and Heath et al. [2]. Within these systematic reviews, the authors identified three major domains of community-based physical activity interventions. These domains include, informational, behavioral/social, and policy/environmental approaches to promoting physical activity in community settings [1,2] (see Table 130.1). This chapter seeks to identify evidence-based interventions that address policy and environmental supports for promoting physical activity that can reinforce a healthy lifestyle and active living assessment and counseling. An intervention strategy that falls under the domain of policy and environmental supports is creating or enhancing access to places for physical activity, combined with informational outreach activities [1,3]. Interventions within this strategy include creating/enhancing existing walking/biking trails or exercise facilities and increasing access to existing facilities by reducing barriers (e.g., increasing safety, enhancing affordability). These efforts often include personnel and/or participant training, social support, and further integration of these structures, facilities, and programs into participants' communities. An exemplary intervention of this type, described by Linenger et al. [4], included new infrastructure (i.e., bike paths), access to facilities (e.g., expanded hours of operation, lighted and integrated paths), and improved programming on a residential Naval base [4]. Recent studies have documented that developing such infrastructure is reasonable from a cost perspective [5].

An emerging strategy within the domain of policy and environmental approaches was more recently described by Hoehner et al. [6]. This strategy consists of community-wide policies and planning that place physical activity within the public policy agendas of communities, emphasize promotion of physical activity guidelines, provide organizational incentives, address institutional and environmental barriers, and use media effectively [6]. An example of this promising intervention approach comes from the work of Gómez et al. [7] on Muvete Bogotá, a community-based physical activity program in Bogotá, Colombia, SA. This multisector physical activity promotion intervention conducted throughout Bogotá, Colombia, consisted of infrastructural change including cycle pathways, pedestrian walkways, and public transport corridors. Worksite- and school-based physical activity programming was also instituted along with neighborhood-specific programming at community centers, public parks, and childcare centers. The health sectors, both public and private, were engaged in awareness and support of community programming. Finally, a series of citywide events were strategically carried out throughout the year to reinforce local and site-specific programming [7].

Policy- and environmental-based interventions that are designed to create or provide access to places where people can be physically active often involve the combined efforts of worksites, schools, coalitions, government agencies, and community members [1]. These interventions are characterized by providing improved access to existing exercise facilities, such as fitness centers (both proprietary and nonprofit), community centers, and walking/bicycle trails, and providing access to school grounds [1,2]. In addition to promoting access, many of these interventions incorporate components such as supervision of equipment use, health behavior education and counseling, risk factor screening, referrals to health services, buddy systems, and promotion of facility use [8].

A more detailed discussion of each of these areas of intervention follows.

TABLE 130.1
Task Force for Community Preventive Services: Physical Activity Intervention Recommendations

Informational approaches

- Community-wide campaigns: These large-scale, highly visible, multicomponent campaigns direct their messages to large audiences using a variety of approaches, including television, radio, newspapers, movie theaters, billboards, and mailings. ***Recommended with strong evidence***

Behavioral and social approaches

- Individually adapted health behavior change programs: These programs are tailored to a person's specific interests or readiness to make a change in physical activity habits. Teaching behavioral skills such as goal setting, building social support, self-rewards, problem solving, and relapse prevention, the programs help people learn to incorporate physical activity into their daily routines. ***Recommended with strong evidence***
- School-based physical education (PE): This approach seeks to modify school curricula and policies, to increase the amount of time students spend in moderate to vigorous activity while in PE class. Schools can accomplish this either by increasing the amount of time spent in PE class or by increasing students' activity levels during PE classes. ***Recommended with strong evidence***
- Social support interventions in community contexts: The goal of this approach is to increase physical activity by creating or strengthening social networks. Examples include exercise buddies, exercise contracts, and walking groups. ***Recommended with strong evidence***

Environmental and policy approaches

- Creating or improving access to places for physical activity combined with informational outreach: Examples include building walking or biking trails or making it possible for people to use exercise facilities in community centers or in the workplace. Informational outreach includes activities such as providing training on equipment, seminars, counseling, risk screening, and health forums and workshops. ***Recommended with strong evidence***
- Point-of-decision prompts to encourage stair use: These signs are placed by elevators and escalators and encourage people to use nearby stairs instead. ***Recommended with sufficient evidence***
- Community-scale urban design land use policies and practices: Examples involve the efforts of urban planners, architects, engineers, developers, and public health professionals to change the physical environment of urban areas of several square miles or more in ways that support physical activity. ***Recommended with sufficient evidence***
- Street-scale urban design and land use policies: Examples involve the efforts of urban planners, architects, engineers, developers, and public health professionals to change the physical environment of small geographic areas, generally limited to a few blocks, in ways that support physical activity. ***Recommended with sufficient evidence***

SCHOOLS

School physical education and health education curricula now provide methods of promoting youth physical activity, and many of these strategies have been shown to be effective [9]. However, currently within the United States, a frustrating paradox often exists in many communities. Although school building and grounds may be the most widely available public resources for physical activity within the community and the design of these facilities are often effective for engaging in physical activity, yet these facilities are often underutilized. A study of 24 middle schools evaluated the relation between the school social and physical environment with students' physical activity [10]. The observers coded environmental characteristics including the accessible play areas; their size; improvements, such as basketball hoops, soccer goals, and playground markings; and the presence of play equipment, supervision, and organized activities. Students' physical activity was observed during periods when they could choose to be active: before school, after lunch, and after school. Although student activity levels generally were low, they were strongly related to the social and physical environments at school. For example, about 10 times as many students chose to be active when supervision and improvements were high than when those supports were absent. There were also interesting sex differences observed in this investigation, which suggests a need for further exploration. In their study, boys tended to be the most active on outdoor courts, whereas girls were most active in indoor facilities. Further understanding these gender differences may create the opportunity to tailor policy and environmental needs for boys and girls.

Most schools have policies in place that restrict access to school grounds by students and community members outside of school hours. Thus, these abundant public resources are underused, and these policies may have the most negative impact on low-income communities, which lack other resources. There are a number of community advocacy groups around the country seeking solutions to change this situation. Among the groups seeking solutions is the Denver Learning Landscapes Alliance (http://thunder1.cudenver.edu/cye/lla/home.html). This group seeks to transform school grounds into community parks, with a focus on low-income communities. Their goal is to transform vacant playing fields surrounded by fences into school grounds that become community parks with play equipment, areas of natural vegetation, gardens, and welcoming gates. The addition of more pleasing landscapes encourages participation and has the potential to improve physical, mental, and social well-being [11].

Active transport by walking and cycling to and from school can provide substantial physical activity for children and youth. One example of leveraging available federal dollars set aside to promote cycling and pedestrian activities in communities through assistance from state departments of transportation. Such an example is the California Department of Transportation (DOT), which provided $66 million in funding over 3 years for "Safe Routes to Schools" grants to 270 schools [12]. Such funding was used to make physical improvements such as sidewalk and bike lane construction or enhancements, traffic calming, and street crossing improvements around schools. Some schools added promotional and educational programs to encourage people to use the improved streets. In Marin County, CA, walking to school increased 64% and biking increased 114% after a combined intervention [13]. A statewide evaluation of 10 schools found that students who passed by the improvements on their way to school increased walking and biking by 15% compared to 4% for those who did not pass the improvements [12].

WORKSITES

The importance of the worksite as a venue for the promotion of physical activity through policy and environmental supports was systematically reported by Heirich et al. [14]. The relative impact of three different approaches to physical fitness promotion at the worksite on cardiovascular risk reduction was examined based on before-and-after health screening of employees and employees' reports of participation in physical activities [14]. Within the setting of an automobile plant, three approaches to promoting physical activity for cardiovascular risk reduction were tested at three sites: (1) a staffed physical fitness facility, (2) one-to-one counseling with at-risk employees, and (3) a combination of one-to-one counseling with employees plus organization of the worksite to encourage peer support and mutual exercise and physical activity at work. A fourth site served as a control site. The program that was centered on a physical fitness facility had little measurable impact on cardiovascular risks and showed results similar to those at the control site. The programs that included a combination of counseling and plant organization, which provided greater access to opportunities to be physically active, were more effective and provided better health outcomes in terms of frequency of exercise, adequacy of blood pressure control (among people with hypertension), weight loss (among the overweight), and smoking cessation. These results provide evidence that systematic, ongoing outreach to enlist employees in various types of exercise programs is more effective than the presence of fitness facilities without such outreach. Moreover, significant increases in the frequency of exercise can be sustained without a substantial investment in facilities. Two more recent worksite-based studies demonstrating the role of policy and environmental approaches to promoting physical activity are the Los Angeles Lift-Off [15] and Move to Improve [16]. Yancey et al. [15] conducted a randomized, controlled, posttest-only trial to evaluate the level of participation in a physical activity promotion program designed to integrate a single 10 min exercise break into regularly occurring meetings or events during work time at Los Angeles County Department of Health Services' worksites. In addition, measures of psychological effects were also examined among participants. The investigators sought to demonstrate that individuals could be engaged in brief bouts of moderate intensity exercise across the weight status and physical activity level continuum, and that this exercise participation would be associated with positive changes in psychological affect. The unique focus of this study included a "minimal" environmental change that was specifically targeting underserved populations. Results indicated that more than 90% of meeting attendees participated in the exercises. Significant improvement in activity levels and self-perceived health status was seen among participants who at baseline were completely sedentary and whose self-perceived health status ratings were significantly poorer than controls. Even more significant was that among intervention participants who initially were not regularly physically active, levels of satisfaction with fitness significantly correlated with self-ranked physical activity stage of change following the intervention. The investigators concluded from their results that captive audiences, such as those attending mandatory meetings and events, may be engaged in brief bouts of exercise as a part of the workday, regardless of physical activity level or stage of change. The results of this experience among attendees may also erode sedentary individuals' inaccurate self-perception of good health and fitness, providing additional motivation for the adoption of a more active lifestyle [15]. Dishman et al. [16] recently reported on the efficacy of a multisite randomized controlled trial consisting of a 12 week intervention that increased moderate to vigorous physical activity (MVPA) among employees of a large retail company by targeting features of the workplace environment as well as employee motivation using personal and team goal setting. Based on management theory, 24 different employee ratings of perceived management support and employee involvement were assessed to confirm implementation and impact of the organizational action component of the intervention. Participants in the intervention had greater increases in MVPA and walking compared to participants in a health education control condition. The proportion of participants that met the *Healthy People 2010* recommendation for regular participation in either moderate or vigorous physical activity remained near 25% at control sites during the study but increased to 51% at intervention sites. During the last 6 weeks of the study, intervention participants exceeded 300 weekly minutes of self-reported MVPA and 9000 daily pedometer steps. The authors concluded that their results support the feasibility and efficacy of the *Move to Improve* intervention and the role of environmental supports and goal setting for attaining increased physical activity levels among worksite employees.

COMMUNITY ORGANIZATIONS

Many community organizations provide physical activity facilities or programs, or they could do so. In the private sector, health clubs, dance studios, martial arts organizations, swimming clubs, and sports leagues are familiar examples. Nonprofit organizations include YMCAs/YWCAs and Boys' and Girls' Clubs as well as sports leagues. Faith-based organizations often have physical activity facilities and programs for their members, which could be made available to others in the community. Private and public housing developments have recreational and fitness facilities. Thus, many resources throughout the nation can be used for recreational physical activity, and with improved promotion, they can become better utilized. However, there do not appear to be any well-designed systematic studies of how the facilities and programs within these community organizations contribute to the physical activity levels of individuals' in surrounding communities. Although there are undoubtedly many exemplary programs in these organizations, there currently are no programs that have been systematically evaluated regarding changes in physical activity behaviors due to policy and environmental supports to promote physical activity.

The public health impact of these facilities and programs can be maximized by increasing the number of participants, by increasing the frequency and duration of activity sessions, and by sponsoring year-round programs, especially for sports organizations. Making resources available to the general community and having reduced fees for low-income participants could help contribute to reduced disparities in physical activity.

PUBLIC RECREATION FACILITIES

Public parks and recreation facilities are widely used, with about 80% of the population making some use of municipal facilities and a smaller but substantial percent using park programs and services [17]. Various studies have shown that 30%–65% of park users were engaged in physical activities or sports [17]. The contribution of public recreation facilities and programs to physical activity could be enhanced by optimizing the design of the facilities to support physical activity of various population groups and promoting use of the facilities. The potential impact of improved park design was indicated by an Australian study that found adults with very good access to large and attractive public open space were 50% more likely to be regular walkers than those without such access [18].

The National Recreation and Park Association has partnered with the National Heart, Lung, and Blood Institute on the Hearts N' Parks Program, whose goal is to promote physical activity in parks to reduce the occurrence of chronic diseases. Interested recreation agencies became magnet centers because of their interest in contributing to public health improvement and their ability to serve high-risk population groups. Youth efforts emphasized after-school and summer camp programs. Adult target populations were senior center attendees, city employees, and the general population of adult park users. A recent evaluation of magnet centers that developed multiple physical activity promotion programs found that 50 Hearts N' Parks magnet centers were operating in 11 states. Participants in programs were found to improve knowledge, attitudes, and physical activity behavior using standardized survey procedures (http://www.nrpa.org/content/default.aspx?documentId=2683). The Hearts N' Parks magnet center program was conducted for 3 years with coordination but no funding from the national partners. This appears to be a valuable national effort that needs to be more widely disseminated.

There is some evidence that park and recreation professionals are enthusiastic about participating more in promoting physical activity. A survey of 44 recreation center directors in San Diego County found that most center directors wanted to provide more physical activity programs to youth, 75% were willing to partner with health professionals to train staff in physical activity leadership, and 59% wanted to improve the marketing of their programs [19]. The most frequently cited barriers to offering more physical activity programs for youth were inadequate staff and training, departmental support, and funding [19]. Increased collaboration between public health and recreation professionals to maximize the use of public recreation facilities for physical activity is indicated.

PROMOTING THE USE OF FACILITIES

According to Missouri state Behavioral Risk Factor Surveillance System data in 1997, 60% of the state population were overweight and 65% were not sufficiently active to meet public health recommendations. To address this health problem, the state health department, with the assistance of a community heart health coalition, helped to fund construction of walking trails in two communities through the DOT. Although a formal evaluation was not conducted, DOT staff had heard that trails were underutilized because of safety concerns and lack of amenities such as playground equipment and well-maintained restrooms. Because other communities were requesting funds to build trails, the state needed to know if the investment would be worthwhile. To promote use of the existing trails, the state funded the health department to conduct an awareness campaign and trail enhancement activities in one of the communities with a year-old trail. If community members were not more physically active after having both access to a walking trail as well as information about the trail and about the benefits of regular physical activity, then the state probably would not fund additional trails.

The health department and a heart health coalition conducted the resulting Take Our Trail Campaign for 3 months [20]. The campaign kicked off with a 3 mile Family Fun-Walk, with t-shirts and refreshments donated by local businesses. For the length of the campaign, signs were placed throughout the community to raise awareness of the trail. A simple brochure was sent to all programs in the local health department, as well as to clinics, church leaders, and the heart health coalition. The brochure contained information about the importance of physical activity, tips to increase walking, safety information, information about the trail, and who to contact for walking club information. The local television station created a public service announcement during the evening news to promote the trail and the importance of regular physical activity. The public transportation system placed signs inside buses. The heart health coalition helped develop walking clubs at worksites, churches, and social organizations. Local law enforcement officials agreed to patrol the walking trail periodically. The coalition worked with local business, city government, and churches to raise money to enhance the trail, adding amenities to the trails such as lights, benches, mile markers, painted lanes, and a water fountain.

The primary purposes of the evaluation were to determine whether a promotional campaign would increase the use of existing trails and increase the number of individuals who met recommended levels of physical activity. The Take Our Trail community had a 35% increase in trail use between 1 month before and 1 month after the springtime campaign compared with a 10% increase in the community without the campaign. Data from the walking trail counter indicated that trail usage was very high during Take Our Trail events.

Use increased more with the formation of walking clubs in both communities (note: in the "control" community, several walking clubs formed on their own and were recorded in the event log system) but the increase in the Take Our Trail community was significantly higher. In addition, Sunday afternoon and Wednesday evening use increased with the creation of the church-based walking clubs.

Interviews with stakeholders revealed that individuals in the campaign community felt safer while walking than people in the community with a trail and no campaign due to walking with partners (e.g., walking clubs), trail lights, and police patrols. More than 60% of trail users in both communities indicated an increase in walking since the trail existed.

All types of people used the trail, but especially women, older adults, athletes recovering from injuries, and people with medical conditions that required a low-impact activity. These included many of the groups who were targeted for use, especially older adults and lower income people. When asked about how they became aware of the trail, most of the respondents indicated that they lived or worked near the trail or they heard about it at church or work, from their physicians, or from friends or family. Very few trail users had seen the fliers or public service announcements and generally were unaware of the promotional campaign.

Evaluation of the Take Our Trail program suggested that the construction of walking trails increased physical activity and the implementation of a campaign to promote trail use further increased physical activity. These findings were shared with DOT with a recommendation to build additional walking trails and support campaigns aimed at increasing trial usage. The report to DOT also suggested that the focus of these campaigns include community-wide involvement in promoting the trail and walking and enhancement of the trails. Increasing safety and security is a must.

Costs/Benefits and Funding

King et al. [21] suggested an environmental and policy intervention should be chosen based on likely potency and cost effectiveness. However, evidence supporting the cost effectiveness is limited. Two economic evaluations of interventions to create or enhance access to places for physical activity have been completed. One 4 year study conducted at a fitness facility in Houston, Texas, for employees of an insurance company conducted a cost-benefit analysis of a structured physical fitness program [22]. The program included regularly scheduled classes in aerobic dancing, calisthenics, and jogging; seminars on obesity, smoking, alcohol abuse, and stress reduction were also offered. Program benefits included savings in major medical costs, reduction in average number of disability days, and reduction in direct disability dollar costs. Program costs included personnel, non-salary operating expenses, and medical claims. The adjusted estimates for benefits and costs for 1 year of the program are $1106 and $451, respectively. Based on the quality assessment criteria used in the *Community Guide*, this study was classified as good [23].

Wang et al. [5] examined the cost of trail development and the number of users of four trails in Lincoln, Nebraska. The first year of trail development cost $289,035, of which 73% was construction cost. Of the 3986 trail users, 88% were active at least 3 days a week. The average annual cost for people becoming more physically active was $98; for people who became active for general health improvement, it was $142; and for those who became active for weight loss, $884. This study provides a set of basic cost-effectiveness measures by compiling actual cost items of trail development, estimating the number and type of trail users, and identifying several physical activity-related outcomes and items. Similarly, in another recent investigation on trail cost effectiveness [24], using multiple days of objective trail counts and community surveys found a slightly higher annual cost of becoming more physically active of $117.29 using the same formula proposed by Wang et al. [5,24]. Nevertheless, in summary, it would appear that the trail benefit to cost analysis suggests that building an unattractive, poorly designed trail with limited useful life may be the perfect storm for ineffective public health spending.

Roux et al. [25], using econometric modeling of data from a list of exemplary community-based interventions, including interventions shaped by policy and environmental supports, concluded that such programs provide a good return on investment in their effectiveness in bringing about improvements in physical activity among persons exposed to such programs.

Undoubtedly, policy and environmental approaches are essential for sustaining improvements in physical activity behaviors within communities. By creating connections across disciplines including land use planning, transportation, public health, and economic development, substantial policy changes may be gained. Improving policy along with engaging community members may be the important formula for enhancing success.

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131 Public Policy and Environmental Supports for Healthy Eating

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CONTENTS

Introduction 1545
Overview of Healthy Eating Trends 1546
Morbidity and Obesity 1546
Availability and Affordability of Healthy Foods 1546
Health Behavior in Healthy Eating 1546
Disparities/Inequities in Healthy Eating 1546
Environmental Factors 1547
Availability of Full-Service Grocery Stores 1547
Food Purchasing Options 1547
Retail Food Stores 1547
Restaurants 1547
Food Vending 1547
Healthy Foods Policy 1548
School 1548
Geographic Availability of Full-Service Grocery Stores 1548
Food Labels 1548
Restaurant Menus 1548
Healthy Eating Recommendations 1549
What Counts as a Cup? 1549
Sales Promotion at Grocery Stores 1550
Summary 1550
References 1550

The national *Healthy People 2010* fruit objective and vegetable objective are to increase the proportion of Americans aged at least 2 years consuming daily ≥2 servings of fruit to 75% and ≥3 servings of vegetables to 50%.

INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), 63% of the adult population is overweight or obese and fewer than 25% of Americans eat fruits and vegetables five or more times per day [1]. More than one in seven children and adolescents aged 6–17 years are considered obese [2]. Currently, research suggests the childhood dietary habits are influenced by various environmental factors that include availability of fast foods and soft drinks, availability of soda and unhealthy food on school campuses, and limited access to healthy foods compared to ready availability of unhealthy foods. Furthermore, the prevalence of advertisement of low-nutrient foods to children and their families encourages unhealthy eating and overconsumption [2]. Many of these contributing factors to healthy eating are even more challenging in low-income communities since healthy and affordable food options are limited. Although most Americans know the relationship between diet and health, eating attitudes remain unhealthy and the consumption of fruits and vegetables remain low [1]. Consequently, public policy and environmental behavior change, and not just individual behavior change, have become a major focus to improve healthy eating. Fruits and vegetables, important components of a healthy diet, are important for child growth, weight management, and chronic disease prevention. Environmental and public policy supports to increase fruits and vegetable access, availability, and affordability are key strategies to help increase healthy food consumption and ultimately improve the overall nutritional status of Americans.

OVERVIEW OF HEALTHY EATING TRENDS

Morbidity and Obesity

Currently, sixteen million Americans have diabetes and the number is significantly rising particularly in Latinos. Currently, African American and Latinos adults are 1.3–1.9 times more likely to have diabetes than white adults [3]. Similarly, the U.S. is facing a childhood obesity epidemic as more than one in seven children and adolescents, aged 16–17 years, are considered obese [2]. Due to the increase of unhealthy food consumption and decrease of physical exercise, the rate at which childhood obesity has grown has been two-fold in the past 20 years. Specifically, African American and Hispanic children are twice as likely to be obese as white and Asian children.

Availability and Affordability of Healthy Foods

Healthy eating recommendations, such as substituting "lite" bread and diet soft drinks, made by associations such as the American Diabetes Association, does not mean that healthier eating choices are available to all neighborhoods. There is evidence to show that grocery stores in low-income and non-white neighborhoods have limited supply of healthy eating choices. The lack of availability of healthy foods makes it challenging for clinicians to prevent and control chronic diseases such as diabetes, a treatment that requires an increased intake of healthier foods, fruits, and vegetables [3]. Furthermore, grocery stores in predominantly black and lower income place the food behind glass storage, which does not allow consumers to easily access healthy food. As a health care professional, it is important to understand that environment support is necessary for a change in dietary practices to occur. For instance, primary and secondary intervention of chronic illnesses such as obesity and diabetes may be more difficult if the recommended food is unavailable in the neighborhood [5].

Health Behavior in Healthy Eating

A study conducted in 2007 found that "the health concern of consuming too many calories from food has a greater effect on healthy eating attitudes than did health concern of developing diseases" [1]. Given that food choice is not definitively associated with having a positive attitude towards healthy eating, it is recommended that health professionals focus on the importance of health and calorie intake instead of weight control. Particularly the eating behavior of an adolescent is important in the maintenance of their health and in their physical development and, thus, why the intake of nutrients needs to be higher than any other growth period. Moreover, adolescence is a time where behavior patterns are developed and consequently have an impact on their eating behaviors in the future as there is an increase of independence and autonomy. Studies show that the eating practices one develops as an adolescent have long-term effects on health status once in adulthood. It is critical as a health care professional that one incorporates healthy eating behaviors into the daily routines of adolescence to reduce the risk of chronic diseases such as heart disease, diabetes, and particularly obesity in adulthood. Although there are standards and guidelines set out by nutrition professionals of a diet low in saturated fat and cholesterol, high intake of fruits and vegetables, and whole grains, adolescents are having nutritional problems due to their inconsistent eating behavior and unhealthy eating.

Studies show that adolescents have a lack of concern for healthy eating patterns, which is attributed to their perception of healthy eating recommendations and the health implications. In 2001, a study was done to determine perception of health and unhealthy foods, eating behaviors, and the importance of healthy eating. The adolescents suggested that "limiting junk or high-fat food and "watching fat and calories" constitates a healthy eating behavior. Most adolescents associated unhealthy eating with their peers but that healthy foods were associated with eating at home with their families. However, despite their awareness of healthy eating, adolescents are not consistently following the nutrition recommendations, and this may be due to barriers that prevent them from developing healthy eating practices. It is important to understand that peer norms play a role into the healthy eating choices of adolescents. For instance, a study in California revealed that 85% of teen girls had a health concern of weight control but only 8.5% had concern over healthy eating. This data were then compared to the National Health Interview Survey Teenage Attitudes and Practice Survey, which showed that weight concern was the second most important, whereas healthy eating was ranked last as a concern [6].

These findings suggest that healthy eating messages based on the Dietary Guidelines for Americans are reaching adolescents, but interventions are needed that assist adolescents with the translation of this knowledge into what it means to have a healthy eating behavior. Interventions should help make healthy eating easy for youth to apply and explain the consequences of unhealthy eating in terms that they value, stressing meaningful short-term benefits [6]. "Eating behavior is carried out with little regard to intention or self-regulation. However, deliberating over a menu seems to be an occasion when cognition plays a role and thus when rational food decisions might be made" [7].

Disparities/Inequities in Healthy Eating

In 2005, the Dietary Guidelines for Americans took note of the low intake of fresh fruits and vegetables, low-fat dairy products, and whole grain food of the U.S. population. It noted that race and income may be a contributing factor to the level of healthy food intake. Due to residential segregation in the United States, it is likely that there is a difference in food choices as a result of their environment. For example, the type of and amount of food stores in a neighborhood varies by race and income. A study conducted in 2008 found that there were more supermarkets that carried healthy food in predominantly white and high-income neighborhoods compared to black low-income neighborhoods. There are

disparities in obesity rates existing among ethnic groups. Black, Hispanic, and Native American children and adolescents have higher rates of diabetes and obesity than do white children and adolescents [2].

According to a recent study in 2010, there is no statistically significant difference in obesity prevalence between 2001 and 2007. However, the income disparity in obesity prevalence more than doubled between 2001 and 2007 when adolescents with family incomes below the poverty line were compared with those with family incomes at or above 300% of the federal poverty line. It also found that male adolescent obesity rates were higher than female rates across income group, especially among Hispanic adolescents, in the United States [8]. Currently, the increasing disparity in obesity prevalence by socio economic status (SES) places lower-income adolescents at a disproportionate risk for adulthood obesity as well as related conditions such as diabetes, hypertension, heart diseases, stroke, and cancer. It is important to identify that physical inactivity, sweetened beverages, and skipping breakfast are targets of intervention to reduce disparities in obesity prevalence.

However, breaking down the barrier of accessing resources for those who have a low socio economic status, particularly African Americans and Latinos, would require environmental and public policy support. Without which, eating healthier will remain a challenge, ultimately preventing the reduction of obesity [8]. Nonetheless, studies show that there are disparities based on income, race, ethnicity, and urbanization in neighborhood access to healthy foods [9].

ENVIRONMENTAL FACTORS

Food environment is affected by many different factors, including price of food, food distribution channels, the perception and knowledge of store managers, and policies affecting the location of various types of stores [5]. The physical environment has an effect on the individual weight status by impacting both energy intake and energy expenditure. The two most important environmental influences are the availability of food retail and type and location of food establishment [10].

Availability of Full-Service Grocery Stores

A study conducted in East Harlem, "Barriers to Buying Healthy Foods for People with Diabetes: Evidence of Environmental Disparities" [3], explored the difference in availability and cost of healthy food in low-income, minority neighborhoods and affluent all-white neighborhood in New York. The results showed that although East Harlem had twice as many food stores per capita than the Upper East Side, only 18% of the food stores carried all five recommended food items of fruits, vegetables, and whole grains compared to 58% of the food stores in the Upper East Side of New York. In areas that have a smaller population, there are food stores that are conveniently located in the neighborhood for its residents. In neighborhoods that have a density of small grocery stores, the average amount of shelf for fruits and vegetables has shown to be smaller than the shelf space for snack food. Furthermore, quality of the fruits and vegetables tend to be poor in food stores in lower-income areas. Consequently, it is difficult to eat healthier if there are not quality food options. Research has shown that small grocery stores are prevalent in poorer, urban areas, thus making it more difficult for those to access healthy food [10].

Food Purchasing Options

Retail Food Stores

Supermarkets tend to have the most variety of high-quality food at the lowest cost, whereas convenient stores typically sell high-calorie, prepared food, and limited fresh fruits and vegetables but at a higher cost. Studies have shown that having the option of a supermarket where you can buy high-quality, low-cost fresh produce is associated with increased daily intake of healthy food. It has been shown that purchasing food at a convenience store is associated with lower intake of fresh fruits and vegetables. Neighborhoods that have large chain food stores or medium-sized non-corporate-owned food stores have only a 21% obesity level compared to neighborhoods that have no access at 32%–40% obesity level. Low-income and rural residents often have limited access to supermarkets or chain grocery stores that provide healthy food options. Rural and farm areas have 14% less chain supermarkets compared to urban areas [9].

Similarly, there are findings that showed that a greater number of convenience stores were located by secondary schools in lower-income neighborhoods.

Restaurants

Currently, the majority of our meals and snacks are purchased at restaurants, which tend to have food high in calorie and food that is low in quality. Food eaten at restaurants typically does not provide nutritional information to encourage healthy eating choices. Studies show that frequently eating outside the home leads to higher intake of fat, sodium, and sugary beverages and lower intake of fruits and vegetables. However, full-service restaurants offer lower food prices, encourage higher food consumption, yet has shown to be associated with fruit and vegetable intake. Full-service restaurants in affluent neighborhoods have more healthy options on the menu. For example, a study conducted in South Los Angeles showed that 40% of restaurants in high-income areas provide at least five healthy food choices. In fact, there was a study that showed proximity to fast food restaurants increases the likelihood of gaining more than 20 kg during pregnancy [10].

Food Vending

Studies show that the number of vending machines present in a school is negatively associated with healthy eating as "preferred food" of sweetened drinks and high-fat foods are being provided to students. The more machines at school represent more low-nutrient snack selections and more opportunity to purchase such items [11]. Similarly, mobile food vendors sell a much smaller range of food options. The mobility of the

vendor means that it can reach areas that otherwise would not have access to food stores and establishments. However, mobile vendors are more prevalent in rural and low-income communities especially in large Latino immigrant populated neighborhoods. Rather than selling nutritious food, more high-fat, energy-dense foods are sold, contributing to the low intake of five servings of fruits and vegetables. Historically, food vendor catered to the poor and foreign immigrants by offering affordable prices, while indoor retail stores catered to the middle and upper class customers. Since the 1800s, mobile vendors face challenges of competing with local business and being prohibited to sell in upscale neighbors. Currently, efforts are being made to change permits, fee, and regulations to encourage "healthy food" vendors that meet the nutritional needs of the residents [12].

HEALTHY FOODS POLICY

School

Studies show that there is an association between school "a la carte" programs and the average daily consumption of fruits, vegetables, and saturated fat. Those who do not have an "a la carte" program tend to eat more closely to the dietary recommendations and thus the quality and variety of food in "a la care" programs have been in need of attention. Schools have become more dependent on the revenue of "a la carte" sales, and students enjoy the tastiness and convenience of fast food, making it challenging to improve healthy eating. School food programs are being encouraged to provide more fruits and vegetables [11]. In 2005, the California Endowment's Healthy Eating, Active Communities Program was established to prevent childhood obesity and diabetes in low-income communities. That is, school policies that targeted improving overall quantity and the quality of food given to students. There was a set of policies proposed that targeted improving the availability and quality of healthy foods.

The following are some of the policies adopted as a result of the *California Endowment's Healthy Eating, Active Communities Program*:

1. Setting standards for quality of nutrition and physical education on campus
2. Regulations on food and beverage marketing and advertising
3. Quality of food offered at fundraisers and classroom parties
4. Eliminating sports drinks
5. Eliminating sale of trans fat foods [2]

Currently, policy makers and public officials are focused on sustainable environmental improvements despite the fact the current economic state has limited the amount of resources public school have access to improve healthy eating at their school. However, these is an increasing demand for effective environmental and policy strategies that focus on mobilizing more efforts in community-based intervention strategies to improve healthy eating.

Moreover, organizational policy, that is, policy changes in a school or work environment, has been shown effective through the "Students Today Achieving Results for Tomorrow" program. The program targeted high-risk populations and low-income and ethnic minority children to increase fruit and vegetable intake during snack time. The snacks contained a (1) dairy product, (2) a serving of meat, (3) a serving of vegetables or fruits or vegetable or fruit juice, and (4) serving of whole grain. By using what was called "5 A Day Guidelines" they were able to increase the intake of five daily servings of fruits and vegetables by 83%. This was accomplished by changing the food vendor at their school. It is important for physicians to encourage their patients to use snack times to eat fruits and vegetables [13].

Geographic Availability of Full-Service Grocery Stores

Studies show that neighborhoods that have a density of small groceries are significantly related to obesity and body mass index of its residents in urban areas. This raises the question of whether it is more effective to offer incentives offer incentives for food retail stores to increase the availability of healthy food or other policies that foster the creation of neighborhood stores specializing in healthy food would be expected to improve food choices and health outcomes for neighborhood residents [10]. There have been policies proposing a tax on high-fat foods at grocery stores to decrease the purchasing of high-fat foods and to increase the intake of fresh fruits and vegetables.

Food Labels

It is recommended that food and beverage manufacturers limit levels of saturated fats, trans-fatty acids, free sugars, and salt in products sold. It is also recommended that they develop new products with more nutritional value and limit the amount of promotion and marketing of processed products. For instance, PepsiCo. permits advertisement of its products to children of all ages although its products are high in fat, saturated fat, cholesterol, sugar, and sodium that exceed the limits recommended by the World Health Organization. Food and beverage advertisement is encouraging consumption of high levels of calories in soft drinks, overeating, snacking instead of eating a full balanced meal, and eating while in front of the television. Rather, there needs to be an effort of encouraging of meals and cooking and discouraging the fact that happiness does not equate to spending.

Restaurant Menus

The United States is spending nearly half of food expenditures in meals in restaurants, which tend to be higher in calories and in fat. Unfortunately, the food descriptions provided on menus do not enable the consumer to make

healthier food choices. It is becoming increasingly difficult to determine which food items on the menu contain the most calories and in fact most tend to underestimate calorie content, specifically in high-calorie items. Although nearly half of the chain restaurants in the United States publicize nutrition information, it is typically not noticed by customers because of where it is displayed. It has been recommended by the state and local governments to require nutrition and calorie labels on restaurant menus, and in fact the 2010 Health Care Reform law includes requiring chain restaurants to label their menus.

A study was conducted to see if labeling menus influenced eating choices in restaurants. The results showed that restaurant menus were associated with calorie, fat, and sodium reduction [7]. Menu labeling would permit health-based food choices in restaurants, but its absence makes such choices virtually impossible. However, menu descriptions alone are inadequate for guiding nutrient-based food decisions. That is, people are typically bias in judging which food items on the menu are unhealthy. It is also important to take into consideration that, for instance, a Reuben sandwich at various restaurants can range from 480 to 1730 cal, 19 to 83 g of fat, and 39 to 182 g of carbohydrates. The variation comes from the differences in side dish, portion size, and ingredients [7].

According to the *CDC State Indicator Report on Fruits and Vegetables 2009 National Action Guide*, the following are key policy recommendations:

1. *Promote the availability of healthier food retail in communities*
   Strategies and policies to improve the food environment can aid fruit and vegetable access, availability, and affordability. The indicators in the subsequent text represent key areas in which policy and environmental support can help make changes in people's community access to fruits and vegetables.
2. *Promote the availability of healthier foods and nutrition services in schools*
   Schools are uniquely positioned to model and reinforce healthful eating behaviors such as increasing knowledge of and access to fruits and vegetables on the school campus and at school-related activities. Schools have the ability to provide fruits and vegetable not only to youth but also to teachers, other school staff, parents, and community members.
3. *Encourage food system support*
   A systems approach to food considers the many factors involved in getting fruits and vegetables from farm to consumer including aspects of food production, processing, and distribution. Also included in a food system approach are the participants in that system, including farmers, processors, industries, workers, governments, retailers, institutional purchasers, communities, and consumers.

HEALTHY EATING RECOMMENDATIONS

What Counts as a Cup?

In addition to fruits and vegetables, a healthful diet also includes whole grains, fat-free or low-fat milk and milk products, lean meats, poultry, fish, dry beans, eggs, and nuts and is low in saturated fats, trans fats, cholesterol, salt, and added sugars [14] (Figure 131.1).

Practical eating guide for patients: "Making Small Steps That Don't Require Major Lifestyle Change"

1. *Make half your grains whole*, grains that contain the entire grain kernel by eating [14]
   a. Oatmeal
   b. Brown rice
   c. Whole wheat tortilla
   d. Whole wheat pasta
   e. Whole wheat crackers
2. *Focus on fruits*
   a. Berries
   b. Cherries
   c. Melons
   d. Apples and bananas
   e. Raisins, plums, peaches, and pears

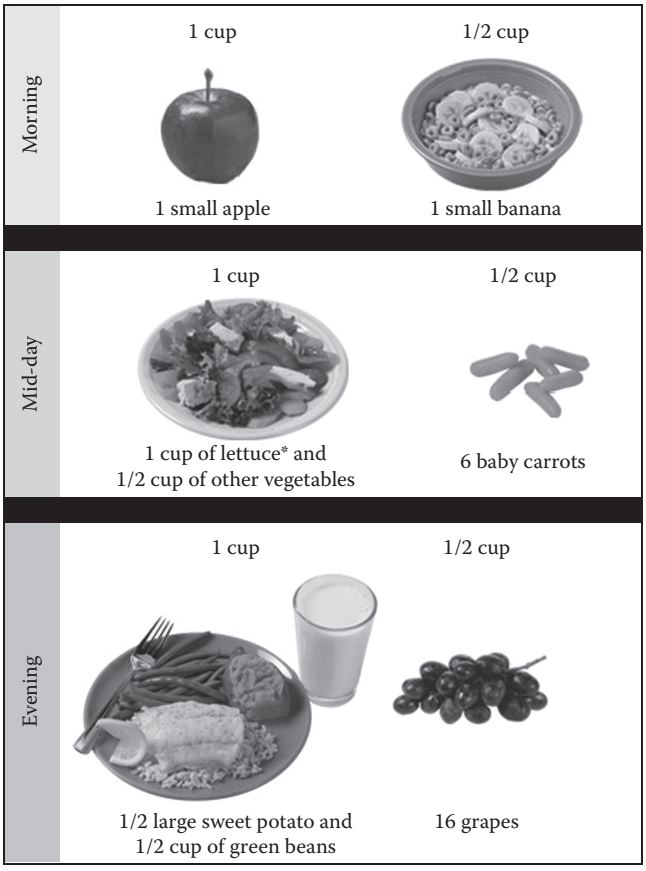


FIGURE 131.1 Fruit and veggies matter. What counts as a cup? (From CDC. http://www.fruitsandveggiesmatter.gov/)

3. *Vary your vegetables*
   a. Dark green vegetables—broccoli, spinach, collard greens, and bok choy
   b. Orange vegetables—carrots, sweet potatoes, and butternut squash
   c. Dry bean and peas—kidney beans, black beans, and black-eyed peas
   d. Starchy vegetables—potatoes, corn, and green peas
4. *Get your calcium-rich foods*
   a. Milk—fat-free (skim), low-fat (1%)
   b. Cheese—fat-free, low-fat
   c. Yogurt—fat-free, low-fat
5. *Go lean with protein*
   a. Low-fat cuts of meat
   b. Lean cuts of poultry—chicken, turkey, ground chicken or turkey
   c. Fish with omega-3 fatty acids such as salmon, trout, and herring
   d. Eggs

An effective tool to help patients integrate the practical eating guide is "My Pyramid Tracker" developed by the United States Department of Agriculture *http://www.mypyramid.gov/tools.html*.

My Pyramid Tracker is an online dietary assessment tool that provides information on one's diet quality, nutrition messages, and links to nutrient information. Once one provides a day's worth of dietary information, one will receive an overall evaluation by comparing the amounts of food eaten to current nutritional guidance. It gives a better understanding of diet over time which can be tracked up to a year.

SALES PROMOTION AT GROCERY STORES

It is important to understand that food is marketed to patients, which influences their dietary behavior, for instance, "buy one get one free" foods that are displayed in the front of the store, free samples provided while grocery shopping, or even "reduced price with purchase" and bonus sized packages. These sale promotion strategies are having more of an impact on what foods we buy and how much we eat. This makes behavior modification more challenging since the sales typically are not on low-fat healthy food items [15].

SUMMARY

Given the obesity epidemic, more attention has been given to how the food environment plays a role. There is a need for better access to healthy food and limits on energy dense, high fat food with poor nutritional value. The availability of healthy food in local food stores is associated with a higher intake of fresh fruits and vegetables and a limit on processed food. While there are methods to increase the purchase of fruits and vegetables within large corporate supermarkets and grocery stores, sales promotions and food advertisements make it challenging by encouraging overeating. Although supermarkets typically sell fresh produce, they are less available and affordable in low income and ethnic minority neighborhoods. Similarly, residents in rural areas have even less access to healthy food at supermarkets compared with urban neighborhoods. Areas without supermarkets, instead have convenience stores and corner stores that typically do not carry food with high nutritional value. It is unreasonable to expect behavior change in eating healthier when there are social, cultural, and environmental factors that do not support such change [16]. Most importantly, encourage eating products of nature and not of the food industry.

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132 Building Strategic Alliances to Promote Healthy Eating and Active Living

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CONTENTS

Strategic Alliances 1552
Partnerships in Action 1552
Charleston, West Virginia 1552
Cuba, New Mexico 1553
Portland, Oregon 1553
Chicago, Illinois 1554
Making the Most of Your Engagement 1554
Group Process 1554
Challenges 1555
Advocacy Starts at Home 1555
Know the Neighborhood Environments 1555
Supporting Partnerships 1555
Leading Community Change 1555
Summary 1556
References 1556

Health-promoting changes to community environments that support physical activity and good nutrition are vital to reducing obesity prevalence, and consequently, to preventing the onset or progression of several chronic diseases correlated with obesity (e.g., heart disease, diabetes, arthritis). Research has demonstrated that in order to effectively change behaviors associated with chronic disease, it is necessary to address individual and cultural factors as well as broader social and environmental conditions [1–4]. In other words, the context within which individuals live needs to change to facilitate rather than hinder healthy choices [5]. Interventions that address multiple levels of the ecological framework are also more likely to be successful in slowing the obesity epidemic because they can benefit all individuals exposed to the environment rather than focusing on improving the health of one person at a time [1–5]. Thus, there is broad recognition of the need for environmental and policy change to promote healthy behaviors [3,6–13].

To create environmental and policy changes, it is important to utilize approaches that build on community strengths and acknowledge the interdependence of individuals, their social networks, and the community structures, norms, cultures, history, and values [14–16]. Because of the importance of these more multilevel, multisectoral changes, many federal, state, and nongovernmental agencies are calling for the development of strategic alliances (i.e., partnerships, coalitions) to promote healthy eating and active living.

Clinicians have a key role to play in strategic alliances to promote healthy behaviors and environments, and there is a growing recognition that involvement in these types of efforts is a professional responsibility. Within the clinical setting, most physicians focus their time and energy on individual and social or family level factors to enhance the health of their patients. This may involve testing, counseling, and referrals to other clinicians and clinical resources (e.g., nutritionists, physical therapists, etc). While these traditional clinical roles are absolutely critical to patient care, many physicians have found that they want to have a role in addressing the other factors that impact the health of their patients. At the same time, professional expectations and spheres of influence are changing to reflect the important responsibility physicians have in advocating for health outside the bounds of the typical patient encounter or the walls of the clinic [17,18] (Figure 132.1).

Physicians are seen as natural leaders in today's society. Their expertise and leadership can help to enhance the work of local, state, national, and international strategic alliances or coalitions seeking to create change. To do so, it is important that physicians understand the role of strategic alliances in community-based work, the characteristics, and the development of alliances to ensure that they are successful in creating environmental and policy changes.

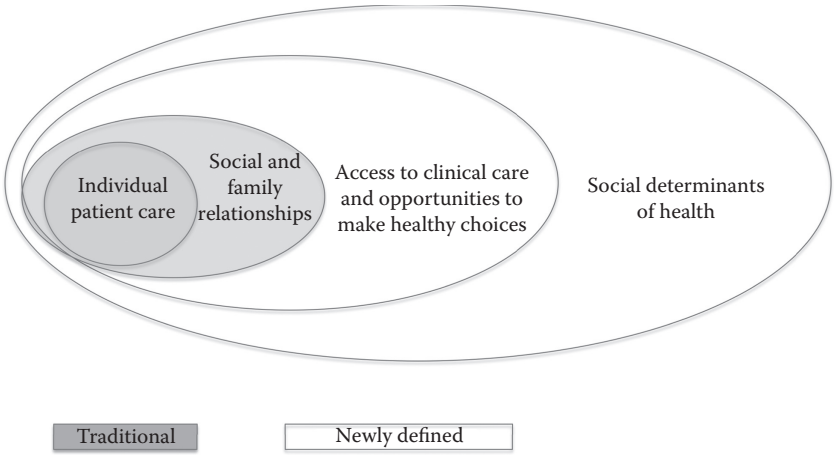


FIGURE 132.1 Physician's spheres of influence: Traditional and newly defined. (Adapted from Gruen, R.L. et al., *JAMA*, 291, 94, 2004.)

STRATEGIC ALLIANCES

Bringing organizations and individuals together from a range of disciplines and sectors of society is necessary to create environmental and policy changes to enhance healthy eating and active living. The resultant groups have been called strategic alliances, coalitions, or partnerships. Each group may go through various stages of development; progressing from initial conversations, regular meetings, development of an organizational structure, development of partnership capacity, development of a mission and vision, action planning, implementation, evaluation, and eventually to sustainability and maintenance. Their intent may be to fulfill a range of operations, each representing a different level of collaboration. The first level of collaboration might include sharing information and referrals (e.g., between clinics and community programs). The next level might be to jointly define a goal with each partner acting individually toward this shared goal (e.g., sending letters to encourage healthy choices at school events). A third level might be to contribute or exchange resources (i.e., money, space, equipment, or personnel) for a common goal. The last and often most difficult level is collaborating on planning, funding, implementing, and evaluating policy and environmental change activities [19,20]. The benefits of these partnerships are wide ranging. Having a variety of partners from different sectors (i.e., transportation, elected officials, schools, businesses, land use planning, etc.) can help navigate unique systems and processes and translate professional jargon. As a result, partnerships can improve their ability to respond to demands and increase information, resources, communication, community input, and utilization of services to improve outcomes [21–23].

PARTNERSHIPS IN ACTION

When physicians and primary care providers join community partnerships to address health, it's typically a win-win arrangement. First, partnerships benefit because physicians command professional respect in most cultures within the United States. Many have earned additional respect from their long-standing position in the community and the trust they have established with their patients. Thus, a physician's voice may add credibility to an alliance's cause. Physicians also provide a unique perspective from their daily interactions with patients dealing with the consequences of lifestyle-related diseases. Seeing so many individual cases and knowing there's a bigger context at play often motivates physician advocates and can enhance the commitment of other partners.

Physicians also benefit from community-based partnerships working to change policy and environments to enhance opportunities for daily physical activity and healthy eating. They help extend the physician's ability to advocate for the health of their patient population. Without reducing the barriers to health that many people face, only the symptoms can be treated. Telling people to be physically active who have no safe places to play or to eat a healthy diet when there are no supermarkets nearby that sell fresh, affordable produce can be counterproductive. Changing the community environments to be more conducive to health may help increase the effectiveness of a physician's counseling for healthy behaviors.

Across the nation, there are many examples of practitioner involvement in community-based alliances. A few examples in the subsequent text describe what led practitioners to these initiatives, how they participated, and some benefits of this participation.

CHARLESTON, WEST VIRGINIA

Significant barriers to healthy lifestyles face residents in the Appalachian community of Charleston, West Virginia. Culturally fat-laden diets and sedentary living combined with low access to healthy foods and places to be active for many residents have resulted in pronounced obesity and poor health, exacerbated by high rates of poverty. Virtually, none of the low-income neighborhoods have enough stores selling affordable healthy foods or safe parks. Sidewalks are nonexistent in many areas or are aging and in disrepair. However, strong neighborhood associations exist along

with recent urban renewal efforts to improve housing and community amenities. Furthermore, a new initiative called KEYS 4 HealthyKids (K4HK) is working to improve odds for Charleston children, particularly those at most risk. K4HK is supported by a strong partnership, the Kanawha Coalition for Community Health Improvement. Partners include health care providers, nonprofit organizations, and local and regional agencies. The project director is Dr. Jamie Jeffrey, a local pediatrician and the Medical Director of the Children's Medicine Center and HealthyKids Pediatric Weight Management Program at Women and Children's Hospital, a division of Charleston Area Medical Center.

Jeffrey approached childhood obesity as a diagnosis until she realized patients couldn't fulfill health-related goals because of barriers in their home, neighborhood, and school environments. Youth told her, for example, their school lunch salad bar only had potato salad and macaroni salad. Parents supported long hours on video games and in front of the TV to keep their children safely inside as opposed to dealing with the threats of crime and violence in their neighborhood. Under Jeffrey's leadership, Charleston is working on policy and environmental change strategies to increase access to healthy food and physical activity. K4HK is focused on childcare nutrition and physical activity policies and practices, developing community gardens infrastructure and joint use agreements, formal agreements between two government entities—often a school and a city or county—regarding the terms and conditions for shared use of public property or facilities.

Jeffrey's role as a pediatrician brings credibility to K4HK and contributes to the diversity of disciplines within the partnership. She also contributes local and national research outcomes and serves as a media spokeswoman. Furthermore, her involvement with community outreach helps her understand the struggles her patients and families face, how difficult it is in Charleston to lead a healthy and active lifestyle especially for low-income families. She believes the only way to reduce pediatric obesity is to treat it within the chronic care model that includes these various environments.

CUBA, NEW MEXICO

In the rural village of Cuba, New Mexico, people have limited access to fresh fruits and vegetables and places to walk and play. Of the nearly 8000 who live within a 35 mile radius, over two-thirds are Hispanic or Native American. Few roads have safe sidewalks or walkways and U.S. Highway 550 cuts through the village without even a stop sign. A local coalition, the Step into Cuba Alliance, and a local 501(C)3 nonprofit, the Nacimiento Community Foundation, are working to change this picture. The alliance includes federal and state agencies (forestry, parks and land management, transportation, and health), the University of New Mexico Prevention Research Center, and local partners such as the Village of Cuba, Sandoval County, the Cuba school district, and many citizen volunteers. Dr. Richard Kozoll, a long-standing, semi-retired local physician, led the development of this group. With dual specialties in family and preventive medicine, he attempts to address the root causes of clinical problems at the community level in addition to their consequences in his clinic. Furthermore, in a small rural community, he knew local and external partners were necessary to accomplish needed change.

Kozoll utilized many connections acquired through the years to coalesce partners under the umbrella of the local nonprofit. The foundation acquired a variety of small grants to improve trails and greenways and work on broader-scale efforts to increase active living and healthy eating. The vision for Step into Cuba is to create a "greener," healthier, and more pedestrian-friendly community with opportunities for extraordinary walking and hiking on surrounding scenic Federal land. The initiative is based on the Center for Disease Control and Prevention's evidence-based recommendations for improving public health in community settings. They are implementing strategies such as improving the built environment, increasing access to the natural environment (including trail connections to the Continental Divide National Scenic Trail), providing social support for walking and hiking, and providing point of decision prompts.

Related initiatives are underway through the award of a multiyear, Robert Wood Johnson Foundation Healthy Kids, Healthy Communities grant. Strategies related to this effort include expanding a community garden to include youth; increasing access to fresh healthy foods in arid, isolated areas; increasing the number of safe play spaces for children; making the village more pedestrian friendly, especially along the stretch of Highway 550 that serves as Cuba's four-lane "Main Street"; and identifying safer and healthier ways for children to get to school on foot.

Kozoll's role as a local physician makes him an effective champion and advocate for change. Many of the residents have been his patients and the rural setting makes for strong relationships through the years. He understands the need for community preventative services and serves as a credible spokesperson. At the area's only clinic network, the diabetes caseload typically runs 500 plus, a number he shares with policy makers when making the case for environmental change. The respect he has earned as a long-standing physician and tireless leader to improve the community for health strengthens his messages and helps him leverage resources for the cause. He recently obtained a donation of private land that was critical to connect the town to the nearest corner of National Forest and obtained partner assistance to create a new trail and trailhead area. With the Alliance and the Foundation, Kozoll extends his reach as a primary care provider far beyond the office.

PORTLAND, OREGON

Dr. Minot Cleveland, the Medical Director for Employee Health and Integrated Leave within Legacy Health in Portland, Oregon, was working to save his children's physical education program during school budget cuts in the early 1990s. Cleveland and other parents testified unsuccessfully

at the local school board meeting. They went to the Oregon Department of Education who told them state lawmakers set curriculum and funding policy. Undeterred, the group enlisted help. Cleveland, as a long-standing volunteer for the American Heart Association, recruited them, and the growing coalition, self-named Physical Education for All Kids (PEAK), advocated for statewide standards for physical education. Again, the group was unsuccessful but more determined than ever.

The Oregon legislature meets every 2 years, so PEAK spent time strengthening their coalition and their strategies. They recruited more nonprofits like the American Diabetes Association, Oregon Medical Association, and the Oregon Sports Authority. They also grew their citizen volunteer base. The additional partners brought staff support, and in 1997, PEAK convinced lawmakers to pass a bill for statewide standards in physical education. Ten years later, another bill set the minimum number of minutes required per week and included $1 million earmarked for tracking minutes statewide and supporting physical education instruction training.

Recently, the coalition came full circle and mobilized locally again because Portland School District (the state's largest district) proposed elimination of all physical education specialists from elementary and middle school. PEAK rallied to "Save Portland PE." Business and corporate entities like Nike, Oregon Public Health Institute, and the Portland Trailblazers helped ramp up their advocacy efforts through social media and paid advertisements. Together with a strong citizen voice, they greatly reduced cuts and worked with federal legislators to acquire Federal Stimulus money supporting physical education.

Cleveland's status as a physician helped when speaking to legislators, who value input from the medical community. Some legislators responded poorly to physical education professionals who testified believing they were simply trying to save their jobs. Cleveland presented data about the value of physical education and the importance of prevention, tying things to health care costs, and other values. He also reminded people that this is a social justice issue as the most disadvantaged students receive the least amount of PE.

While this was clearly a group effort, Cleveland believes policy work is one of the most important things he has done as a physician. In his work as a staff physician in Legacy Emergency Departments, he knew he wasn't dealing with the underlying problems that brought people there. As an advocate for physical education, he can help ensure that hundreds of thousands of children have the opportunity to be healthy and equipped to be active for life.

CHICAGO, ILLINOIS

In Chicago, physicians have played a key role in the successes of the Consortium to Lower Obesity in Chicago Children (CLOCC; www.clocc.net). CLOCC has been recognized as one of the largest and most effective obesity-centered strategic alliances in the country since it was formally created in late 2002. The work of two physicians is at the roots of CLOCC's successes. Dr. Katherine Kaufer Christoffel launched CLOCC with support from a local foundation (the Otho S.A. Sprague Memorial Institute) and housed the offices of the coalition within Children's Memorial Hospital. A few months later, Dr. Matt Longjohn became CLOCC's founding executive director. Together, these two advocates worked to build a coalition that has ultimately engaged dozens of physicians at multiple stages of medical education and practice (i.e., medical students, residents, private and academic practitioners, clinical researchers). As a result, numerous CLOCC-sponsored projects and studies have centered on improving the quality and connectedness of clinical interventions by engaging physicians in public education, community networking, and advocacy activities.

The effectiveness of this large partnership, which was built on the need to connect physicians and medical providers into all other sectors of Chicago life for the purposes of preventing childhood obesity, is evident. CLOCC's work has involved a total of over 3000 individuals from more than 1200 organizations over the past 9 years. Consortium partners, often physician leaders, have engineered numerous policy and environmental changes at the city and state level in that time. A great deal of community-based research, capacity building, and community organizing has also been funded because of CLOCC's efforts. In just 1 year of its work (2004–2005), CLOCC organized state-level advocacy efforts to design and advocate for five new laws in Illinois. For the past 5 years, CLOCC has facilitated the work of the City of Chicago's Interdepartmental Task Force on Childhood Obesity. CLOCC is currently the fiduciary agent for the city's 2-year, $5 million Communities Putting Prevention to Work project, which was funded by the Centers for Disease Control and Prevention. As a group, physicians involved in CLOCC have been an important voice within its efforts to curb pediatric obesity in Chicago.

MAKING THE MOST OF YOUR ENGAGEMENT

As the examples mentioned earlier demonstrate, there is a spectrum along which physicians can become engaged in strategic alliances to effectively connect their clinical work (and patients) to advocacy and health-promoting resources. In order to most effectively partner with a community-based strategic alliance, it's important to understand the key characteristics identified as helping strategic alliances to be successful [22–27]. These include components of how the alliance is structured and functions (group processes) and the way they carry out the work (action planning, implementation, and evaluation).

GROUP PROCESS

In terms of group process, it is important for the partnership to develop a common mission and vision. The group will need leadership with formally defined roles and responsibilities, as well as explicit problem solving, decision making, and conflict management structures. To be most effective,

the partnership should include a wide variety of organizations from different sectors, racial/ethnic backgrounds, and geographic areas/neighborhoods. Any group that is likely to be affected by the partnership's activities should have a place at the table. As new partners join, there need to be processes in place to share the group decision making, problem solving, and conflict management strategies. Meetings should be structured with an agenda, an opportunity to review the minutes of the previous meetings, and time should be allowed for questions and discussion. Communication between meetings should reflect the desires of the group in terms of the frequency and the method of communication (e.g., email, phone). Depending on the level of collaboration, there may need to be resources allocated to ensure that the alliance can be appropriately managed.

In terms of action planning, implementation, and evaluation, it is important that the alliance partners thoroughly assess the issue to be addressed and develop a common understanding of the implications of the assessment. From there, an action plan can be developed, implemented, and evaluated. This may involve individuals who are part of the alliance or may require the hiring of new staff or consultants. The types of activities might include anything from monthly meetings to development of new initiatives to create policies or environmental changes. The activities chosen should reflect the alliance's stage of development. It is often best to start small and focus on sharing of information and contributions that each organization can make prior to planning large interorganizational initiatives.

CHALLENGES

There are certainly many challenges that strategic alliances face, which can minimize their success. First, if any of the aforementioned factors for success are absent, the challenges are greater. In addition, it is important for alliances to consider the contextual and structural factors that can impede success [28]. For example, the way municipal structures have been historically created can cause challenges for regional policy change. Similarly, school district policies may have restrictions that impede easy policy or environmental changes. Moreover, economic and racial disparities may hinder policies from being truly inclusive.

Keeping these attributes and challenges in mind, there are many places one can start to become involved in policy and environmental change work to improve access to healthy eating and active living.

ADVOCACY STARTS AT HOME

As physicians and primary care providers see the community as part of the equation for their patients' health and wish to extend their reach, an easy first step is to assess the immediate environment of the clinic or practice. Consider ways to show consistency when advocating for a healthier environment. Are there policies that can be institutionalized to remove soft drinks from the waiting room? Is the importance of physical activity and eating healthier food consistently shared with patients, and is material readily available (perhaps produced by local partnerships) about where to be active and find fresh fruits and vegetables in the community? Is there a policy within the medical institution that establishes advocacy for obesity prevention as an expected part of the job?

KNOW THE NEIGHBORHOOD ENVIRONMENTS

Primary care providers, especially those serving low-income communities and areas of high health disparities, are faced daily with the consequences of poor environments. However, physicians are unlikely to have a full understanding of the specific nature of these environments. It may be helpful to ask clients where they shop for fruits and vegetables, where their children play, how they get to work. Better yet, physicians may benefit by walking the neighborhoods and communities to experience the environments first hand. Walking from a school to a park allows one to immediately understand safety concerns, dangerous traffic, and the saturation of unhealthy food retail that lines the street, for example. Some new medical schools are training residents about the social determinants of health. Florida International University's College of Medicine in Miami, for example, is utilizing a community-based medical curriculum, pairing each medical student with a neighborhood in the Miami area and a family from that neighborhood. Their goal is improve the health of the family and the quality of life in the neighborhood [29].

SUPPORTING PARTNERSHIPS

There are many opportunities for providing testimonials or advocating for change without being the lead champion for the cause. Community engagement is an important component of the work for multidisciplinary partnerships. During public meetings, it is helpful to have a credible, trusted voice of authority supporting the vision and goals of the group or sharing relevant data and experiences that build the case for change. Testimonials before policy makers at the local, regional, and state level are also powerful ways to be involved.

Physicians are also in a position to help leverage the medical community, talk to hospital administrators, health insurers, and clinics about their own policies as well as their potential role in supporting community partnerships. Physicians might refer patients to community resources or programs that are operating in their neighborhood as a way to support partnerships while encouraging behavior changes. In addition, alliances often need to disseminate information to community members, need in-kind or financial support, evaluation assistance, or other support that aligns well with the strengths of physicians and related institutions.

LEADING COMMUNITY CHANGE

As stability in a practice increases and time becomes more flexible, some physicians are taking the lead around this type of policy and environmental change work. Strong existing

connections are leveraged to develop a partnership that can expand over time. With strong partners, physicians can help organize and step up as credible spokespersons without being consumed by the effort. Drawing on institutional supports and other community leaders helps distribute the load and ensure that the strengths of all partners are well utilized.

SUMMARY

Physicians can play a key role with strategic alliances in creating environmental and policy changes that are critical for the health and well being of their patients and the community as a whole. Furthermore, there is growing recognition that this involvement is a professional responsibility. Participation can be achieved through a variety of roles and levels of involvement. Regardless of the role, it is helpful to be aware of how alliances can be structured to be most effective in accomplishing their goals. The support of physicians (through participation and/or leadership) can greatly enhance the success of strategic alliances, and their community-based work can also extend the physician's ability to advocate for the health of their patient population and increase the effectiveness of a physician's counseling for healthy behaviors.

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133 Obesity and Health

James M. Rippe, MD and Theodore J. Angelopoulos, PhD, MPH

CONTENTS

Definitions of Overweight and Obesity 1558
Adults 1558
Children and Adolescents 1558
Health Effects of Obesity 1559
Role of Adipocytes 1559
Health Effects of Obesity in Adults 1559
Obesity and Diabetes 1559
Obesity and Heart Disease 1559
Obesity and Cancer 1560
Obesity and MetS 1560
Obesity and Arthritis 1560
Obesity and Other Medical Conditions 1560
Economic Impact of Obesity 1561
Public Health Implications 1561
Public Policy and Environmental Strategies 1562
Searching for Solutions 1562
Food Environment 1562
Physical Activity 1564
Genetics 1564
Closing the Energy Gap 1564
Small Steps Approach 1564
Need for Health Care Professional Involvement 1565
Summary/Conclusions 1565
References 1565

The obesity epidemic represents an enormous global health problem affecting both developed and underdeveloped nations, both genders, and every ethnicity [1–4]. As discussed in other chapters in this section, and later in this chapter, obesity is typically defined utilizing body mass index (BMI) criteria. According to criteria from the National Heart, Lung, and Blood Institute, healthy weight range for adults is a BMI of 19–28.9 kg/m^2 and obesity is a BMI $\geq$ 30 kg/m^2. By any criteria, obesity has reached worldwide epidemic proportions. In the United States, for example, the prevalence of obesity is currently 32.2% in adult men and 35.5% in adult women [5]. In European countries, obesity ranges from 20% to 30% of the population and it is even higher in Polynesia, Australia, and South America [6]. The World Health Organization estimates that, if current trends continue, there will be 1.5 billion obese individuals worldwide by 2015 [6].

The most recent estimates from 2010 in the United States indicate that 33.8% of adults, over 66 million individuals, are obese (30 million men and 36 million women), while an additional 74 million (42 million men and 32 million women) are overweight. The prevalence of obesity has grown a shocking 40% in the past 30 years [7].

While the rate of increase in obesity has appeared to have leveled off over the past 2 years in the United States [5], these are, nonetheless, sobering data, which carry enormous health consequences. Furthermore, the prevalence of severe obesity (BMI $\geq$ 40 kg/m^2) and very severe obesity (BMI $\geq$ 50 kg/m^2) have grown disproportionately rapidly during this period of time [8].

Obesity not only carries adverse health consequences in and of itself but it is also strongly associated with multiple other metabolic abnormalities. For example, obesity is strongly and independently associated with coronary heart disease (CHD), the leading killer of both men and women in the United States [9,10]. Moreover, obesity is also associated with a number of risk factors for CHD including hypertension, dyslipidemia, diabetes, physical inactivity, and poor nutrition [11,12].

It is estimated that 80%–85% of all type 2 diabetes (T2DM) is related to obesity [13]. Obesity is associated with over 35% of cancers, and it is predicted to become the leading lifestyle-related risk factor associated with cancer in the next decade surpassing even cigarette smoking [14–16]. According to data from the Framingham Heart Study, over

50% of hypertension is associated with obesity [17] and approximately 50% of lipid abnormalities are associated with obesity [18]. The metabolic syndrome (MetS), which is strongly associated with obesity, is currently estimated to affect 25%–35% of the adult population in the United States [19]. Moreover, 35%–40% of the adult population has glucose intolerance, which is also a strong predictor of diabetes and closely associated with obesity [20].

Obesity is in many ways the quintessential lifestyle disease. It is abundantly clear that obesity is a complicated multifactorial problem resulting from numerous internal and external influences, which impact on the obese individual. It has been argued that in the United States and most of the Western world, we live in an obesogenic (some have even called it a "toxic") environment for weight gain. In addition to individual choices related to nutrition and physical activity, there are also significant impacts on the risk of developing obesity from family, culture, community, government, and world food policies [21]. Genetic influences clearly play a role since some individuals are more likely to gain weight than others and some ethnic groups (e.g., Hispanic and black women) [5] are much more affected than others, although all ethnicities and both genders are affected by obesity.

The fact that obesity represents an urgent national health imperative has been underscored by numerous evidence-based documents. For example, the Dietary Guidelines for Americans 2010 characterizes obesity as the "leading nutritional health problem" facing the United States [22]. The Healthy People 2010 document originally set a goal of limiting obesity to no more than 15% of the adult population [23]. This lofty goal can now be seen in retrospect to be wishful thinking. In the United States, we are moving rapidly away from this goal rather than toward it. The goal of reducing obesity prevalence to 15% of the adult population has also been incorporated into the Healthy People 2020 Guidelines [24].

With all this as background, it is no longer a viable option for health care professionals to remain on the sidelines as both individual practitioners and community leaders when it comes to the urgent problem of both adult and childhood obesity.

In this chapter, we will summarize some of the known evidence linking obesity to adverse health consequences. We will also briefly discuss potential initiatives and frameworks seeking solutions. The chapter will close with recommendations for individual health care professional involvement to help stem the epidemic of obesity with a particular emphasis on the interaction of healthy eating and active living as key components of energy balance.

DEFINITIONS OF OVERWEIGHT AND OBESITY

Adults

Overweight and obesity in adults are generally defined using BMI, which is a measure of weight related to height, which is also correlated to total body fat and health outcomes. The National, Heart, Lung, and Blood Institute defines healthy weight for adults as a BMI of 19–24.9 kg/m^2, overweight as a BMI of 25–29.9 kg/m^2, obesity $\geq$ 30 kg/m^2 and extreme obesity $\geq$ 40 kg/m^2 [25]. It is important to note that body fat distribution also impacts on risk of chronic disease [26–29] with abdominal obesity particularly strongly correlated with risk of diabetes and heart disease. For this reason, both waist circumference and waist to hip ratio are added in some guidelines.

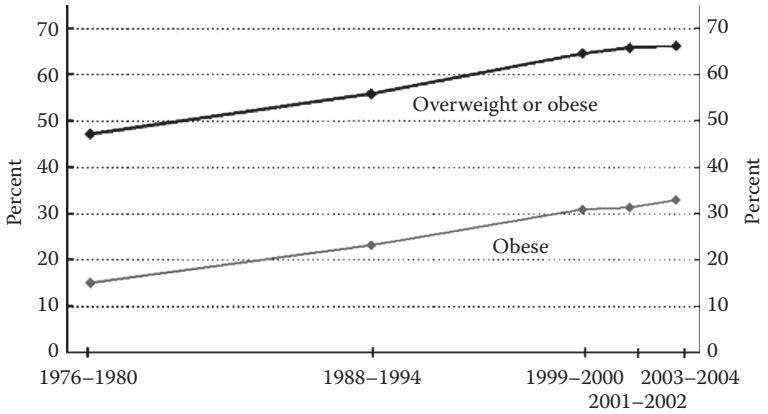
Children and Adolescents

Several different criteria are utilized in children and adolescents up to the age of 20 years to define "overweight" or "obese." The Centers for Disease Control and Prevention (CDC) uses the term "overweight" for children and adolescents with BMI at or above the 95th percentile for sex-specific BMI for age values from the 2000 CDC Growth Charts [30]. The CDC uses the term "at risk" for overweight for children and adolescents who are between a BMI of 85th and 95th percentiles. The American Medical Association and other organizations have recommended that this terminology be changed so that children and adolescents who are over the 85th percentile for BMI values be classified as "overweight" and over the 95th percentile classified as "obese" [31].

Epidemiologic data related to obesity in the United States are based almost exclusively on BMI derived from measured height and weight. The National Center for Health Statistics of the CDC conducts standardized physical examinations on large representative samples of children, adolescents, and adults through the National Health and Examination Survey Program (NHANES). NHANES includes oversampling of African Americans, Mexican Americans, as well as other groups to improve estimates for these groups. The description of obesity rates and trends in the United States presented in this chapter is based on NHANES data.

Rates of overweight and obesity have risen dramatically over the past 30 years in the United States (see Figure 133.1). During this timeframe, the prevalence of obesity more than doubled in adults (from 15% to 33%), while the prevalence of obesity and overweight in children tripled (from 6% to 19%) [5,7]. Estimates from 2010 indicate that 33.8% of adults are obese and that 17% (or 12.5 million) of children and adolescents are obese [5,7]. The population rates of obesity in some segments are substantially higher, which may be a result of interactions between culture, environment, and genetics. A particularly alarming trend is the increase in extreme obesity (Grade 3; BMI $\geq$ 40 kg/m^2) [7]. Over a most recent 7–8 year span, the percent of extreme obesity in adults 20 years of age or older has increased from 4.7% to 5.7%, which equates to about 2 million additional people in the extreme obesity category in the United States [7].

There are also demographic characteristics associated with overweight and obesity. Age-adjusted prevalence rates of obesity are generally higher in older versus younger cohorts, women versus men, and in racial/ethnic groups compared to Caucasians. Approximately 35.5% of women (16.0% of female children and adolescents) and 32% of men (18.2% of male children and adolescents) were obese according to



Note: Age-adjusted by the directed method to the year 2000 US Bureau of the Census estimates using the age groups 20–39, 40–59, and 60–74 years. Overweight defined as BMI >= 25; Obesity defined as BMI >= 30.

FIGURE 133.1 Trends in adult overweight and obesity ages 20–74 years. (Courtesy of The National Center for Health Statistics, Hyattsville, MD.)

NHANES 2007–2008 [5,7]. The odds of being obese are higher in adult women than men but not related to gender in children and adolescents. Mexican Americans and non-Hispanic blacks display higher rates of obesity compared to Caucasians. The most extreme example is found in women where non-Hispanic black women had a rate of obesity exceeding adult Caucasian women by 24% (53.9% vs. 30.2%) [5,7]. Age also brings about increases in obesity, particularly for non-Hispanic Caucasian men and Hispanic females [7]. For example, the prevalence of obesity for Caucasian males between 20 and 30 years of age is 26.3% but increases to 38.4% after the age of 60 years.

HEALTH EFFECTS OF OBESITY

Role of Adipocytes

Historically, adipocytes were thought to be primarily storage sites for excess fat. Research over the past two decades, however, has demonstrated that adipocytes are, in fact, highly complicated, inflammatory, endocrine, and metabolic cells. Thus, adipose tissue essentially serves as a complex endocrine organ and a potent source of inflammatory molecules such as tumor necrosis factor-α, interleukin-6, and many others [32–35]. These complex properties of adipocytes may underlie the strong linkage between obesity and chronic metabolic conditions such as diabetes, CHD, and the MetS. Adipocytes located in the abdominal region appear to be particularly complicated and active from a metabolic and inflammatory point of view [26–29].

HEALTH EFFECTS OF OBESITY IN ADULTS

Obesity and Diabetes

An estimated 9% of Americans (26 million individuals) have diabetes, and over 79 million adults display evidence of "pre-diabetes" [36]. There is a clear association between obesity and T2DM. Individuals with a BMI of >35 kg/m^2 have 42.1 times the risk of T2DM in men and 93.2 times the risk in women compared to normal BMI controls. The risk of developing T2DM diabetes is elevated the longer one is obese [37–39]. A meta-analysis pooling data from 32 studies between 1966 and 2004 found that the relative risk of T2DM was 1.87, 1.87, and 1.88 per standard deviation of BMI, waist circumference, and waist to hip ratio, respectively [40].

The Nurses Health Study, which followed over 80,000 female nurses over a 16 year span, demonstrated that being overweight or obese is the single most important predictor of T2DM [41]. In another meta-analysis that studied BMI across categories (normal to overweight to obese), relative risks were 3.9 and 12.4 for overweight and obese women, respectively, and 2.4 and 6.7 for overweight and obese men, respectively [42].

The relationship between obesity and diabetes in children is also potent. In the SEARCH for Diabetes in Youth Study, it was estimated that approximately 3700 adolescents per year are now diagnosed with T2DM and that this number is increasing [43]. T2DM is now the most prevalent form of diabetes diagnosed in adolescents [44]. Insulin, fasting insulin, and insulin to glucose ratio are significantly higher in obese versus control 8–11 year olds and impaired insulin sensitivity becomes more apparent as the duration of obesity increases [45–47].

A detailed discussion of the relationship between obesity and diabetes is found in Chapters 33, 34 and 107 and has been reviewed extensively elsewhere [48].

Obesity and Heart Disease

Multiple large-scale studies have linked obesity to risk of cardiovascular disease. In a recent meta-analysis, the relative risk among obese men and women compared to normal weight men and women was 2.4 for CHD, 2.1 for hypertension, 1.5 for stroke, 1.8 for congestive heart failure, and 3.5 for pulmonary embolism [38]. Longitudinal data from the Framingham Heart Study found that age-adjusted relative risk for cardiovascular disease was 1.64 in women and 1.46 in men comparing obese to normal weight individuals.

Obesity is also associated with multiple other established risk factors for CHD including hypertension, dyslipidemia, diabetes, and an inactive lifestyle. The multiple links between obesity and heart disease as well as the risk factors for CHD is beyond the scope of the current chapter and has been reviewed extensively elsewhere [49].

Obesity and Cancer

Multiple prospective studies have established a significant association between obesity and cancer [38]. In one large, 16 year longitudinal study involving nearly one million subjects, all-cause mortality for all cancers was 62% higher in women and 52% higher in men with a BMI > 40 kg/m^2 compared to subjects with a normal BMI [50]. In another study involving 1.2 million women between the ages of 50 and 64 years, obesity was associated with significantly higher rates of 10 of the 17 most common types of cancer [51]. Current evidence suggests that obesity prevention may be more advantageous than weight loss in reducing incidence of obesity-related cancer [52]. The relationship between obesity and cancer has been extensively reviewed [53].

Obesity and MetS

MetS, which represents a clustering of risk factors related to impaired glucose and lipid metabolism is strongly associated with obesity in general and abdominal obesity in particular [54–56]. MetS is a significant risk factor for both diabetes and heart disease. Current estimates suggest that MetS is present in 25%–35% of the adult population in the United States [19]. Weight reduction by itself or occurring in combination with lifestyle changes, such as increased exercise, is associated with a significant drop in the prevalence of MetS [57,58]. Even moderate amounts of weight loss (20 lb) result in a significant reduction in the prevalence of MetS [58]. The pathophysiology of MetS and its linkage to obesity has been extensively reviewed elsewhere [59].

Obesity and Arthritis

There are strong linkages between obesity and multiple forms of arthritis, but particularly osteoarthritis [60,61]. Obesity is the leading cause of osteoarthritis in women and the second leading cause of osteoarthritis in men [61]. The linkage between obesity and arthritis appears to be partially mediated through increased pressure on weight bearing joints but also may relate to the systemic inflammation that often accompanies obesity [61]. The linkage between obesity and arthritis has been extensively reviewed elsewhere [62].

Obesity and Other Medical Conditions

Obesity is significantly associated with multiple other risk factors and diseases in both men and women. A partial listing of these conditions is found in Table 133.1. Obesity is related to multiple maternal and fetal problems in pregnancy [63–65].

TABLE 133.1
Medical Conditions Associated with Obesity

- Metabolic conditions
  - Type 2 diabetes
  - Metabolic syndrome
  - Glucose intolerance
- Cardiovascular disease
  - Coronary heart disease
  - Stroke
  - Heart failure
  - Deep venous thrombosis
- CHD risk factors
  - Dyslipidemia
  - Hypertension
  - Inflammation
  - Hypercoagulability
- Pulmonary diseases
  - Obstructive sleep apnea
  - Hypoventilation syndrome
  - Asthma
- Cancers
  - Colorectal
  - Esophageal
  - Endometrial
  - Breast (post menopausal)
  - Kidney
- Gastrointestinal diseases
  - Non alcoholic fatty liver disease
  - Gallstones (cholecystitis)
  - Gastroesophageal reflux
- Other conditions
  - Gout
  - Kidney stones
  - Osteoarthritis
  - Psychological disorders
  - Fertility and pregnancy complications
  - Erectile dysfunction

Obese individuals are also at increased risk of depression and other psychiatric disorders [66–68]. Obesity is strongly related to the increased prevalence of gallbladder disease [69,70] and obstructive sleep apnea [71]. NHANES data suggests that individuals with a BMI of ≥35 kg/m^2 lose an average of 9–13 years of life compared to normal weight individuals [72].

Obesity is also related to a number of disease of risk factors and diseases in children and adolescents [73]. Obesity is strongly related to MetS in children and adolescents [56] as well as a variety of cardiovascular complications including hypertension, left ventricular hypertrophy, dyslipidemia, and sleep apnea [74–79]. Obese children and adolescents also experience more psychological abnormalities including loneliness, poor self-perception, depression, and anxiety disorders [80–83]. Furthermore, obesity in adolescent years carries a significant increased risk of severe obesity in adulthood [84].

ECONOMIC IMPACT OF OBESITY

In addition to the enormous health toll attributed to obesity, substantial costs are being driven by the obesity epidemic. For example, in the United States, it is estimated that obesity may cost as much as $147 billion per year [85]. Some of this burden of these expenditures is shared by the government (i.e., taxpayers), while the rest is largely paid through private insurers [86]. Thus, taxes and employee insurance premiums (which are paid by all employees regardless of weight) finance most of the cost of treating obesity or its related conditions.

It is estimated that an obese individual costs a health plan 47% more in health care expenditures, and an overweight individual generates 16% more costs than healthy weight individuals [87]. During the period between 1998 and 2006, direct annual medical costs associated with obesity increased from 6.5% to 9.2% of total health costs [88,89]. This computes to obese individuals spending an average of $1429 annually in 2006 for medical care, which equates to more than 42% more annual costs compared to individuals of average weight [90].

For all of these reasons, multiple stakeholders including taxpayers, the government, employers, and employees all have significant motivation to restrain the rising costs of obesity if only for its financial impact.

PUBLIC HEALTH IMPLICATIONS

Obesity was first recognized as a public health issue by the National Institutes of Health in 1985 [91]. Recent data for the CDC indicate that obesity in the United States remains a major health problem [88,89]. Obesity now outranks both smoking and drinking alcohol in its adverse effects on morbidity and mortality as well as health costs. Obesity is associated with a 36% increase in in-patient and out-patient health care costs compared to a 21% increase in spending for smoking and excessive alcohol consumption [92]. As already indicated, the Healthy People 2010 objectives related to obesity stated the goal of reducing prevalence of obesity in adults in the United States to 15% [49]. This goal has been carried over to the Healthy People 2020 objectives. However, no state in the United States has achieved this objective [31].

One significant public health concern related to obesity is the increased risk of premature mortality. A number of investigations have clearly demonstrated that as body weight increases so does mortality from diabetes, cancer, and heart disease [51,93,94]. If the American population were able to lose its excess body weight, mortality would be reduced by 15%, which corresponds to 3 years in average life expectancy for every citizen in the United States [93].

As already indicated, obesity is a complicated chronic condition with multiple underlying causes including, lifestyle, culture, genetics, socioeconomic, and psychological factors all contributing. For this reason, obesity should be viewed as a chronic condition similar to heart disease and diabetes and its treatment must be multifactorial, focusing not only on the individual level but also from the public health perspective of the community and national level.

A comprehensive and coordinated approach will be required to reverse the epidemic of obesity in the United States including policy and environmental changes to transform communities to support and promote healthy lifestyle choices for all U.S. citizens. The CDC recently convened an expert panel, which identified 24 recommended strategies for obesity prevention together with suggested measurements for each strategy that communities can utilize to track progress [95]. A list of these strategies is found in Table 133.2. To help accomplish this, the strategies together with implementation and measurement guide will be published and made available through the CDC website: http://www.cdc.gov/nccdphp/dnpao/publications/index.html.

In addition to the CDC initiative, multiple other private and governmental initiatives have been announced in an attempt to reduce the health impact of obesity in general and childhood obesity in particular. For example, First Lady Michelle Obama's "Let's Move" campaign has established the goal of ending childhood obesity within the next generation [96].

TABLE 133.2
CDC Task Force Recommendations for Steps That Communities Could Take to Help Combat Obesity

- Increase availability of healthier food and beverage choices in public service venues
- Improve availability of affordable healthier food and beverage choices in public service venues
- Improve geographic availability of supermarkets in underserved areas
- Provide incentives to food retailers to locate in and/or offer healthier food and beverage choices in underserved areas
- Improve availability of mechanisms for purchasing foods from farms
- Incentives for the production, distribution, and procurement of foods from local farms
- Restrict availability of less healthy foods and beverages in public service venues
- Institute smaller portion size options in public service venues
- Limit advertisements of less healthy foods and beverages
- Discourage consumption of sugar-sweetened beverages
- Increase support for breastfeeding
- Require physical education in schools
- Increase the amount of physical activity in PE programs in schools
- Increase opportunities for extracurricular physical activity
- Reduce screen time in public service venues
- Improve access to outdoor recreational facilities
- Enhance infrastructure supporting bicycling
- Enhance infrastructure supporting walking
- Support locating schools within easy walking distance of residential areas
- Improve access to public transportation
- Zone for mixed-use development
- Enhance personal safety in areas where persons are or could be physically active
- Enhance traffic safety in areas where persons are or could be physically active
- Communities should participate in community coalitions or partnerships to address obesity

Other efforts such as the collaboration between the William J. Clinton Foundation and numerous health care and commercial organizations in the "Partnership for Healthy America" have articulated similar goals and an increased sense of urgency [97].

PUBLIC POLICY AND ENVIRONMENTAL STRATEGIES

Policies and policy-informed environmental supports will all be required on a national, state, and local level to promote active living, healthy eating, and the prevention of obesity. These strategies have been discussed by Heath elsewhere [98]. Heath divides these public policy and environmental initiatives into the following four areas:

- Agricultural and food supply policies that support healthy eating
- Health care service policies
- Educational and school-based policies
- Urban design, land use, and transportation policies for active living/health eating

Initiatives in all these areas will be required to improve energy balance behaviors for active living and healthy eating to help combat the obesity epidemic.

Searching for Solutions

Given the complexity of underlying causes for the obesity epidemic, comprehensive solutions will be required to ameliorate this problem. Such approaches must involve multiple levels of influencers and involve multiple areas of intervention. One framework for approaching obesity and weight management has been proposed by the Dietary Guidelines Advisory Committee [99]. Figure 133.2 depicts the socioeconomic framework offered by the Dietary Guidelines Advisory Committee (DGAC) for approaching the obesity epidemic. This framework stresses that maintaining proper energy balance is complicated and factors influencing this issue are multiple and interconnected, thus mandating a multifaceted approach to amelioration.

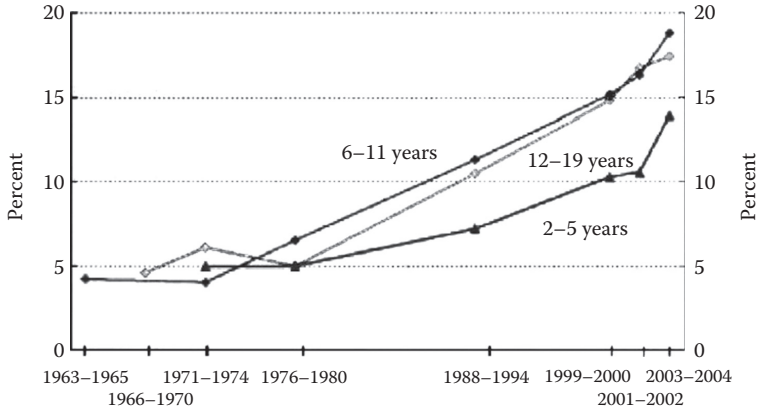
Food Environment

A comprehensive approach to the modern food environment will clearly be required to help solve the global obesity problem. In the United States, for example, the average caloric consumption has dramatically increased over the past 40 years [100]. As depicted in Figure 133.3, the average daily caloric consumption in the United States has increased from 2057 kcals in 1970 to 2674 kcals in 2008.

While significant increases have occurred in virtually every category of food, the increases are particularly prominent in the areas of added fats and oils, flour, and cereal products [100]. It has been argued by Swinburne et al. [101] that increased caloric consumption in the United States during the past four decades alone is more than sufficient to explain the U.S. epidemic of obesity. Other investigators, however, have challenged this notion and argue that other aspects of the environment such as diminished physical activity have also contributed significantly to the obesity epidemic [102,103].

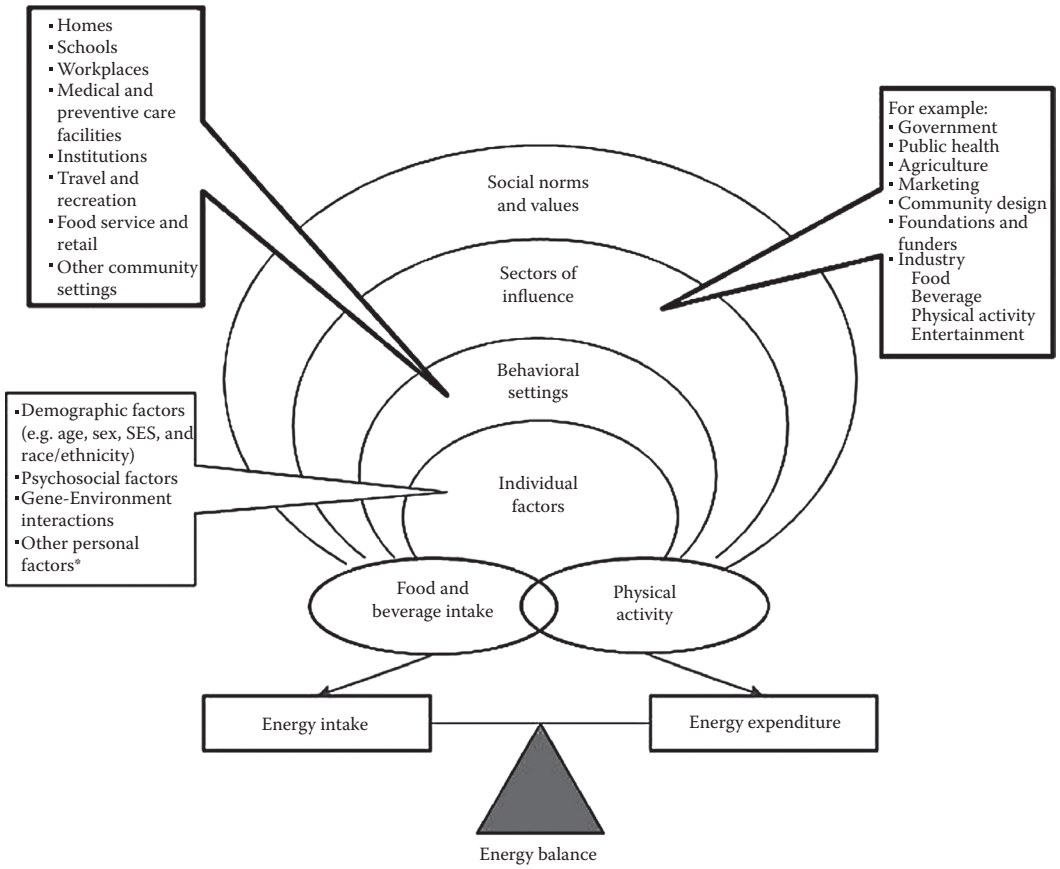
It is clear, however, that individuals in the United States are not adhering to the guidance from various iterations of the Dietary Guidelines [104]. As shown in Figures 133.4 and 133.5, the American population is falls far short when it comes to fruit and vegetable and dairy consumption compared to MyPyramid recommendations [105].

It has also been argued that both the increased number of meal occasions and increase in portion sizes both play significant roles in the obesity epidemic in the United States [106]. While the number of meal occasions appears to be relatively stable over the past 25 years [107], the number of calories consumed in snacking has increased by approximately 25% during this period of time [107]. There is ongoing debate about whether snacking per se significantly contributes to the weight gain in the American



Note: Overweight is defined as BMI >= gender- and weight-specific 95th percentile from the 2000 CDC Growth Charts.
Source: National Health Examination Surveys II (ages 6–11) and III (ages 12–17), National Health and Nutrition Examination Surveys I, II, III and 1999–2005, NCHS, CDC.

FIGURE 133.2 Trends in childhood overweight. (Courtesy of The National Center for Health Statistics, Hyattsville, MD.)



*Note: Other relevant factors that influence obesity prevention interventions are culture and acculturation; biobehavioral interactions; and social, political, and historical contexts.
Sources: Adapted from IOM (2007); CDC (2006).

FIGURE 133.3 Factors influencing obesity and weight gain. (From Centers of Disease Control and Prevention, Division of Nutrition, Physical Activity, and Obesity, State Nutrition, Physical Activity and Obesity Program: Technical Assistance Manual, Available at: http://www.cdc.gov/obesity/downloads/TA_Manual_1_31_08.pdf- pg 41 of the document, Accessed: October 28, 2011, January 2008.)

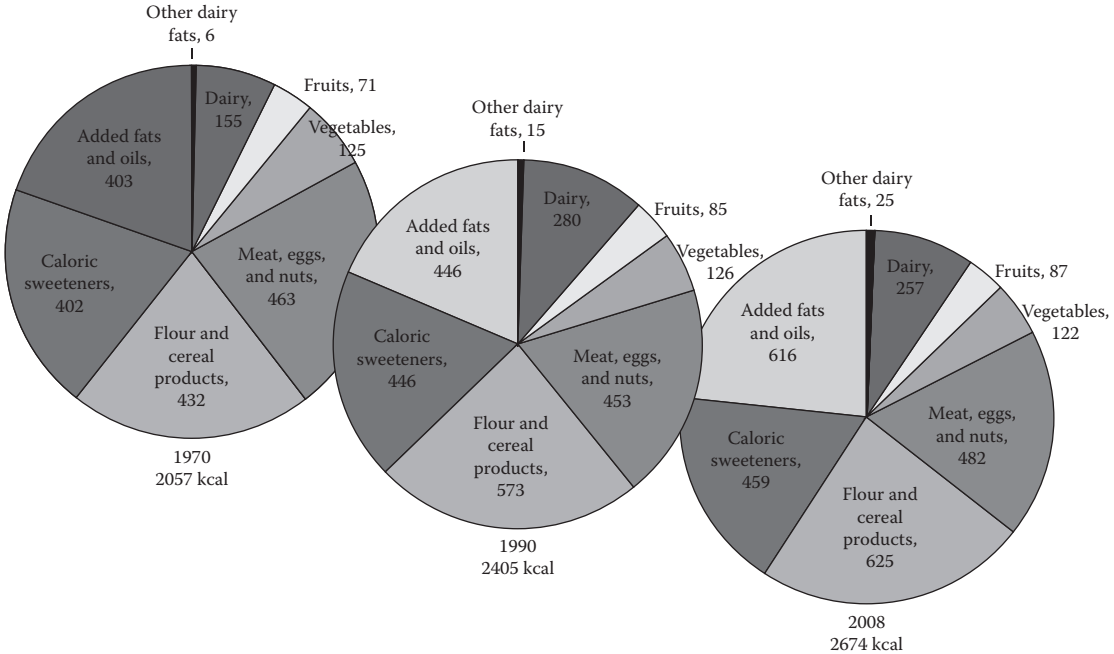


FIGURE 133.4 Average daily per capita calories from the U.S. food availability in 1970, 1990, and 2008, adjusted for spoilage and other waste. (Courtesy of ERS Food Availability (Per Capita) Data System, http://www.ers.usda.gov/Data/FoodConsumption/)

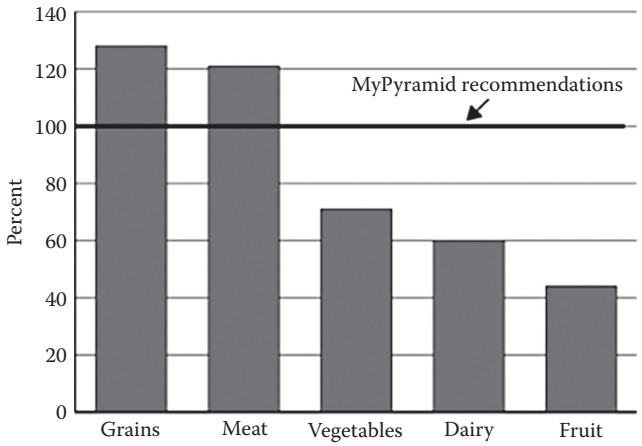


FIGURE 133.5 The loss-adjusted per capita food availability in comparison to MyPyramid recommendations for a 2000-cal diet. Availability of grains (128%) and meat (121%) were above recommendations, while availability of vegetables (71%), dairy (60%), and fruit (44%) were below recommendations. *Note*: Based on a 2000-cal diet. (Courtesy of USDA, Economic Research Service, Food Availability (Per Capita) Data System, Available at http://www.ers.usda.gov/AmberWaves/March10/PDF/TrackingACentury.pdf)

TABLE 133.3
Changes over Time in the Average Portion Size of Selected Food Items Sold in the U.S. Marketplace

	Portion Size (Year)	Portion Size (Year)	Percent Increase
Beer, can	12 oz (1936)	8–24 oz (2002)	33–100
Beer, bottle	7 oz (1976)	7–40 oz (2002)	0–471
Chocolate bar, milk chocolate	0.6 oz (1908)	1.6–8 oz (2002)	167–1233
French fries	2.4 oz (1955)	2.4–7.1 oz (2002)	0–196
Hamburger	3.9 oz (1954)	4.4–12.6 oz (2002)	13–223
Soda, fountain	7 oz (1955)	12–42 oz (2002)	71–500
Soda, bottle, and can	6.5 oz (1916)	8–34 oz (2002)	23–423

Source: From Report of the DGAC on the Dietary Guidelines for Americans, 2010, available at www.cnpp.usda.gov; Young, L.R. and Nestle, M., *J Am Diet Assoc*., 103, 231, 2003.

population [108,109]. There is general agreement, however, that increases in portion size have contributed significantly to overall increase in caloric consumption [110]. As demonstrated in Table 133.3, portion sizes of common foods sold in the United States have increased between 100% and 1000% over the past 50 years [110].

While these data support that the food environment does not currently support healthy eating patterns in the United States, solutions to this issue will require participation of many stake holders in the food system including not only individuals themselves but also supermarkets, the commercial food industry, and farmers.

Physical Activity

The U.S. population remains far too sedentary. The Dietary Guidelines for Americans 2010 concluded that there was "strong, consistent evidence" that physically active people are at reduced risk for becoming overweight or obese." [22] In addition to the benefits related to prevention of obesity and assistance in long-term weight maintenance, multiple other benefits accrue to physically active people. These have been summarized in detail in the Physical Activity Guidelines for Americans 2008 [104].

Genetics

There is no question that genetics play an important role in the modern obesity epidemic. Most investigators conclude that about 40% of obesity may be related to an individual's genetic make-up [111–113]. The interaction between genetic make up and the environment plays a particularly prominent role. A detailed discussion about obesity and genetics is beyond the scope of this chapter and has been reviewed extensively elsewhere [111–114].

While specific areas of the genome controlling food intake, physical activity, and weight gain are under active investigation, this work is far from ready for clinical application. Researchers anticipate, however, a time when genetic research may yield important information to help make issues of weight control more individualized and precise.

Closing the Energy Gap

It has been argued by Blackburn et al. that health care professionals should focus first on individuals with extreme obesity (BMI of $\geq$40 kg/m^2) since this is the segment of the obese population, which is most rapidly increasing [115]. These investigators have put forth the concept that interventions for obese individuals should address the "energy gap."

By their estimates, an energy gap of approximately 400 kcals per day exists currently in the United States, which was not present in the 1970s. These investigators further suggest that an approach involving improved dietary composition, calorie restriction, and increased physical activity as key components of a comprehensive lifestyle intervention to close this energy gap.

Small Steps Approach

A recent task force report from the American Society of Nutrition concluded that current initiatives designed to combat obesity have not succeeded in reversing the obesity epidemic [116]. An alternative strategy was presented by this panel based on promoting small changes in physical activity and nutrition to prevent further weight gain rather than focusing on weight loss. Such approaches are supported by a variety of lines of evidence and appear to hold some promise to help combat obesity.

NEED FOR HEALTH CARE PROFESSIONAL INVOLVEMENT

Given the severity of the obesity epidemic and its potential significant adverse health consequences, it is critically important that health care professionals become actively involved and knowledgeable in multiple aspects of this issue. Clearly, this is an area where components of lifestyle medicine will play critically important roles. After all, the goal of *Lifestyle Medicine* is to help people understand how their daily habits and practices impact on their short- and long-term health and quality of life and their likelihood of developing chronic diseases such as obesity.

As we have already indicated, obesity represents the quintessential lifestyle disease. It carries significant health risk both to individuals and to our population as a whole. It is, therefore, incumbent upon health care providers to take actions now. Some specific steps that individuals and clinicians can make are outlined by Utter et al. [117] who offer the following recommendations:

Health care providers and medical clinicians should counsel their patients to

- Eat more fruits and vegetables and fewer foods high in fat and sugar. See http://www.choosemyplate.gov/
- Drink more water instead of sugary drinks
- Limit TV watching in children to less than 2 h a day and do not put a TV in their room at all
- Support breastfeeding
- Promote policies and programs at school, at work, and in the community that make the healthy choice the easy choice. This includes policy and environmental supports for both healthy eating and active living.
- Try going for a 10-min brisk walk, 3 times a day, 5 days a week [117]

SUMMARY/CONCLUSIONS

There is no longer any serious doubt that we are in the midst of a worldwide pandemic of obesity. Both adult and childhood obesity represent health problems for all nations. Obesity is strongly linked to a variety of co-morbidities including diabetes, heart disease, cancer, the MetS, and arthritis. Obesity also results in an enormous psychological and financial burden both for its individual sufferers and for the health of every nation. For all of these reasons, it is incumbent for health care professionals to become knowledgeable about and assist in the treatment not only of individual patients who are obese but also help influence public health, public policy, and environmental changes to provide a multifaceted approach to this major health problem.

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ISBN: 978-1-4398-4542-4
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