Nutrition and Health
Series Editors: Adrianne Bendich · Connie W. Bales

Norman J. Temple
Ted Wilson
David R. Jacobs, Jr.
George A. Bray *Editors*

Nutritional Health

Strategies for Disease Prevention

Fourth Edition

Humana Press

Nutrition and Health

The Nutrition and Health series has an overriding mission in providing health professionals with texts that are considered essential since each is edited by the leading researchers in their respective fields. Each volume includes: 1) a synthesis of the state of the science, 2) timely, in-depth reviews, 3) extensive, up-to-date fully annotated reference lists, 4) a detailed index, 5) relevant tables and figures, 6) identification of paradigm shifts and consequences, 7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, 8) suggestions of areas for future research and 9) balanced, data driven answers to patient/health professionals questions which are based upon the totality of evidence rather than the findings of a single study.

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Norman J. Temple • Ted Wilson
David R. Jacobs, Jr. • George A. Bray
Editors

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Editors
Norman J. Temple
Centre for Science
Athabasca University
Athabasca, AB, Canada

David R. Jacobs, Jr.
Division of Epidemiology
and Community Health
University of Minnesota School
of Public Health
MINNEAPOLIS, MN, USA

Ted Wilson
Department of Biology
Winona State University
Winona, MN, USA

George A. Bray
Pennington Biomedical Research Center
Louisiana State University
Baton Rouge, LA, USA

ISSN 2628-197X ISSN 2628-1961 (electronic)
Nutrition and Health
ISBN 978-3-031-24662-3 ISBN 978-3-031-24663-0 (eBook)
https://doi.org/10.1007/978-3-031-24663-0

This Humana imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To Valentina

Norman J. Temple

My special thanks to Don Beitz, Bridget Cassady, Sarah Baker, Stephanie Hunter, Megan Settell, Jessica Szczepanski, and many others. You remind me that there are always exciting people to help with the exploration of nutritional health. Also my special thanks to Karen, Dirk, Jack, and Moki.

Ted Wilson

To my children, Stephen, Hank, and Adam, who are a blessing in my life.

David R. Jacobs, Jr.

Mitzi my companion and best friend for 70 years and to my children.

George A. Bray

Foreword

The science of nutrition has evolved exponentially in the past century. From the chemical characterization of molecules in food, to the biological significance of foods, and the position of food in sustainable development, the areas covered are expansive. Given that food consumption sustains life, the concept of nutritional health has also come to encompass disease prevention. This comprehensive text led by eminent Canadian and US scientists provides updated reviews from a wide range of authors on key areas of nutritional health and strategies for disease prevention.

An important emerging concept that runs through this text is that of food synergy. It reflects the appreciation of food as originally having a biological footprint, sourced either from plants or animals. The natural composition of foods reflects this footprint, such that nutrients do not exist in isolation but rather as part of a whole system, as indeed is the case of nutrient function within the human body. This understanding adds a level of complexity: the interdependence between nutrients, foods, and whole dietary patterns, bearing in mind the total diet delivers the complete nutritional package.

In turn, challenges for nutrition science emerge, reflected in evolving research methods and in translation to policy and practice. An important starting point is measuring what people eat and making sense of the associations with health outcomes. The first section of this text provides a thoughtful overview of the challenges posed, in particular for epidemiology and dietary assessment methodology. This section of the book also addresses the primary concern of nutrition in disease prevention: the double burden of malnutrition resulting from under- and overconsumption of food. It goes on to expose the significance of the food system as nutritional problems are played out, particularly for Indigenous communities on the American continents.

Focusing on specific areas of the diet–disease interface helps identify the dietary components that can be targeted in nutrition interventions. The work begins at conception through to the development of disorders and chronic disease itself. In this section of the text, we learn that obesity, which remains at the core of many subsequent problems, is a "chronic relapsing" condition that is still far from being solved. An appreciation of the influence of adipose tissue on the biological system has helped in the development of new therapies, but prevention remains the primary goal. Other section contributors take various approaches to review the relevant nutrition science. As the topic of lipids has been under study for many decades, there is a large weight of evidence available for review. This leads to advisory conclusions.

Specific foods, beverages, and diets have also attracted attention from recent advances in nutrition science. For example, with evidence suggesting that plant-based diets may be protective, unique plant components (phytochemicals) have come under scrutiny, particularly for their antioxidant potential. The chapter on this topic, however, reminds us that, as with vitamins, these phytochemicals underpin the integrity of plant foods. Knowing about them primarily supports the health promotion message of eating more fruits and vegetables in a plant-based diet. Still, translating the evidence on healthy diets remains one of the challenges of health promotion programs. The text appropriately finishes here with the recognition that individual behavior change is only part of the picture. Opinions are presented on a number of strategies for influencing the food environment in which consumers can make healthier dietary choices.

Looking to the future, the central concept of food synergy continues to thread through the chapters. As an integrative concept, food synergy sits well with cutting edge areas of nutritional endeavors that link to a range of scientific disciplines, from genetics and immunology to sustainable development. For example, exciting new knowledge of the gut microbiome introduces many possibilities for disease prevention. In the related chapter, we learn of the impact on health of this "body-specific ecosystem" by individual food components (in particular carbohydrate and fiber), bearing in mind that overall positive influences are achieved by dietary patterns. On a much broader scale, the "global food ecosystem" reflects the dominant types of foods consumed in dietary patterns, which in turn can have a significant impact on planetary health. The related chapter introduces another conceptual framework, Environmental Nutrition, which connects the components of the food system to that of the natural world and human societies. This "big picture" helps us to see where the various strands of nutrition science can make their contribution.

The presence of multiple stakeholders, let alone advances in science and technology, creates challenges for contemporary nutrition science, all deserving of commentary which can be found at the end of this text. The supporting examples that set the context relate largely to North America, but as nutrition science is universal and food trade is global, there are implications. At the heart of any shared enterprise is communication, in this case coupled with the need for clear messages relating to food and health. The search for common ground is an important initial goal. "Thinking food first" and taking its biological role seriously will help guide the way. *Nutritional health: Strategies for Disease Prevention* provides a very useful reference text for those keen to make the journey.

School of Medical, Indigenous and Health Sciences, Faculty of Science, Medicine and Health, University of Wollongong
Wollongong, NSW, Australia

Linda C. Tapsell

Preface

Nutrition science has traveled a long and bumpy road. The following four quotes illustrate this.

George Bernard Shaw said "Everything I eat has been proved by some doctor or other to be a deadly poison, and everything I don't eat has been proved to be indispensable for life. But I go marching on."

Herman Boerhaave (1668–1738) was a great Dutch physician. One story is that he left a book in which he had set out all the secrets of medicine. All the pages of the book were blank except for the one in which it was written: "Keep the head cool, the feet warm and the bowels open."

It was not so long ago that vegetarians were seen as cranks. Here is what George Orwell had to say on this in *The Road to Wigan Pier*, written in 1936:

> I have here a prospectus [from a socialist summer school] which… asks me to say 'whether my diet is ordinary or vegetarian'. They take it for granted, you see, that it is necessary to ask this question. This kind of thing is by itself sufficient to alienate plenty of decent people. And their instinct is perfectly sound, for the food-crank is by definition a person willing to cut himself off from human society in hopes of adding five years on to the life of his carcass; this is a person out of touch with the common humanity.

Drummond and Wilbraham published a seminal book entitled *The Englishman's Food* in 1939. Jack Drummond was a major nutrition authority in the 1920s and 1930s. They wrote:

> So much precise research has been done in the laboratory and so many precise surveys have been made that we know all we need to know about the food requirements of the people….The position is perfectly clear-cut [with respect to Britain].

It would be foolhardy to believe that people today are more accurate in their predictions than their folks. Indeed, it is undeniable that there is much confusion among both the public and health professionals about what and how much to eat. A simple walk through the self-help section of a book store will confirm the existence of many differing opinions of what "preventive nutrition" is all about, many verging on quackery and others built upon solid facts.

The first edition of *Nutritional Health* was published in 2001, the second edition in 2006, and the third edition in 2012. An overview of nutrition science in the third decade of the twenty-first century reveals that much water has flown under the bridge of the advancing river that is nutrition research and practice. At the same time, cultural change at a global, national, and

regional level means that our nutrition habits will continue to evolve. We see this most clearly with the huge numbers of new foods that are continually appearing in supermarkets. Another indicator of the rapid pace of change is the hundreds of new "breakthrough" diet and health books that are published every year. With these large accumulations of developments in

the field of nutrition, the need for a new edition of this book is obvious.

During the last century of nutritional advancement, we have frequently been faced with great opportunities that were brilliantly disguised as insoluble problems. Perhaps we are biased but in our eyes problems associated with nutrition are among the most exciting of those in the life sciences.

With a scattering of brilliant exceptions, until the 1970s few gave serious consideration to the notion that our diet plays an important role in chronic diseases such as heart disease and cancer. Today, we have a vastly greater understanding of the role of diet in disease. We know, for example, that the risk of developing heart disease, cancer, obesity, and type 2 diabetes is affected by foods such as whole grain cereals, fruits, vegetables, the kinds of meats that are eaten, and the beverages consumed.

Our vastly improved nutrition knowledge gives us the capability of preventing a sizable fraction of the chronic diseases that afflict the people of our world, but only if these discoveries can be translated into effective action at the population level. In the words of Confucius: "The essence of knowledge is that, having acquired it, one must apply it." But, ironically, despite overwhelming evidence that nutrition has such enormous potential to improve human well-being—at modest cost—there is still a chasm between nutrition knowledge and its full exploitation for human betterment.

Nutritional Health endeavors to address the needs of those who would most benefit from up-to-date information on key areas in the field of nutrition. Accordingly, this book contains chapters by experts in a diverse range of nutrition-related areas. Our aim is not so much to cover all the leading edges of nutrition but rather to discuss recent thinking and discoveries, especially in relation to topics that have the greatest capacity to improve human health and nutritional implementation.

At risk of oversimplifying, the chapters of this book can be divided into two main groups as follows:

1. Those that present the current state of knowledge on topics that have been on the radar of nutrition scientists for a decade or longer. Each of these chapters includes important information on recent developments. Chapters (or sections of chapters) in this area include those on research methods, obesity, heart disease, cancer, phytochemicals, the health effects of alcoholic and nonalcoholic beverages, functional foods, the Mediterranean diet, front-of-package food labels, the importance of government policy, and genetically modified organisms.
2. Those that present information on emerging trends. Chapters (or sections of chapters) in this area include: food synergy, genomics and gene-based personalized nutrition, the gut microbiome, and food sustainability.

Some readers may disagree with some of the opinions presented, but differences of opinion in the field of nutrition are unavoidable. Owing to the constant changes in our diet, nutrition is by nature in constant dynamic flow, as are our opinions of what constitutes the best nutritional habits. The views expressed in *Nutritional Health* are in many cases particular interpretations by the authors of each chapter on their areas of specialization.

Athabasca, AB, Canada — Norman J. Temple
Winona, MN, USA — Ted Wilson
Minneapolis, MN, USA — David R. Jacobs, Jr.
Baton Rouge, LA, USA — George A. Bray

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Editors and Contributors

About the Series Editors

Adrianne Bendich Ph.D., FASN, FACN, has served as the Nutrition and Health Series Editor for more than 25 years and has provided leadership and guidance to more than 200 editors that have developed more than 90 well-respected and highly recommended volumes in the Series.

In addition to *Nutritional Health 4th Edition* edited by Norman J. Temple, Ted Wilson, David R. Jacobs, Jr., and George A. Bray, the newest editions published from 2012 to 2023 include:

Nutritional Anemia, edited by Crystal Karakochuk, Michael B. Zimmermann, Diego Moretti, and Klaus Kraemer, 2023

Nutrition Guide for Physicians and Related Healthcare Professions, Third Edition, edited by Ted Wilson, Norman J. Temple, and George A. Bray, 2022

Nutrition and Infectious Diseases: Shifting the Clinical Paradigm, edited by Debbie Humphries, Marilyn Scott, and Sten H. Vermund, 2020

Nutritional and Medical Management of Kidney Stones edited by Haewook Han, Walter Mutter, and Samer Nasser, 2019

Vitamin E in Human Health edited by Peter Weber, Marc Birringer, Jeffrey B. Blumberg, Manfred Eggersdorfer, and Jan Frank, 2019

Handbook of Nutrition and Pregnancy, Second Edition, edited by Carol J. Lammi-Keefe, Sarah C. Couch, and John P. Kirwan, 2019

Dietary Patterns and Whole Plant Foods in Aging and Disease, edited as well as written by Mark L. Dreher, Ph.D., 2018

Dietary Fiber in Health and Disease, edited as well as written by Mark L. Dreher, Ph.D., 2017

Clinical Aspects of Natural and Added Phosphorus in Foods, edited by Orlando M. Gutierrez, Kamyar Kalantar-Zadeh, and Rajnish Mehrotra, 2017

Nutrition and Fetal Programming, edited by Rajendram Rajkumar, Victor R. Preedy, and Vinood B. Patel, 2017

Nutrition and Diet in Maternal Diabetes, edited by Rajendram Rajkumar, Victor R. Preedy, and Vinood B. Patel, 2017

Nitrite and Nitrate in Human Health and Disease, Second Edition, edited by Nathan S. Bryan and Joseph Loscalzo, 2017

Nutrition in Lifestyle Medicine, edited by James M. Rippe, 2017

Nutrition Guide for Physicians and Related Healthcare Professionals, Second Edition, edited by Norman J. Temple, Ted Wilson, and George A. Bray, 2016

Clinical Aspects of Natural and Added Phosphorus in Foods, edited by Orlando M. Gutiérrez, Kamyar Kalantar-Zadeh, and Rajnish Mehrotra, 2016

L-Arginine in Clinical Nutrition, edited by Vinood B. Patel, Victor R. Preedy, and Rajkumar Rajendram, 2016

Mediterranean Diet: Impact on Health and Disease, edited by Donato F. Romagnolo, Ph.D., and Ornella Selmin, Ph.D., 2016

Earlier books included *Alcohol, Nutrition and Health Consequences* edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi; *Nutritional Health, Strategies for Disease Prevention, Third Edition* edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr.; *Chocolate in Health and Nutrition* edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi; *Iron Physiology and Pathophysiology in Humans* edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren; *Vitamin D, Second Edition* edited by Dr. Michael Holick; *Dietary Components and Immune Function* edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi, and Dr. Victor R. Preedy; *Bioactive Compounds and Cancer* edited by Dr. John A. Milner and Dr. Donato F. Romagnolo; *Modern Dietary Fat Intakes in Disease Promotion* edited by Dr. Fabien De Meester, Dr. Sherma Zibadi, and Dr. Ronald Ross

Watson; *Iron Deficiency and Overload* edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; *Nutrition Guide for Physician*s edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple, and Dr. Mary Struble; *Nutrition and Metabolism* edited by Dr. Christos Mantzoros; and *Fluid and Electrolytes in Pediatrics* edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include: *Handbook of Drug-Nutrient Interactions* edited by Dr. Joseph Boullata and Dr. Vincent Armenti; *Probiotics in Pediatric Medicine* edited by Dr. Sonia Michail and Dr. Philip Sherman; *Handbook of Nutrition and Pregnancy* edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch, and Dr. Elliot Philipson; *Nutrition and Rheumatic Disease* edited by Dr. Laura Coleman; *Nutrition and Kidney Disease* edited by Dr. Laura Byham-Grey, Dr. Jerrilynn Burrowes, and Dr. Glenn Chertow; *Nutrition and Health in Developing Countries* edited by Dr. Richard Semba and Dr. Martin Bloem; *Calcium in Human Health* edited by Dr. Robert Heaney and Dr. Connie Weaver; and *Nutrition and Bone Health* edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich served as President of Consultants in Consumer Healthcare LLC and has edited ten books including *Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fifth Edition*, co-edited with Dr. Richard Deckelbaum (www.springer.com/series/7659). Dr. Bendich serves on the Editorial Boards of the *Journal of Nutrition in Gerontology and Geriatrics* and *Antioxidants* and has served as Associate Editor for *Nutrition,* the international journal, served on the Editorial Board of the *Journal of Women's Health and Gender-Based Medicine*, and served on the Board of Directors of the American College of Nutrition.

Dr. Bendich was Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare and provided medical leadership for many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI) intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid-containing multivitamins significantly

reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. She is recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety, and the cost-effectiveness of vitamin/mineral supplementation. She continues to serve on the Editorial Board of the journal *Antioxidants*, which she has done since its inception in 2010.

Dr. Bendich received the Roche Research Award, is a *Tribute to Women and Industry* Awardee, and was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences.

Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. In 2012, she was recognized for her contributions to the field of clinical nutrition by the American Society for Nutrition and was elected a Fellow of ASN (FASN). Dr. Bendich served as Adjunct Professor at Rutgers University. She is listed in Who's Who in American Women.

Dr. Adrianne Bendich was included in Stanford University's List of the World's Top 2% of most widely cited Scientists published in 2022.

Connie W. Bales has recently joined as Co-Series Editor of the Nutrition and Health series. Dr. Bales is a well-recognized expert in the field of nutrition, chronic disease, function, and aging. Over the past three decades, her laboratory at the Duke School of Medicine has explored many different aspects of diet and physical activity as determinants of health during the latter half of the adult life course. She has also studied direct nutritional influences on the aging process and collaborated on a number of large, randomized NIH trials of key significance in the nutrition arena, including the DASH trial, the STRRIDE-PreDiabetes trial, and the CALERIE trial. Her current research focuses on the impact of higher protein intake during obesity reduction on muscle quality and cardiometabolic risk in functionally limited older adults, as well as racial differences in these responses. Other new work is examining the influence of dietary bioactives on a variety of health attributes in older adults. Dr. Bales

has served on NIH, VA, and USDA grant review panels and is Editor-in-Chief of the *Journal of Nutrition in Gerontology and Geriatrics*. She has edited three editions of the *Handbook of Clinical Nutrition in Aging* in the Nutrition and Health Series and has editorial roles with two other journals, *Current Developments in Nutrition* and *Cogent Gerontology*.

About the Volume Editors

Norman J. Temple Ph.D., is Professor of Nutrition at Athabasca University in Alberta, Canada. He has published 95 papers, mainly in the area of nutrition in relation to health. He has also published 14 books. Together with Denis Burkitt he coedited *Western Diseases: Their Dietary Prevention and Reversibility* (1994). This continued and extended Burkitt's pioneering work on the role of dietary fiber in chronic diseases of lifestyle. He coedited *Nutritional Health: Strategies for Disease Prevention* (2012; third edition), *Beverage Impacts on Health and Nutrition* (2016; second edition), *Community Nutrition for Developing Countries* (2016), and *Excessive Medical Spending: Facing the Challenge* (2007). He conducts collaborative research in Cape Town on the role of the changing diet in South Africa on the pattern of diseases in that country, such as obesity, diabetes, and heart disease.

Ted Wilson Ph.D., is Professor of Biology at Winona State University in Winona, Minnesota. His research examines how diet affects human nutritional physiology and whether food/dietary supplement health claims can be supported by measurable physiological changes. He has studied many foods, dietary supplements, and disease conditions including walnuts, pistachios, low-carbohydrate diets, cranberries, cranberry juice, apple juice, grape juice, wine, resveratrol, creatine phosphate, soy phytoestrogens, eggplants, coffee, tea, energy drinks, heart failure prognosis, diabetes, and obesity. Diet-induced changes have included physiological evaluations of plasma lipid profile, antioxidants, vasodilation, nitric oxide, platelet aggregation, and glycemic and insulinemic

responses using in vivo and in vitro models. With Dr. N. Temple he edited *Nutrition Guide for Physicians* (Humana Press First edition—2010, Second edition and Third edition—2022), *Beverages in Nutrition and Health* (Humana Press First edition—2005, Second edition—2016), *Nutritional Health: Strategies for Disease Prevention* (Humana Press First edition—2001, Second edition—2006, and Third edition—2012), and of course this Fourth edition. He also enjoys teaching courses in Nutrition, Physiology, Cardiovascular Physiology, Cell Signal Transduction, and Cell Biology. When not working in the laboratory he enjoys family time, the outdoors, and farming.

David R. Jacobs, Jr. Ph.D., holds the degree of Ph.D. in Mathematical Statistics (1971) from the Johns Hopkins University. He has been on the faculty of the School of Public Health, University of Minnesota since 1974 and has held the rank of Professor of Epidemiology since 1989. He concurrently holds a guest professorship at the Department of Nutrition at the University of Oslo, Norway (1999–present). He is a fellow of the American Heart Association and the American College of Nutrition. He was Deputy Editor of the *British Journal of Nutrition* (2006–2011), is on the editorial board of *Clinical Chemistry*, and is a Statistical Reviewer for the *Journal of the American Heart Association* (JAHA).

He has written over 1200 articles on various topics concerning the epidemiology of chronic diseases and their risk factors, including the epidemiology of specific molecules, and particularly those relating to cardiovascular diseases, diabetes, and other chronic diseases. Since 1994, he focused extensively on whole grain intake and health. His work was influential in the 2000 decision of the USDA Dietary Guidelines Advisory Committee to add a specific guideline to "eat a variety of grains, especially whole grains," and in the strengthening of this message in the 2005 USDA Dietary Guidelines. He has written several articles on the health implications of synergies of different plant foods and dietary patterns and popularized the

term "food synergy." He is also expert in diverse subclinical markers of cardiovascular disease. He was a consultant to the California Walnut Commission from 2002 to 2019.

George A. Bray M.D., M.A.C.P., M.A.C.E., is Boyd Professor Emeritus at the Pennington Biomedical Research Center of Louisiana State University in Baton Rouge, Louisiana, and Professor of Medicine Emeritus at the Louisiana State University Medical Center in New Orleans. After graduating from Brown University summa cum laude in 1953, Bray entered Harvard Medical School graduating magna cum laude in 1957. His postdoctoral training included an internship at the Johns Hopkins Hospital, Baltimore, MD, a fellowship at the NIH, residence at the University of Rochester, and a fellowship at the National Institute for Medical Research in London and at the Tufts-New England Medical Center in Boston. In 1970, he became Director of the Clinical Research Center at the Harbor UCLA Medical Center in Torrance, CA. He organized the First Fogarty International Center Conference on Obesity in 1973 and the Second International Congress on Obesity in Washington, DC, in 1977. In 1989 he became the first Executive Director of the Pennington Biomedical Research Center in Baton Rouge, a post he held until 1999. He is a Master of the American College of Physicians, Master of the American College of Endocrinology, and Master of the American Board of Obesity Medicine. Bray founded the North American Association for the Study of Obesity in 1982 (now the Obesity Society), and he was the founding editor of its journal, *Obesity Research*, as well as co-founder of the *International Journal of Obesity* and the first editor of *Endocrine Practice*, the official journal of the American College of Endocrinologists. Dr. Bray has received many awards during his medical career including the Johns Hopkins Society of Scholars, Honorary Fellow of the American Dietetic Association, the Bristol–Myers Squibb Mead-Johnson Award in Nutrition, the Joseph Goldberger Award from the American Medical Association, the McCollum Award from the

American Society of Clinical Nutrition, the Osborne–Mendel Award from the American Society of Nutrition, the TOPS Award, the Weight Watchers Award, the Stunkard Lifetime Achievement Award, the Presidential Medal from the Obesity Society, and in 2019 the W.O. Atwater Award from the USDA and American Society for Nutrition. During his 50 academic years Bray authored or coauthored more than 2000 publications, ranging from peer-reviewed articles and reviews to books, book chapters, and abstracts reflected in his Hirsch (H) Index of 147. Bray has had a long interest in the history of medicine and has written articles and a book on the history of obesity.

Contributors

Kelly C. Allison Center for Weight and Eating Disorders, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Jamy D. Ard Wake Forest School of Medicine, Winston Salem, NC, USA

Malek Batal Nutrition Department, Faculty of Medicine, Université de Montréal, QC, Canada

Andrew Berardy Loma Linda University School of Public Health, Loma Linda, CA, USA

Tricia Blalock Department of Health, Human Performance and Recreation, Baylor University, Waco, TX, USA

Bradley W. Bolling Department of Food Science, University of Wisconsin-Madison, Madison, WI, USA

George A. Bray Pennington Biomedical Research Center, Baton Rouge, LA, USA

Walnut Creek, CA, USA

Sarah F. Brennan Centre for Public Health, Queen's University Belfast, Belfast, UK

Maija B. Bruzas Health Psychology Associates PC, Greeley, CO, USA

Greta Caprara Department of Experimental Oncology, IEO, European Institute of Oncology, IRCCS, Milan, Italy

Catherine M. Champagne Pennington Biomedical Research Center of LSU, Baton Rouge, LA, USA

Eliza S. Dahly Department of Biology, Winona State University, Winona, MN, USA

Karen Davison Health Science Program, Kwantlen Polytechnic University, Richmond, BC, Canada

Kwantlen Polytechnic University, Richmond, BC, Canada

Ana Deaconu Faculty of Medicine, Nutrition Department, Université de Montréal, QC, Canada

Achsah Dorsey Department of Anthropology, University of Massachusetts, Amherst, MA, USA

Marina Ferrari Centre for Public Health, Queen's University Belfast, Belfast, UK

Karen M. Gibson Department of Family and Consumer Sciences, Carson-Newman University, Jefferson City, TN, USA

Drew E. Gonzalez Exercise and Sport Nutrition Laboratory, Department of Kinesiology and Sport Management, Texas A & M University, College Station, TX, USA

Sarah Gonzalez-Nahm Department of Nutrition, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA, USA

Anna Groysman Joslin Diabetes Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

TanYa M. Gwathmey Wake Forest School of Medicine, Winston Salem, NC, USA

Biotech Place, Winston Salem, NC, USA

Samar Hafida Joslin Diabetes Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Yu Hasegawa Department of Food Science, University of Wisconsin-Madison, Madison, WI, USA

David R. Jacobs, Jr. Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA

Richard B. Kreider Exercise and Sport Nutrition Laboratory, Department of Kinesiology and Sport Management, Texas A & M University, College Station, TX, USA

Penny M. Kris-Etherton Department of Nutritional Sciences, The Pennsylvania State University, PA, USA

Scarlett Lin Latt Department of Health, Human Performance and Recreation, Baylor University, Waco, TX, USA

Brian Leutholtz Center for Exercise, Nutrition and Preventive Health Research, Department of Health, Human Performance and Recreation, Baylor University, Waco, TX, USA

Pao-Hwa Lin Duke University Medical Center, Durham, NC, USA

Rui Hai Liu Department of Food Science, Cornell University, Ithaca, NY, USA

Zhenhua Liu Department of Nutrition, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA, USA

UMass Cancer Center, University of Massachusetts Chan Medical School, Worcester, MA, USA

Julia McCarthy New York Health Foundation, New York, NY, USA

Kelsey McLimans Department of Nutrition and Dietetics, Viterbo University, La Crosse, WI, USA

Roeland J. W. Middelbeek Joslin Diabetes Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Derek C. Miketinas Department of Nutrition and Food Sciences, Texas Woman's University, Houston, TX, USA

Maria Morgan-Bathke Department of Nutrition and Dietetics, Viterbo University, La Crosse, WI, USA

Rachel A. Murphy Cancer Control Research, and the School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada

Fidela Mushashi School of Population and Public Health, University of British Columbia, Vancouver, Canada

Jason M. Nagata Department of Pediatrics, University of California, San Francisco, San Francisco, CA, USA

San Francisco, CA, USA

Kristina S. Petersen Department of Nutritional Sciences, Texas Tech University, Lubbock, TX, USA

Ashwini Rajasekaran Department of Pharmacology-Physiology, Université de Sherbrooke, QC, Canada

Anne Roesler Department of Biology, Winona State University, Winona, MN, USA

Joan Sabaté Loma Linda University School of Public Health, Loma Linda, CA, USA

Omar M. Sajjad Geisel School of Medicine at Dartmouth, Hanover, NH, USA

Philip A. Sapp Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA

David A. Sela Department of Food Science, University of Massachusetts, Amherst, MA, USA

Lara Steinhouse Nutrition Department, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada

Laura P. Svetkey Duke University Medical Center, Durham, NC, USA

Norman J. Temple Centre for Science, Athabasca University, Athabasca, AB, Canada

Kent L. R. Thornburg Knight Cardiovascular Institute, Center for Developmental Health, School of Medicine, Oregon Health & Science University, Portland, OR, USA

Bob and Charlee Moore Institute for Nutrition and Wellness, School of Medicine, Oregon Health & Science University, Portland, OR, USA

Crystal C. Tyson Durham, NC, USA

Sheri D. Weiser Division of HIV, Infectious Diseases and Global Medicine, School of Medicine, University of California San Francisco, San Francisco, CA, USA

Eric C. Westman Division of General Internal Medicine, Department of Medicine, Duke University Medical Center, Durham, NC, USA

Ted Wilson Department of Biology, Winona State University, Winona, MN, USA

Jayne V. Woodside Centre for Public Health, Queen's University Belfast, Belfast, UK

William S. Yancy Jr Division of General Internal Medicine, Department of Medicine, Duke University Medical Center, Durham, NC, USA

Guodong Zhang Department of Food Science and Technology, National University of Singapore, Singapore, Singapore

Part I

Understanding Nutrition

Methods in Nutrition Research

1

David R. Jacobs, Jr. and Norman J. Temple

Key Points

- Many different research designs are available for investigating nutrition-related questions. Each one has strengths and weaknesses.
- Much nutrition-related research is carried out using epidemiological study designs.
- Many epidemiological studies use observational designs; these include prospective cohort studies, case-control studies, cross-sectional studies, population studies, and historical studies.
- Results from randomized controlled trials (RCTs) are internally valid and are usually more reliable for causal inference than those from observational epidemiological studies. However, many kinds of nutritional studies do not fit well into the RCT framework.
- A recent development is the use of systematic reviews and meta-analyses. First, the literature is reviewed according to strict criteria. Findings from the studies are then analyzed in order to make pooled risk estimates. These gain power by increasing sample size; however, variables and concepts will vary across studies.
- This strategy can be valuable in evaluating consistency and in considering the possibility of residual confounding when only observational studies are available.
- Experiments on animals are often used for nutrition-related research. However, animal models have many differences from the human situation.
- Much mechanistic research is carried out where researchers study the details of body functioning such as physiology and biochemistry. This can illuminate detailed cellular and molecular relationships, but integrating such findings with the biology of intact humans is problematic.
- There is evidence of conflict of interest in studies that potentially affect profit of the research funder, most typically in industry funding. This indicates a need for particular care in interpreting such studies.
- A sufficient pool of research funds, independent of the food industry, is highly desirable to support needed research.
- Research studies involving human subjects require approval from an ethics committee.

D. R. Jacobs, Jr. (✉)
Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA
e-mail: Jacob004@umn.edu

N. J. Temple
Centre for Science, Athabasca University, Athabasca, AB, Canada

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_1

Introduction

Excellent research designs are essential for efficiently and accurately answering nutrition-related questions. The answers to these research questions generate important information which can serve various purposes, including advice from the perspective of health about what foods people should eat, what foods industry should supply, and whether some compounds should be consumed as dietary supplements. Areas of inquiry cover a broad range and include studying molecular mechanisms in cells, animals, and humans; examining what population groups eat; discovering the effects of food, nutrients, and other substances on clinical outcomes and intermediate variables; and investigating how behaviors, policies, and cost structures influence food preparation and consumption.

Formulating research questions carefully, as an essential part of choosing a research design and interpreting data, can optimize scientific discovery. Coupled with the right methods for a particular issue, these principles can make a research budget go further. However, over the years many findings in the field of nutrition have been reported in scholarly journals, with seemingly strong supporting evidence, only to be disproved by later research. Particularly telling in the category of disproved nutrition research are two assumptions which are unlikely to be correct. The first questionable assumption is that isolated compounds behave in the same way as they do as part of a food matrix. The second questionable assumption is that all of a macronutrient (i.e., total fat, total carbohydrate, or total protein) behaves in a common way. Disproved research and rescinded health messages lead to widespread confusion in the scientific community and among the general public. Knowledge about methodologies used in nutrition research confers a greater ability to comprehend research studies and to critically evaluate new research findings. That is our primary objective in this chapter.

We present an overview of the major methods used in nutrition research and describe the strengths and weaknesses of each one. Nutrition is connected to many areas of biomedical science. For that reason the methods described here are also valid for diverse fields of health.

We emphasize that this chapter is far from comprehensive. There are excellent texts and articles available that cover this subject in greater detail (e.g., references [1–3]).

Much of nutrition research is intended to discover causal pathways, e.g., if a person eats certain foods or nutrients, will there be a health benefit or harm? Because much of this research is observational, the reader is also encouraged to read Bradford Hill's classic 1965 paper [4] in order to better understand the fundamentals of causal inference in the absence of the "mathematical guarantee" for internal validity of causal conclusions afforded in randomized controlled trials (RCTs).

Fundamental Principles of Research Design

The idea of "contrast" is fundamental to all research: to ascertain the effect on some outcome of an exposure of interest contrasted to the outcome under an alternate condition (i.e., when there is less or no such exposure). In nutrition research, the exposure of interest is consumption of food or a food derivative (often an isolated compound found in food and taken as a supplement). There are similarities and differences between nutrition research and pharmacologic research in which the exposure of interest is a drug. In many ways, pharmacologic research has set a standard for identifying causal pathways; understanding areas in which nutrition and pharmacologic research part ways is therefore important for nutrition scientists. The outcome variable is often a health construct, including death, disability, a clinical disorder, worsening of a clinical disorder, subclinical disease (such as asymptomatic atherosclerosis or neoplastic cells), or an intermediate marker variable (assumed to be on the pathway to disease, such as obesity, blood cholesterol, immune status, or prostate specific antigen). Alternatively, the outcome variable may be maintenance of health, quality of life, or good functioning (such as low absenteeism from work

or school). The research target may be cost or other economic aspects. The research may be turned around, in which the outcome is food or nutrient intake and the exposure of interest is individual behavior, industry-related issues (such as advertising, placement of food outlets, and provision of more or less healthy food products), or population policy strategies (such as dietary guidelines intended to influence both food production and consumption).

In all of these cases, the research design adapts the basic principle of contrast: comparing one state of being to another on a level playing field, within a structure of assumed understanding of what the variables mean. We must first ask whether we are measuring what we think we are measuring, and whether that measurement is sufficiently precise to answer the research question? These are questions that deal with concepts such as validity, reliability, accuracy, precision, within-person variation, and bias. These considerations hold for both the exposure and the outcome measures.

Special to nutrition research is the structure of food intake. An individual's food intake varies widely from day to day, although this variation is often within a more stable pattern, such as vegetarian, Mediterranean diet, or Western diet [5]. For acute outcomes, such as the blood glucose response to a meal, the foods would likely be tightly controlled and well defined. For chronic outcomes, however, average food intake over a long period is most salient. Recalled or stated usual intake is highly variable. It may be understated (as is typical of energy intake in obese persons) or overstated (as might be the case for whole grain foods, where the participant knows the desirable answer). Most commonly, the bias of a statement of dietary intake is not great, but consumption is a moving target. The stated amounts may be correct on average over a population of people, but much too low or much too high for any given individual.

The second issue is confounding, defined as correlation of the exposure and the outcome with other variables. Such correlation may mask true associations or produce false associations. For example, in a general population study, whole grain food intake could be positively associated with mortality if whole grain food intake increased sharply with age, because age is almost always strongly positively associated with mortality. Confounding assumes that the correlated variable is not on a causal pathway linking the exposure and the outcome. A similar situation is mediation, in which the correlated variable is on the causal pathway between the intake and the outcome. For example, whole grain food intake may lead to both lower body mass index (BMI) and less incident type 2 diabetes. Here we might conclude that whole grain food intake is associated with incident type 2 diabetes in part because it lowers body weight.

Finally, the third issue is effect modification, wherein a given association is not homogeneous across a whole population; for example, when a nutritional factor leads to a good outcome in women but not in men (interaction with sex) or leads to a bad outcome only in people with a certain genetic makeup (e.g., phenylalanine in phenylketonuria, interaction with genes).

Errors, Bias, and Within-Person Variation in Dietary Assessment

Methods of self-report of dietary intake are discussed in the following chapter on research challenges in nutritional epidemiology (Chap. 2). Dietary assessment is prone to significant error [6]. Estimates of alcohol and energy intake, for example, are usually substantially underestimated in heavy drinkers and obese persons, respectively. Errors in dietary assessment are not exclusively random and appear to vary with age, BMI, and race/ethnicity [7]. Dietary intake varies greatly from day to day [1]; many days of recall may be needed to arrive at a stable individual estimate of intake [8]. It may be difficult for a participant to accurately estimate their average intake in a food frequency assessment, whether for issues of memory, ability to synthesize, or rapidly changing intake which does not seem to be amenable to averaging. Nutrients that are derived from few foods (for example, the dairy-specific fatty acid C15:0) may be more precisely

measured than those that require precise input from many foods (such as total fat). Foods that are eaten in a regular pattern, such as breakfast cereal with milk as a typical breakfast, may be more precisely estimated than foods that are eaten irregularly or rarely.

Epidemiological Studies

Epidemiology is the study of the incidence, distribution, control, and prevention of disease. Many epidemiological studies share a common objective to discover the factors that cause or prevent disease. Related studies aim to describe food or nutrient intake in general or across population subgroups, or to understand factors that lead to intake of a given food. We shall now look at the major types of epidemiological studies. These studies are often referred to as "observational" as they are based on observing relationships. Another type of epidemiologic studies use experimental testing, under a high level of experimenter control. These include, most notably, randomized controlled trials (RCTs) and are discussed in section "Randomized Controlled Trials".

Cohort Studies

Cohort studies—also known as prospective or longitudinal studies—are a highly flexible, utilitarian, and informative research design. Under the right circumstances, they can yield reliable inferences about causal pathways. The first step in a study is the recruitment of large numbers of subjects; typically in the range 30,000–100,000, but sometimes as many as half a million. Cohorts of a small number of people are also useful. There are variations in the inclusion/exclusion criteria: participants may be recruited from the general population; they may be free of serious disease or may be specifically selected because they have a disease (e.g., survivors of childhood cancer).

At baseline the participants are questioned or examined to determine each person's exposure to the particular factors under study, as well as many other variables that might be of importance as confounders, mediators, or effect modifiers. The subjects are then monitored for a long period of time, typically from 5 to 20 years, by which time a sufficient number have developed the conditions or diseases of interest. A variant would be a life course study where participants are observed even longer, even from birth to death.

After a sufficient amount of observational follow-up has occurred, the data are analyzed to determine the association between dietary and other lifestyle variables and risk of disease. If the participants are known to be free of the disease at study baseline, predictors of incident disease are of particular interest as it is then known that the exposure and outcome occurred in a temporal ordering consistent with a causal association.

The outcome results for low vs. high intake are presented as risk difference (appropriate to computing attributable risk) or relative risk (RR) (appropriate to characterizing disease that develops at a faster rate over time in one group than in another), hazard ratio (HR, used in life table-based methods), or odds ratio (appropriate to methods such as logistic regression that are based on odds [probability of having an event relative to not having it] rather than probability itself).

In a format typically used for long-term studies of an outcome relative to a dietary pattern, a food, or a nutrient, the subjects are divided into five equal sized groups (quintiles) based on their exposure to the variable of interest. It may be more valid and informative to categorize the subjects into substantively sensible groupings in order to capture important contrasts in level of exposure or to divide the subjects into fewer groups if the sample size (especially of outcome events per category) is small or range of intake is limited. Another approach is to examine the association continuously, for example, using a restricted cubic spline.

The relative risk of the disease in the category with the lowest exposure may be arbitrarily called 1.0. The risk in the other categories is then calculated relative to this reference group. If subjects in the quintile with the highest exposure have a 57% higher risk of the disease, then the RR is stated as 1.57. If subjects in that quintile have a 20% lower risk of the disease, then the RR is stated as 0.80.

Typical findings from a cohort study on lifestyle and risk of stroke might be that exercise has a RR of 0.80 while smoking has a RR of 1.9. The RR values are normally given for all quintiles, not just the extreme quintiles. The pattern of absolute risks or of RR values is also examined for linearity and thresholds. Outcome variables may also be continuous in cohort studies.

It is good practice to examine both absolute and relative risks to get a good picture of the magnitude of association. For example, in a disease that occurs in 1% of the unexposed population, a relative risk of 2 means an absolute excess of 1%, whereas for a condition that occurs in 20% of the unexposed, it would occur in 40% among the exposed. Even a small absolute risk may be important in the face of a substantial relative risk because the risk may build to considerable proportions over time. The same relative risk of 2 in the context of an incidence of 1% per year followed for 20 years would correspond to approximately 20% in the unexposed group but 40% in the exposed.

The outstanding strength of cohort studies is that information is collected before the disease develops and this removes a major source of bias, namely that many participants may have started eating the food in question after or because of the disease outcome, in which case the situation would be one of reverse causality where disease causes dietary exposure.

However, there are still significant sources of error. Besides inaccurate diet assessment, diet and other aspects of lifestyle, such as smoking and exercise, tend to change over time. It is indeed remarkable that a single assessment in mid-life of smoking, serum cholesterol, and blood pressure in the Framingham [9] and many other studies predict heart disease incidence far into the future. In contrast, for many variables a single measurement is not accurate or stable enough to predict disease over the long term. Therefore, data recorded at the start of a cohort study may not reflect actual lifestyle a decade later. Some cohort studies endeavor to minimize this source of error by repeating the data collection every few years and accounting in data analysis for these changes. Such dietary changes may be incorporated by changing the dietary assessment every couple of years, for example, when the intake is thought to influence disease over the short run only, or by averaging all dietary observations since baseline so that the exposure assessment becomes a more and more precise estimate of long-term diet as the study progresses. For example, Stringhini et al. [10] found that repeated measures of diet explained much more of the association between socioeconomic status and mortality than did baseline diet. Cigarette smoking tends to occur daily over many years so that a single indication that a person is a smoker anytime during life is indicative of a constant and long-term situation. Perhaps, not surprisingly, repeated measures of smoking did not add information in this case. The repeated diet measures approach has been very successful in studies of nurses and other health professionals [11].

For nonfatal outcomes, such as body size and insulin resistance, change in the outcome may also be examined according to change in the exposure; this strategy would tend to remove confounders that are constant within an individual, such as race/ethnicity or sex.

The greatest challenge in analyzing data from cohort studies is confounding. Let us suppose one is studying the relationship between dietary factor A and disease X. The findings may indicate that persons with a relatively high intake of dietary factor A have a 50% increased risk of developing disease X. However, further investigation reveals that dietary factor A is associated with smoking which is also associated with disease X. This means that the association between dietary factor A and disease X may be spurious.

Confounding is of great importance in epidemiological studies as lifestyle factors tend to cluster together in the natural setting, that is when the lifestyle associations are not artificially diminished by the action of an experimenter, as in an RCT. Most often this lifestyle clustering takes the form of some people leading a healthy lifestyle with respect to diet, smoking, and exercise, while others lead a generally unhealthy lifestyle. We can illustrate this by looking at findings from a cohort study on the relationship between meat intake and mortality [12]. Comparing men

who were in the top quintile for intake of red meat with those in the bottom quintile, the former led a generally less healthy lifestyle: they were more likely to be smokers (14.8% vs. 4.9%), were less likely to engage in regular vigorous physical activity (16.3% vs. 30.7%), had a higher BMI (28.3 vs. 25.9 kg/m^2), and consumed less fiber but more saturated fat (8.8 vs. 13.2 and 12.7 vs. 7.7 g/1000 kcal, respectively). Thus, even if red meat has no effect on health, we can predict that a relatively high intake of red meat will still be *observed to be associated* with increased risk of death. Another factor associated with an unhealthy lifestyle (and with a high intake of red meat in this study) is having less years of education. It should be noted that this type of clustering of behaviors tends to reflect popular beliefs about what is healthy at the time of data collection. Thus, the postmenopausal women who attempt to follow the healthiest lifestyle may typically also have been more likely to have used hormone replacement therapy decades ago but not in studies that were initiated more recently. However, lifestyle associations may also reflect causal pathways among behaviors. People may feel less heaviness when eating less meat and may therefore be more likely to exercise. Smoking, in contrast, may lead to upper respiratory symptoms that tend to extinguish any desire to do vigorous activity.

Epidemiologists attempt to overcome the error caused by confounding by making statistical corrections. In the above example, men in the top quintile for intake of red meat had a hazard ratio (HR) for death from all causes of 1.44 in comparison with those in the lowest quintile (i.e., they had a 44% increased risk of death during the period of the study) [12]. However, when the data were corrected for the various sources of confounding that were listed above (plus others not mentioned), then the HR was reduced to 1.31. This is known as attenuation.

Two related variations within the cohort design study are the nested case-control design and the case-cohort design. These are based on the collection of biological samples, usually blood, at the time of initial recruitment of the subjects. Years later, when a sufficient number of them have developed a disease of interest, their stored samples are analyzed for selected substances. The difference between the two methods is in how the comparison group is selected. For comparison in the case-control design, samples from randomly selected or matched controls, free of the disease, are also analyzed. For comparison in the case-cohort design, participants randomly selected from the total cohort (which will include some of the cases) are selected. Contingent on the existence of suitable cohort studies, these strategies have two strong advantages over the more usual design that examines complete cohort studies. First, only a limited number of samples must be analyzed. Second, they allow the researchers to respond to recent research findings. For example, evidence might have been published recently that suggests that phytochemical P is protective against disease D. The original dietary analysis data may not be appropriate for determining the intake of the phytochemical but blood analysis may allow this to be done. There are some advantages and disadvantages between the two designs. The nested case-control design can be highly specific to a disease outcome of interest, with confounding controlled at the outset through matching or post hoc by regression analysis. The case-cohort design is much more flexible: the cohort subset is a miniature of the cohort itself, and can be used for any purpose that the full cohort can be used for, given only the sample size constraint. Only post hoc deconfounding is possible in the case-cohort design.

Case-Control Studies

In general, case-control studies have the same goal as cohort studies, namely to explain why particular individuals within a population suffer from certain diseases. In all case-control studies, a direct comparison is made between healthy subjects and people who already have the disease of interest. As noted earlier in a nested case-control study, the sampling rate is higher in cases (often all available cases) than in controls, which are typically a tiny subset of all existing non-cases. Controls should be selected from the same

source population as the cases. This happens automatically in a nested case-control study (all cases are derived from the cohort participants), but can be difficult to actuate in a non-nested case-control study, in part because it is not always obvious what the source population for cases is.

Non-nested case-control studies lack the advantage of nested case-control studies of known temporality of exposure and outcome, but are often the only alternative in the study of cancer and other rare diseases. Typically, between 50 and 500 people with the disease of interest are recruited. One (sometimes two or more) healthy—but otherwise similar—people are also recruited for comparison with each case. Subjects are asked about their diet at some past time. One may think of the case-control study as being done backwards with respect to research intent. Because selection is within cases, an exposed-to-unexposed ratio can be estimated in cases. The same is true for controls, and a relative exposure ratio can be estimated. Thus, because cases are oversampled compared to non-cases, the only excess risk measure available in a case-control design is the odds ratio for being a case in exposed vs. nonexposed participants. Fortunately, for rare diseases, the odds ratio is a close approximation to the relative risk. Absolute risk is not estimable (unless the different sampling rates for cases and for controls are known, in which case a rough reconstruction of the full population could be made).

From a practical point of view, non-nested case-control studies have several advantages over cohort studies. First, far fewer subjects are needed (hundreds rather than tens of thousands). This greatly reduces the cost. Second, the results are generated far more quickly as there is no need to wait years for diseases to develop.

Unfortunately, case-control studies can have serious inherent errors [13]. The first is known as "the healthy volunteer effect." When patients with cancer are asked to participate, typically a high proportion agrees. But recruitment of "matched" controls is usually more problematic as a much lower proportion of healthy subjects agree to participate. Moreover, the healthy subjects tend to include an overrepresentation of health-conscious people. The effect of this is that even if patients with a particular type of cancer have a history of eating, on average, an identical diet to the rest of the population, the results of case-control studies will likely indicate that their past diet was relatively unhealthy, such as having a low content of fruits and vegetables. The second problem is recall bias. This refers to the tendency of patients who have recently been diagnosed with cancer to have a distorted recollection of their past diet, usually in the direction of overstating its unhealthy features. Of note, a healthy volunteer bias can also enter the cohort study design, but exclusion of unhealthy, unwilling participants from the cohort baseline would not affect that relationship of exposures to future disease in those who do enter the study.

Studies of the relationship between consumption of fruits and vegetables and risk of cancer demonstrate the systematic bias that can be generated by case-control studies. Well over 200 case-control studies have been published and these consistently indicate that a generous intake of fruits and vegetables are strongly protective against several types of cancer. However, findings from large cohort studies, mostly published after 2000, have reported only minor protective benefits. We can best illustrate this serious inconsistency by looking at the estimate of the decrease in the risk of developing cancer with each extra 100 g/day of fruits and vegetables. The findings from case-control studies suggest a figure of about 10% [14], whereas cohort studies suggest a much lower figure, about 3% [15].

It should be remembered that if sampling is done well and exposure information is reliable, the non-nested case-control study is both valid and efficient. Exposures that are easy to recall accurately, such as smoking or exposures at work, may meet the needed standard of the case-control study. Furthermore, if the risk following exposure is short term, a cohort study will fail to detect the risk, while a case-control study would likely find such risk. Short-term risk is the rule by definition in identification of triggers of sudden death. A case-control study could be used in this case. However, the case crossover study is a better design here with each case serving as his/

her own control. In the sudden death outcome, a proxy would be asked about possible triggering behavior in the period immediately before death and again the same behavior at a more remote time. This method was used successfully in identifying a bout of physical activity as a trigger for sudden death, much more so in untrained than in trained people [16]. It is interesting that this study successfully decomposed a mixture of situations: trained people had lower overall risk for sudden death even though their immediate risk increased somewhat for each bout of physical activity.

Cross-Sectional Studies

In the cross-sectional design, the sample is selected to be a snapshot in time. The sample may be selected at random from the general population. Cross-sectional studies are often used to look at body parameters that increase by increments, such as BMI and blood pressure. Let us suppose that an investigator wishes to study the relationship between lifestyle and BMI in children. He then recruits several hundred children from the general population and measures both lifestyle factors and BMI. The results might reveal, for example, a positive association between hours of TV watching and BMI.

In principle, the information gathered in a cross-sectional study can refer to any time in the past or present. A question like, "When did you start smoking?" is obviously historical. However, cross-sectional studies usually attempt to determine current lifestyle, including diet, whereas case-control studies, in line with their particular focus, usually ask about lifestyle at a former time before diagnosis. Accordingly, cross-sectional studies, for the most part, reveal nothing about temporal sequence, whereas case-control studies attempt to determine this. Because of the paucity of information about temporal sequence typical in the cross-sectional design, it cannot distinguish causal direction, even if other aspects of the data lead to a belief that a causal relation is present. Let us look again at the study of the relationship between lifestyle and BMI in children. If that study reveals that children who spend more hours watching TV tend to have a higher BMI, this could mean that TV watching causes children to become overweight, or, conversely, that overweight children tend to watch more TV. Resolving this problem can only be properly addressed by studying children prospectively (i.e., monitoring a cohort of children over several years). A plausible but inferentially riskier strategy would be to ask people about their past BMI and TV watching, thereby emulating a prospective study, but without the security of measuring BMI and TV watching at their time of occurrence.

As with case-control studies there are significant errors that can easily enter into data collection. For example, obese people tend to underestimate their energy intake. This creates the potential error of recall bias when comparing energy intake across the BMI range. The healthy volunteer effect may also be a source of error.

Population Studies

Population studies—also known as ecological studies—have a long history in epidemiology and have yielded enormous amounts of valuable information. Typically, two dozen or more different countries are compared. Data are collected from each country on exposure to different diets and to possible risk factors and these are compared with disease rates. The findings indicate which variables are most strongly associated with each disease. Population studies take advantage of the enormous variations around the world in many aspects of lifestyle and in disease patterns.

There are several major sources of error in population studies. One is that disease statistics are often unreliable, especially in less developed countries. Food consumption data can also be misleading. In richer countries, for example, much food is wasted. Let us take a hypothetical example to illustrate how researchers might easily reach seriously flawed conclusions. They are investigating the relationship between consumption of potatoes and colon cancer. The data reveal that the populations of countries in Group A eat

30% more potatoes than those in Group B and also have a 30% higher incidence of colon cancer. On the surface, this suggests that potatoes may cause colon cancer. But closer inspection of the data reveals significant sources of error: first, countries in Group A are rich and waste 30% of their potatoes, while countries in Group B are poor and fail to diagnose 30% of their cases of colon cancer. This means that, in actuality, people in the two groups of countries eat a similar amount of potatoes and have a similar incidence of colon cancer.

As with other types of epidemiological studies, confounding presents a serious challenge to the interpretation of findings. In the case of population studies, confounding is a reflection of different populations having many lifestyle factors that cluster together. This is best illustrated by studies that have investigated the relationship between diet and chronic diseases of lifestyle. Since the 1970s many such studies have compared populations in highly developed countries and those still living a more traditional lifestyle (before the arrival of the nutrition transition). What the findings typically reveal is a strong association between a Western diet and many chronic diseases of lifestyle, including colon cancer, breast cancer, coronary heart disease (CHD), and type 2 diabetes. Detailed analysis reveals a strong correlation between all components of the Western diet (such as a high intake of dietary fat, animal protein, and sugar, and a low intake of dietary fiber) and several different diseases.

Many researchers have stressed that population studies may suffer from the "ecologic fallacy." This refers to an incorrect assumption about an individual based on aggregate data for a group. For example, a population study may report that some countries have high rates of both alcohol consumption and breast cancer. However, the data may fail to reveal that it is mainly men who consume alcohol, whereas it is women who suffer from breast cancer. In fact, ecologic variables do not necessarily even have the same substantive meaning as their individual counterparts. For example, gender at the individual level brings to mind a man, a woman, sex hormones, social roles, etc. Ecologically, gender is not very informative; it is generally about 50% male and 50% female. A variable such as the taking of antihypertensive medication means something about high blood pressure and its treatment at the individual level, while the corresponding ecologic variable may have more to do with the structure and focus of the health-care system and prescribing habits [17].

In 1975, Armstrong and Doll [18] published a paper using this methodology in order to explore the relationship between diet and cancer. This paper has become a classic and played a major role in sparking serious interest in the relationship between diet and risk of cancer. According to Google Scholar, the paper had been cited 3200 times by 2021. The association between diet and breast cancer mortality in 27 countries illustrates the nature of the findings. The correlations (r) were as follows: animal protein 0.83, eggs 0.80, meat 0.74, and milk 0.73. The strongest association was seen for total fat: a correlation of 0.89. Conversely, cereals manifested a correlation of −0.70. Many investigators seized on the impressive association between fat intake and breast cancer and became convinced that there must be at least a small fire amid so much smoke. Alas, the search for solid supporting evidence has been largely futile. With the wisdom of hindsight what these findings really show is that a Western diet (and its associated lifestyle) is strongly *associated* with risk of breast cancer. Making inferences as to *cause-and-effect relationships* for single dietary components should only be done with much caution, particularly when the evidence in favor of the existence of the association is based solely on ecologic data.

Population studies can be done within a country; for example, comparisons of the states of the United States. The degree of variation between states is obviously far less than that seen between highly developed and developing countries. This has the advantage of greatly reducing the problem of confounding (e.g., differences in disease rates between states are not likely to be due to such factors as dietary intake of meat or sugar or errors in disease diagnosis). However, the relatively small state-to-state variation in nutritional factors and disease

rates limits the potential use of this technique. This approach has proven useful in situations of strong geographical variation in dietary status. One recent example of this is using regional variation in sunshine exposure as a surrogate marker for vitamin D status. Results from such studies have lent support to the view that vitamin D is protective against cancer [19].

A variant of the population study performs cross-sectional studies in several countries, as was done in Intersalt [20]. This study showed a strong association between 24-h urinary sodium and blood pressure in most of 52 populations and was then able to show the generality of this finding by displaying these between individual slopes across countries. This study greatly reduced the likelihood of confounding by displaying within-country relationships, adjusted for confounding, rather than the simplistic display of whole-country means of urinary sodium arrayed against whole-country means of blood pressure.

Another variant of the population study is one in which an integral ecologic characteristic is studied; for example, when an intervention is performed to alter lifestyle behavior with the community as the unit of analysis, or when the question is instances of food-borne bacterial infection as a function of the number of food production sites.

Historical Studies

The relationship between nutritional patterns and changing disease rates often provides valuable clues as to the role played by dietary components in the causation or prevention of different diseases. Such information suffers in the same way as population studies from potential ecologic biases, but can be helpful if used carefully, particularly in conjunction with other evidence.

A strong piece of evidence that supports the role of smoking in causing lung cancer comes from historical studies. The disease was rare at the time of the First World War. At around that time millions of men took up the habit of smoking. Starting around 1930, lung cancer became progressively more common and is now by far the leading cancer in terms of numbers of deaths. Among women, by contrast, the rapid escalation in the numbers dying from the disease was delayed until around 1960. This much later date accords with the fact that smoking among women became common much later than it did for men.

Another example illustrating this method comes from looking at the relationship between the intake of folate by women and their risk of giving birth to a child with a neural tube defect (NTD). NTDs, such as spina bifida, are a serious congenital disorder. Strong evidence has accumulated showing that a low dietary intake of this vitamin increases the risk for NTD. As a result in 1998 fortification of grain products with folic acid became mandatory in Canada and the United States. The effectiveness of this policy was confirmed by the sharp fall in the incidence of NTD in the years following the implementation of this policy [21, 22].

The following example also used this approach to confirm that a particular intervention would deliver the promised benefits. The Pap smear is a test used for the detection of precancerous changes of the uterine cervix. This allows for interventions that help prevent the progression to actual cervical cancer. Different countries or regions have adopted screening programs at different times. Several historical studies from different countries have shown a large fall in deaths from cervical cancer in the years following the implementation of such programs [23]. This evidence provides valuable confirmation that utilization of the Pap smear does indeed substantially reduce the risk of death from the disease.

Randomized Controlled Trials

Randomized controlled trials (RCTs) are often referred to as the "gold standard." In the clinical setting, these are known as randomized clinical trials. A single pool of participants is recruited who would potentially benefit from an intervention; randomization into intervened and control groups eliminates any correlations between intervention/control and confounders that would be present if the intervention variable was encountered in an

observational setting. Therefore, the RCT has low risk of bias for comparing intervention to control. For that reason, the findings generated are usually much more reliable than those from observational studies. However, they are still subject to some possible errors and other limitations.

RCTs have the following key features:

- Subjects are recruited who meet predetermined criteria, such as age, gender, willingness to accept and comply with either intervention or control, and equipoise in respect to treatment effectiveness.
- Subjects are randomized into at least two groups: a control (i.e., untreated, usual care, placebo, known standard treatment) group and one or more intervention (test, treatment) groups.
- The number of subjects is carefully calculated so that the results will be meaningful. For example, based on the assumption that the intervention will cause a change in the target outcome parameter of 10% over a specified period of time, the researchers estimate that 50 subjects are needed in both the test and control groups in order to have a 90% chance of the results being statistically significant.
- Studies are carried out "double-blind" when possible. This means that neither the subjects nor the personnel who are in direct contact with them know which group each subject is in. This is important in order to avoid various types of bias.
- Given perfect compliance within the treatment group assignments, inferences about the relation of treatment to outcome are based solely on a mathematical computation; the scientific thinking is done entirely in the set-up of the RCT. In the face of noncompliance, data analysis assumes "intention to treat," that is, that the randomized groups are compared to each other, even if there is some noncompliance to the intervention or crossover between intervention and control during the study. This feature assures that the confounding that was broken up by randomization is not reinstituted by noncompliance. This "rescue" from noncompliance works less and less well, the more the noncompliance. Indeed, it would be patently absurd if most of the control group received the intervention, while most of the intervention group did not receive it.

Additional characteristics of RCTs in relation to observational cohort studies are provided in section "Comparative Strengths and Weaknesses of Randomized Controlled Trials vs Cohort Studies".

Systematic Reviews and Meta-Analyses

Research methods are constantly evolving and being improved. An excellent example of this is the move toward systematic reviews and meta-analyses. In many fields of health-related research, a dozen or more human studies are carried out on the same topic. In the traditional literature review, experts have then examined each study, one at the time, and made an overall evaluation. A typical conclusion might be: "While the evidence lacks consistency, the majority of studies indicate that a diet with a high content of vitamin X is associated with a reduced risk of disease Y. On balance, this suggests that supplements of vitamin X may reduce risk by 20–30%." This approach has a strong element of value judgment which makes it easy for the reviewer to reach a somewhat biased conclusion.

A trend in recent years has been the publication of systematic reviews and meta-analyses. In a systematic review, the literature is reviewed using search engines according to strict criteria. These criteria might include the date of publication, language, the subject under study, and the type of study. Each paper that meets the criteria is then carefully read and relevant information extracted. The findings from these papers are compiled and then summarized as objectively as possible.

A meta-analysis takes this process one step further. Instead of guesstimating a "batting average" of what the results indicate, the reviewers make formal pooled risk estimates calculated using the weighted average according to set rules that con-

sider both within-study and between-study variance. By this means larger studies usually receive more weight than smaller ones. While it is clearly helpful in many instances to make a quantitative summary of evidence, it should be recognized that this activity involves a trade-off. The pooled estimate gains power by increasing sample size but at the expense of loosening definition of variables and concepts which will vary across studies despite the use of strict criteria.

Experiments Using Animals

From a statistical design perspective, experiments on animals are comparable to RCTs on humans. In particular, the experimenter sets up different treatment options, paralleling the intervention and control set-up in human RCTs. Compared to RCTs, experiments on animals have obvious advantages and disadvantages. The advantages are as follows:

- The conditions can be far more rigidly controlled. So if, for example, the investigator wishes to test the effect of a low-fat diet, he can be confident that all the experimental animals have consumed the intended diet, and that there are no other differences between the test and control groups. Such control is rarely possible in studies using human "guinea pigs."
- The animals used in experiments are usually from a single breed and therefore have far less genetic variation than is the case with human subjects.
- The animals can be genetically modified to have or to knock out the capability to produce the biochemical under study, enabling tight control over highly specific pathways. Reporter genes can be introduced to indicate which tissues metabolize the treatment substance.
- Experimental animals can be subjected to dangerous treatments; later they can be killed and their tissues studied, whereas in humans only easily obtainable tissue can be studied, such as blood and urine, and occasionally small biopsies.

Experiments on animals do, however, have major disadvantages. This is especially the case in the area of nutrition in relation to health and disease. The dominant problem here is the vast genetic, metabolic, and physiologic gap separating animals from humans. On top of that, humans live a completely different lifestyle to animals in a laboratory. For these reasons, we often find that experimental animals react very differently from humans when their diets are altered. Animals rarely get diseases of interest for humans, and "disease" models that exist are only approximations of human disease. For example, some mice have been bred to become obese and to develop diabetes, and in some models diabetes is induced by a drug that greatly harms the pancreas. It is uncertain whether these forms of "diabetes" are relevant to the types of diabetes encountered in humans. Accordingly, while animal models can elucidate biological pathways in living tissues and thereby advance our knowledge about how tissue and life work, data generated from these studies can only be extrapolated to humans with much caution.

Mechanistic Research

For many decades, nutritionists have followed the strategy that the road to understanding nutrition is to learn the details of body physiology and biochemistry, such as intermediary metabolism, and thence how the various chemicals in food are involved in health or disease. Certainly, this strategy has revealed a great deal about the role played in the body by vitamins, minerals, amino acids, and other substances, and why deficiencies of them lead to specific symptoms. It is also true that the discovery of several important new drugs has grown out of an understanding of metabolic processes and cell physiology, such as cell receptors.

But when we look at the wider arena of health research, this mechanistic strategy has serious weaknesses, as has been argued previously [24–26]. In particular, in the field of nutrition, the strategy is achieving less and less success in recent decades. The reason for this is really quite

simple: the human body is so complex that it is extraordinarily difficult to fully comprehend the finer details of the pathways that lead to health and disease. Compounding this, foods have such great complexity that there are vast numbers of possible interactions between food components and body processes. As a result attempts to translate an understanding of intermediary metabolism and cellular function into practical nutritional advice on preventing or treating disease seldom achieve success. This argument perfectly complements the parallel arguments we present in our chapter on food synergy (Chap. 23). Nevertheless, as with animal studies, studies of the composition of food and of the effects of food on performance of cells in vitro can be helpful as part of a total package of knowledge about nutrition, not standing alone, but contributing to inferences about important causal pathways.

All nutrition-oriented research designs contribute knowledge about biology. However, our understanding of human nutrition can be led astray if too much reliance is placed on aspects of intermediary metabolism and cellular function and this information is used in an attempt to better predict how best to protect health and prevent disease. We argue that a better strategy is to tie such mechanistic studies to metabolic features and nutritional aspects that have already been shown to have an effect in humans, that is, to use mechanistic studies to explain known nutritional associations rather than to find new ones.

Comparative Strengths and Weaknesses of Randomized Controlled Trials: Drugs vs. Foods

We now turn our attention to critically evaluating the strengths and weaknesses of various research methods used in nutrition. A major focus is the limitations of RCTs. This is well illustrated by comparing how typical RCT features play out for drugs compared to foods:

1. Randomization is relatively easy to achieve with a drug, while it is possible, but hard to maintain long term, in the case of a food intervention.
2. Double blind is relatively easy with drugs, where look-alike placebos are fairly easy to produce. However, side effects may reveal the drug regimen. Food, in contrast, is hard to mask. Partial solutions exist, such as incorporation of different fats in margarine or different nuts in muffins, but complete masking is often impossible.
3. Compliance is relatively easy with a drug delivered in a tasteless pill although side effects of the drug may be limiting. Food, however, is at the center of life. Required drinking or not drinking of coffee, for example, or change in an entire dietary pattern can have a major effect several times a day. Factors such as taste, convenience, and effect on laxation are big issues in delivery of food, while they are usually not factors in drug delivery.
4. Long duration of a drug trial may be expensive but is possible. Food studies usually last only a few weeks. Long-term food studies are both expensive and likely to be compromised by compliance difficulties.
5. Specificity of intervention is helpful in defining what is being studied. Drugs are often a single compound or a simple combination of compounds. Food, by contrast, is much more complex, being an average over time, due to varietals, growing conditions, various preparations, food groups of similar foods, and substances such as salt and emulsifiers that are added by the food manufacturer.
6. The outcome variable of most relevance is a clinical event. It is relatively easy to design a drug trial so that a sufficient number of clinical events occur. But food trials have mostly intermediate outcomes due to short duration. The relevance of such outcomes to clinical events may be questionable, particularly where multiple pathways are possible.
7. Control in a drug trial is well defined; it may be a placebo or a comparison drug. By contrast, there are myriad possibilities for energy-bearing food; for example, saturated fat may be replaced by polyunsaturated fat, another fat, carbohydrate, or protein. This may result in changes in the dietary content of not only

macronutrients but also to many other substances contained in food.

For these reasons, it is therefore much more difficult to effectively study foods than drugs when using an RCT design. But many of the disadvantages of RCTs for food become advantages in an observational setting. For example, dietary patterns established and relatively consistent over many years are observable, with subsequent long-term follow-up for clinical events.

Neither study design is perfect. For example, observed drug taking is beset by indication bias. RCTs have clearly shown the efficacy of blood pressure lowering drugs for reduction of cardiovascular disease rates, but use of blood pressure lowering medication is often observed to be associated with higher risk. The explanation is that drug taking is confounded by the indication for taking the drug, namely that those taking the drug were at higher risk at the outset. Thus, indication bias can induce reverse causation, even in a prospective observational study design.

Comparative Strengths and Weaknesses of Randomized Controlled Trials vs Cohort Studies

The RCT design is highly regarded for its internal validity. One of its major advantages is that differences between intervention and control can be interpreted as being cause and effect. Nevertheless, all study designs have strengths and weaknesses. Kish [27] catalogued what he called "the three Rs of research design," namely randomization, representation, and realism. The first of these, randomization, refers to aspects of comparison and internal validity that may be rated as excellent in RCTs, but only good in observational studies. The second and third design dimensions, however, favor observational studies. Representation in RCTs is limited and is restricted to eligible persons in whom treatment is considered safe; in addition, the rigors of compliance to a specific intervention regimen may limit and possibly bias participation. By contrast, in the observational design, representation tends to be comprehensive. Realism in the RCT is limited by a stylized treatment delivery, designed to maximize internal validity but at the expense of somewhat altering the intervention itself. But in the observational design, treatment delivery is naturalistic.

Other design criteria also differ between the two research methods. The exposure period in the RCT tends to be relatively short (weeks or years), while in the observational study it is long (e.g., whole prior life, adult life, since onset of condition). Confounding by baseline characteristics is controlled probabilistically in the RCT (that is, randomization to treatment induces a high probability that each measured and unmeasured covariate is equally distributed between treatment groups). By contrast, residual confounding is always possible in observational studies. The possibility of an important biasing effect of residual confounding is reduced when many observational studies in many settings concur, and when they also concur with animal or mechanistic evidence. Less well appreciated may be that confounding by changes during the study period are a problem in both designs. Finally, level of investigator control is a strong point of the RCT; clever design and procedures may help in this respect in observational studies. Thus, we conclude that each study design has strong and weak points, at the same time agreeing that the internal validity of RCTs is a short and secure path to causal inference.

There is a widespread view among medical researchers that RCTs are the "gold standard" and can potentially demonstrate cause and effect. That is generally true for many types of study such as the effectiveness of drugs. Cohort studies, by contrast, are generally deemed as being less reliable. However, the above discussion has highlighted strengths and weakness of both methods. What is still uncertain is which method is more reliable in the area of research in the area of diet, health, and disease.

Temple [28] highlighted serious limitations of RCTs in comparison with cohort studies. The key points are as follows. An RCT on whether a dietary supplement prevents a disease will often use subjects who have a history of the disease or

are at high risk of it. For example, a study on cancer may use subjects who have been smokers for many years while an RCT on whether fish oil prevents heart disease may use subjects who have a history of cardiac disease. In each case, the study period may be no more than 3 or 4 years. These design features much reduce the numbers of subjects needed and therefore the cost of the study. What these RCTs are really studying is whether a dietary change can block the late stages of the disease process. It is unsafe to extrapolate the results to the question of whether the dietary change can achieve primary prevention. By contrast, cohort studies usually recruit only subjects who are reasonably healthy. In many cohort studies, the subjects are then followed for 10 years or longer. This time period is sufficiently long that it will probably cover most of the stages of disease development from start to finish. With this study design, therefore, the findings tell us whether the dietary change truly prevents the disease. Based on these considerations, Temple concluded that the findings from cohort studies may often be at least as reliable as RCTs and may even be more reliable.

A recent study attempted to shine light on this question [29]. A comparison was made of the findings from 97 pairs of studies where diet-disease outcomes had been investigated using both RCTs and cohort studies. The authors came to the conclusion that RCTs and cohort studies have a fairly good degree of agreement.

Evaluating the Evidence

Reports regularly appear suggesting that a particular food, nutrient, or other substance in food either increases or reduces risk of a particular disease. But often the evidence is weak or inconsistent. Unfortunately, there have been numerous instances of such evidence being widely accepted despite its weaknesses. This then leads to exaggerated confidence in the new finding. This inevitably creates confusion before a clearer picture emerges. Well-known examples include the role of dietary fat in various diseases, and the possible protective benefit of vitamin E against CHD and of beta-carotene against and cancer.

The lesson from how various types of study have led to our present knowledge, often after several major errors were made, is that nutrition research is inherently uncertain. Mechanistic research consumes a large share of research resources. While it has led to important new drug discoveries, it has a poor track record in the area of advancing our understanding of how nutrition is related to the prevention or treatment of disease. We are not against mechanistic research but rather against having excessive faith in it as a methodology that will explain the relationship between foods, nutrients, and health. Mechanistic research that puts more emphasis on studying food rather than nutrients may prove to be a valuable form of inquiry. We see, time and time again, that in recent decades the large majority of our information of practical value regarding how diet is related to the prevention or treatment of disease has come from observational epidemiology and RCTs. But we must constantly bear in mind that observational epidemiology is still prone to throwing up many misleading findings while RCTs also have important limitations.

The process of concluding that an observed relationship is causal can only be made after evaluating all aspects of the evidence. Convergent evidence that comes from different types of research methods, including animal and mechanistic studies, multiple observational results in which residual confounding is unlikely to be the same across studies, and short-term RCTs may make causal inference reasonable.

The Problems of Conflict of Interest and of Inadequate Research Funding

In the final analysis, science is based on trust. If a researcher publishes a study, one assumes that he has done what he says he has done and the results are indeed those that were seen. Occasionally, a researcher publishes fraudulent data. This, of

course, causes much confusion, wastes the time of many people, and tarnishes the good name of scientists. But such events are fairly rare.

A much more common problem is created by conflict of interest. There is an enormous amount of money tied up in the results of research studies. This problem is most strongly associated with pharmaceutical research [30, 31]. Reports have appeared that suggest that conflict of interest does occur in nutrition research and can distort the findings of some research studies. An analysis was made of studies conducted between 1999 and 2003 on soft drinks, juice, and milk [32]. The findings of each study were classified as being favorable or unfavorable to the industry that sponsored the study. For interventional studies, none of the studies with industry financing reported a finding that was unfavorable, whereas 37% of studies with no industry funding did so. For all types of study, including observational studies and reviews, those with industry financing were 7.6 times more likely to report a finding favorable to industry than studies with no industry financing. Much the same has been reported concerning research on olestra, a fat substitute [33].

In 2009, proposals were made for dealing with conflict of interest with regard to studies which have industry funding, particularly in the area of health, nutrition, and food safety [34].

These problems are very large in nutrition research, perhaps more so than in pharmaceutical research, because of the funding infrastructure. Stringent government regulations of pharmaceuticals have led to huge expenditures to identify and prove new drugs, followed by a period of cost recovery and profit for the patent-protected "winning drugs." Drug research and development operates along relatively simple pathways and leads to potentially valuable findings that can be pursued in government-funded basic research studies. Independent scientists serving as peer reviewers tend to like these detailed mechanistic studies, and many are therefore funded. Nearly everything in this scenario is the opposite of nutrition research. Food is considered "safe" and regulation is in areas such as ensuring that food is safe to eat rather than investigating how food works to promote health or disease. There is no regulatory-induced pot of money directing certain foods into definitive RCTs. Furthermore, unlike drugs, studies of food are not as well suited to detailed mechanistic studies. Such studies then are de facto less appealing to peer reviewers. For that reason government funding, which is not tainted by a profit motive for the product under study, is hard to come by. The food researcher is therefore often left with one obvious source for funding: the food industry. However, we have arrived back at the beginning of the story: the food industry has no incentive to discover aspects of their products that are counter to their profits. The ideal solution to the problem of conflict of interest is probably to create a sufficient body of funds to perform food-based research without such conflict.

Ethical Approval

In most Western countries, research studies involving human subjects can only be carried out after approval has been obtained from an ethics committee. This safeguard is designed to protect the rights of subjects. The procedure is that the research scientist makes an application to an ethics committee. The application must explain the procedures to be used, the potential risks to the subjects, and what safeguards will be taken. Normally, the degree of scrutiny is in proportion to the potential risk. Therefore, the process is normally much quicker and simpler for a study that poses minimal risk than for the test of, for example, an experimental anticancer drug.

One universal rule is "informed consent." This means that at the time that subjects are recruited, the purpose of the study must be explained as well as any potential hazards. This must be done in a way that the person is able to properly understand. Subjects must be free to refuse to participate without feeling pressured and must be free to withdraw from the study at any time without penalty. Therefore, a professor is not allowed to pressure students into "volunteering" for a study and a physician's patients must not feel

concerned that if they decline to participate in a study, this might somehow reduce the quality of the treatment they receive.

A fundamental rule is that the interests of the patient come before the interests of society. Accordingly, even if a researcher sincerely believes that a study is of great importance but poses a risk to the subjects, this does not justify carrying out the study. For example, if the researcher wishes to investigate the effects of consuming a possibly toxic substance, this can only be done by studying people who have accidentally or deliberately consumed the substance; it cannot be done by giving the substance to volunteers. This rule obviously restricts the design of RCTs.

Ethics also covers the protection of patient confidentiality. This means that all personal information collected must be securely stored and can only be viewed by those research personnel who need to see it. Moreover, when the research results are published, no information may be included that identifies any subject (unless the subject gives permission).

Ethical approval must also be obtained in the case of experiments on animals. The rules here are, of course, quite different than with humans. Animals must not be subject to severe pain; there is a blanket ban on such experiments. Moreover, animals must be cared for humanely; they should not be subject to any unnecessary distress except where the experimental procedures being carried out make this unavoidable.

Summary

Excellent research designs are essential for efficiently and accurately answering nutrition-related questions. The answers are of great value in allowing policies to be developed and for transmitting reliable advice to the population regarding, for example, what foods people should eat for health and whether particular substances should be consumed as dietary supplements. Areas of inquiry range from molecular mechanisms in cells, animals, and humans; to descriptions of what population groups eat; to effects of food and nutrient intake on intermediate variables and clinical outcomes; and to behaviors, policies, and cost structures that influence the diet.

This chapter has reviewed the major methods employed in nutrition-related research. Observational epidemiology, which includes several different types of study, has been of major importance in generating a large part of our current knowledge. Cohort studies, in particular, have been of enormous value. Randomized controlled trials (RCTs) are widely viewed as being the most reliable method and can potentially demonstrate cause and effect. However, RCTs have important limitations when used for studying diet–disease relationships. It is debatable whether they are more reliable than cohort studies.

Much research is carried out using mechanistic studies. A critical evaluation indicates that this type of study produces little of any real value in the area of nutrition and health. In contrast, a strong strategy is to base judgments in nutrition on mutual evaluation of both observational and RCT data.

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2 Challenges in Research in Nutritional Epidemiology

David R. Jacobs, Jr.

Key Points

- Diet is a complex aggregate of foods and behaviors.
- Foods are constituted of a wide variety of intended and unintended chemicals which may act singly on human metabolism, but more likely act in groups in a synergistic fashion.
- The study of nutrition and disease in aggregates of people—nutritional epidemiology—is hampered by the difficulty in accurately characterizing what people are eating.
- Reasons for this difficulty include the large day-to-day variability in what is eaten, finding efficient and accurate ways to collect dietary information, minimizing participant burden, and maximizing utility of the data for investigators.
- Much progress has been made in nutritional epidemiology in recent years owing to the use of food frequency questionnaires. These pose little participant burden and are relatively easy to analyze. However, such data collection instruments are still characterized by high within-person variation. They also severely limit collection of important details about the diet.
- A critical concept is whether the participant or the researcher synthesizes the dietary information, including issues such as defining the time period over which to average diet, what to do with unusual information, what constitutes a serving, how foods are grouped (for example, whether fruit juice and fruit drink are grouped together), and what emphasis to put on brand names.
- Progress has been made on protocol changes and computer technology advances that might allow more complete and accurate diet data collection, but problems still exist with these methods.
- It is important to study foods, food groups, and food patterns as well as nutrients and other substances contained in food.
- Where many substances in a food act synergistically, an association will be found with the food.
- There may or may not be associations with individual substances.
- The associations of food patterns with risk provide feedback to policy makers on the likely success of nutritional pronouncements.

D. R. Jacobs, Jr. (✉)
Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA
e-mail: Jacob004@umn.edu

Much has been written about the practice and challenges of research in nutritional epidemiology. For general details concerning this topic, the reader is referred to existing and extensive source

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_2

materials, including *Design Concepts in Epidemiology*, edited by Margetts and Nelson [1] and *Nutritional Epidemiology* by Willett [2]. These books provide myriad technical details on the goals of nutritional epidemiology and the conduct and interpretation of studies, with discussion of potential pitfalls. This chapter focuses on two issues that are particularly challenging in nutritional epidemiology: (1) how to find out what people eat and (2) how to think about the effect of diet on health.

How to Find Out What People Eat

The Nature of Dietary Information

A full characterization of a person's diet would consist of a large number of discrete pieces of information. There are thousands of foods, prepared in myriad ways, and eaten in various amounts and combinations. Even a single "food" such as a carrot [2] or olives [3] presents a challenge, as there are many varieties and genetic variation; growing conditions are influential in food composition. Food industry handling and processing of food tend to alter the food. The timing and context of eating, as well as the number of meals eaten, may all contribute to metabolism of food. Willett [2] discusses at length the actual consumption varies widely from day to day. It may take months for individual diets to settle down to a steady state average.

Each food supplies myriad chemicals. Among these chemicals, Willett [2] lists essential nutrients (vitamins, minerals, lipids, amino acids), major energy sources (fat, protein, carbohydrate, alcohol), additives (preservatives, flavorings), agricultural contaminants (pesticides, growth hormones), microbial toxins (aflatoxins), inorganic contaminants (cadmium, lead), chemicals formed in the cooking or processing of food (nitrosamines), natural toxins (natural pesticides), and other natural compounds (including DNA, enzymes, and enzyme inhibitors, many of which he says are thought of as "incidental to the human diet"). All of these chemicals pertain to each food eaten and can be summarized over the entire diet. The complete characterization of diet, foods, and the chemicals eaten is clearly formidable. At some point in the research process, this large volume of information must be synthesized to be used in data analysis, that is statistical variables such as food groups and nutrients must be defined based on the available information. Detailed information on energy content and nutrients, along with a few natural compounds, is readily available in a variety of food tables, while assessment of the remaining categories requires specialized databases.

Methods of Dietary Assessment

Two primary classes of methods have been used historically to assemble individual dietary information and synthesize it into something usable in data analysis, described in detail by Willett [2]. The first method includes dietary recalls and records. Dietary recalls are obtained by an interviewer assisting the participant to remember precisely what was eaten, usually over the past 24 h. Dietary records, on the other hand, are obtained by having the participant write down what was eaten, shortly after it was consumed; in practice, participants often wait until the end of the day to do their recording so that the record easily transmutes to a self-administered recall. Variations in these methods include weighing foods before eating; collecting a duplicate portion of the food for subsequent chemical analysis; and recording onto partially precoded forms. Dietary recalls may differ in how intensively they inquire about different aspects of diet; for example, an interviewer may inquire deeply and pointedly, to a greater or lesser extent, for hard-to-obtain full information on such topics as alcoholic beverages, salt-containing condiments, or brand names of products. Timing of eating may be obtained so that the integrity of individual meals can be maintained in the database. In both recalls and records, the data consist of a description of the food eaten and its portion size, perhaps with notes on brand names and preparation methods. The fact that a

hamburger and a bun were eaten will generally be maintained in the database, but it is fairly common not to maintain whether the two were eaten as a sandwich.

The second method is a food frequency questionnaire (FFQ), characterized by asking the participant general questions about diet. A typical question would be: "Do you eat hamburgers, and, if so, how often and what is the portion size?" Other kinds of general questions are also common. For example, one might ask: "When you eat a hamburger, is it usually a low-fat variety?" The scope of questions may include related aspects, for example: "Do you prefer white bread or whole wheat bread?" An important aspect is that foods are often grouped: "How often do you eat apples or pears?" FFQs come in several varieties, e.g., from 12 to 250 questions, with and without information about portion size. Those that ask about portion size are called semi-quantitative FFQs. In a popular variant, the Willett-style questionnaire, a portion size is given for each food and frequency of portions is queried. In the other popular variant, the Block-style questionnaire, frequency of eating occasions is queried for each food, with a separate question about portion size. Additional variants exist, for example, in which pictures or food models are provided to facilitate food recognition and portion size estimation.

The dietary history method is closely related to the FFQ. Here, time is spent in general discussion of the diet prior to recording answers to the formal questions; this discussion is thought to improve the context of the interview and help the participant to put together the information needed. In the diet history, the close-ended questions may be general, e.g., "Do you eat red meat?" with an open-ended elicitation of foods eaten for those who answer affirmatively. The CARDIA Diet History [4–6] is of this form: 1609 food codes or recipes were endorsed by at least one of over 5000 participants in one of two administrations of this questionnaire through 1993. Due to expansion of the specific products supplied by industry, the number of food codes endorsed expanded dramatically in the 2005–2006 administration of this questionnaire.

It is probably a coincidence of history that the primary approach to dietary assessment used in cardiovascular disease epidemiology in most major studies through the early 1980s was 24-h recalls; used, for example, in the Lipid Research Clinics [7, 8] and the Multiple Risk Factor Intervention Trial [9, 10]. Special attention was paid to translating the myriad pieces of information into energy and nutrient intake. The synthesis of the data proved quite difficult, and relatively little work was done to study the associations of individual foods or food groups on long-term health outcomes. Where food grouping was done, it was done inflexibly so only certain combinations of foods could be examined. Examination of nutrients within food groups (e.g., monounsaturated fat from plant vs. animal foods) has received little attention. In principle, the data are available for such analyses, but it is unlikely that anyone will ever have the time, money, and study connections for such purposes.

In contrast, cancer epidemiologists have long used FFQs [11]. This choice may be related to the traditional use of the case-control design for uncommon cancers. The desired information was the diet before diagnosis, and this would not be obtainable by recording or recalling current diet. In the cancer epidemiology field, much more has been written about foods and food groups than in the cardiovascular disease epidemiology field. In contrast to analyses of dietary recall data, nutrient analyses within food groups are fairly common. On the other hand, the FFQ obtains much less information than does the recall/record method. For example, information about "yellow and green leafy vegetables" may be all that is collected; therefore, no information is obtained regarding which vegetables were eaten.

An example of a local effort that addresses this issue is the foods and nutrient database maintained in the Department of Nutrition at the University of Oslo, which has long had a food grouping code for each food. As a result analysis of many foods has been available independent of the nature of the method of dietary data collection. Such analysis has been performed fruitfully, also allowing diet pattern analysis to take place

[12]. Further, partially addressing this issue, the Nutrition Coordinating Center in the early 2000s added a food grouping system with 166 food subgroups in its Nutrition Data System for Research (NDS-R) diet analysis system (University of Minnesota, Minneapolis, MN, http://www.ncc.umn.edu, accessed 29 November 2021). The CARDIA database added these for its diet history data in 1985–1986, 1992–1993, and 2005–2006, which has enabled substantial food group analyses. Nevertheless, a great number of details in the CARDIA diet database remain inaccessible, primarily for reasons of cost in pulling those data (other than the preformulated food group) from those massive databases.

Ability to Represent Usual Diet

Two major conceptual differences exist between the recall/record and FFQ methods. The first relates to representativeness of usual diet. The strength of the recall/record method is that it can collect accurate and detailed information about actual consumption of particular meals. However, the particular day or meal is rarely of interest in nutritional epidemiology. It is well agreed that a single day's recall or record is inadequate as a representation of the typical intake [2]. The general experience has been that the recall/record method has not worked well in studies of diet and chronic disease outcomes. Nevertheless, multiple days of recalls or records can represent the typical diet quite accurately, as in the Framingham Children's Study [13, 14]. However, it is rare for large studies to undertake more than one or possibly 2 days of recalls.

The FFQ class of methods, in contrast, asks about the typical dietary pattern during a longer time frame, typically the past year. Many studies have found associations of nutrients and/or food groups with chronic disease outcomes using this method [15]. An even more powerful method uses repeated FFQ assessments during follow-up in a cohort study [16]. When the typical diet is not changing greatly over several years, averaging results from repeated FFQ assessments can be quite powerful.

Who Synthesizes Dietary Information?

The second major conceptual difference between the recall/record and FFQ methods relates to how the myriad dietary details get synthesized into data analytic variables. This refers to the acts of summarizing, as an average, or otherwise characterizing, such as eating or not, discounting or upweighting unusual days or periods, dealing with unusual items, setting defaults for portion size and other aspects that are not specifically known, such as food eaten in restaurants, making fine distinctions, such as between fruit, fruit juice, and fruit drink, focusing on brand names, or not, and how to deal with food that is wasted. In the recall/record method, a huge database is created with near infinite flexibility. The researcher is responsible for putting this information together in a manner that is usable in data analysis. In practice, this synthesis is often limited to energy and nutrient intake analysis; however, it is quite possible that the inherent flexibility of this method may be better utilized in coming years as computer technology continues to improve; for example, as indicated above this has occurred in the interactions between the Nutrition Coordinating Center and the CARDIA study.

In the FFQ class of methods, the participant synthesizes the information. Much potential detail, and therefore flexibility, is lost, but the vastly reduced amount of information collected tends to make it a relatively small job to create arbitrary combinations of food and nutrient variables. It seems likely that the investigators' formal synthesis of multiple recalls or records would be more accurate than the participant's informal synthesis. However, if the investigators' synthesis never gets done, then the participant's synthesis is likely to be of value, despite variability in synthetic capability across participants and difficulty in defining typical patterns. For example, if a person actually drank 20 glasses of milk in a month, including one stretch of 5 days in which 10 of the glasses were drunk, one might say that the typical pattern is two-thirds of a glass per day. As a result of chance, a recall might easily be done on a day when no milk or two glasses

were drunk, thus getting the wrong answer, but it is easy for a person to summarize their pattern into something like a glass every other day.

Some cleverness may be needed in the FFQ mode to get at nutritional concepts with which the public is less familiar, such as whole grain bread. A prime example is the use by Willett of the term "dark bread" to elicit breads that were most likely to have at least moderate whole grain content. Although "dark bread" is a somewhat oblique reference, asking directly about whole grain bread might not have been well understood by participants, and most breads containing a substantial amount of whole grain are darker than American white bread. Dark bread is oblique due to exceptions popular in the US, including pumpernickel cooked with molasses and rye bread made with refined rye. Despite these potential problems, the reference to "dark bread" succeeded in eliciting breads that were inversely associated with coronary heart disease mortality in the Iowa Women's Health Study [15]. Another interesting Willett innovation in an attempt to get at an important detail, and also used in the Iowa Women's Health Study, was the additional query of the brand name of the usual breakfast cereal eaten [15]. Despite the fact that many people eat more than one breakfast cereal, this detail provided the ability to categorize brands, a great boon in the study of whole grains and health.

Similarly, the CARDIA Diet History was innovative in that it was designed to blend recall and synthesis. It asked for the last 30 days of typical intake, recent enough for some level of recall to assist the participant in synthesizing. It also allowed tremendous detail in the participant's self-assessment of typical intake by prompting the participant with 100 general food categories (e.g., eggs), then asking the participant to name all foods consumed within each category. The question, "How often do you eat at fast food restaurants?", while not specifically asking about foods consumed, falls within the FFQ type of query. It has been used fruitfully in finding, for example, that fast food intake appears to promote obesity and insulin resistance [17–19], while eating at "slow food restaurants" does not have the same effect [17, 18].

Can Accurate Dietary Information Be Obtained?

A great deal of progress has been made in understanding the relationship of diet with chronic disease. A great many of our most valuable findings have come from cohort studies where the dietary assessment is based on the use of a FFQ. Nevertheless, validation studies of FFQs against 1–4 weeks of food diaries are somewhat discouraging. It is difficult for most people to summarize their diet accurately. There are several reasons for this including that such summarization requires considerable quantitative ability; that most people simply eat, without making habitual summaries of what they are eating; that diet varies considerably and what is typical for the past month might be different from what is typical for the past year; and that the researchers' questions might not be the optimal formulation for eliciting particular dietary facts. Criterion measures have revealed correlations in the range of 0.3–0.6 between the two methods [5, 20–22]. The resulting within-person error leads to serious problems in interpretation of dietary data [1, 2, 23].

Certain data analytic and interpretive approaches can be helpful. Cautious statements and consistency checks are called for. For example, an assertion that a nutrient is related to incident disease will be stronger if all the foods that contain the nutrient are individually also related to that disease, given that different foods contain different mixes of nutrients [2]. Conversely, if an apparent relationship of disease with a nutrient exists only for a single food that was eaten often and is high in the nutrient, that would be more consistent with the concept that the food, not the nutrient, is causally related to incident disease. Then the causal pathway might rely on a synergy of the components of the food or on a different single nutrient. An example of this type of finding was that phosphorous from dairy, but not from other sources, was inversely related to future hypertension [24]. While this type of finding could reflect synergy of some type, other possible explanations include selective misclassification of the nutrient across the food groups

(e.g., phosphate may be preferentially underestimated for processed foods) or introduction of new confounding. Meta-analysis showing consistency of findings across studies can also be helpful [25, 26]. Nevertheless, the FFQ method appears to have intrinsic limitations in how precisely it can define individual intake.

Here are some possibilities for improvement of the FFQ method: increased precision and innovation of questions; repeated administrations of the questionnaire with averaging to reduce the influence of within-person variation in intake; and enhanced dietary awareness of participants, for example, by encouraging or requiring the participants to keep informal dietary records for a few days prior to filling out the questionnaire or by giving advance instruction in portion size determination.

Because of intrinsic day-to-day variation, a single recall or record does not accurately represent typical dietary information [2]. In contrast, in the Framingham Children's Study, the clarity of findings in only 95 children with repeated diet assessments is impressive [13, 14], but they obtained many more diet records than is typical of studies in nutritional epidemiology. The detail obtained from many repeated dietary records is seductive from a research perspective. This approach, in its flexibility for the researcher, far outstrips the already successful studies, for example, at Harvard and the University of Minnesota, that have relied on FFQs. The multiple diet record method is a powerful cohort study design that generates unlimited accurate dietary characterization and follow-up for many different chronic disease outcomes. However, even with the added power from such a large number of diet records, it is probable that thousands of participants would be needed in studies of remote and rare chronic disease outcomes. In most practical epidemiological situations, the possibilities are limited for obtaining 4–12 24-h diet records per person per year in the assembly line fashion that would be needed for a cohort study of a chronic disease. Given present methodologies, it is unlikely that many studies will achieve this standard. Nevertheless, we can dream.

The success of the internet and the surge in computer power have led to better methods. In particular, there is now widespread collection of self-administered dietary information on the internet, with full software including help and dialog boxes to assist in an interview or to simulate the support currently given by an interviewer. With this technology, the dietary collection instrument could even be a mixture of recall and synthesis. The open-ended methods of the CARDIA Diet History might be helpful. Branching logic for finding food codes could be employed, similar to that currently used by the NDS-R, a "Windows-based software package incorporating a time-tested, highly accurate database with an up-to-date interface," released in 1998 and updated continuously by the Nutrition Coordinating Center of the University of Minnesota [27]. The U.S. National Cancer Institute has the freely available, fairly comprehensive Diet History Questionnaire (DHQ). It is web-based only, including frequency of consumption of 135 food and beverage line items (some have embedded follow-up questions such as type of soft drink) and 26 dietary supplement questions. Versions are available for the past year or past month, with and without questions about portion size when the item is consumed. There is a U.S. version (DHQ III) and a Canadian version (DHQ II available, DHQ III under development). https://epi.grants.cancer.gov/dhq3/, accessed 29 November 2021. The DHQ III remains a fixed questionnaire. One could even envision questionnaires filled out over the telephone or internet, with automated voice prompts to assist in accuracy. As questionnaires accrued, the foods database could automatically expand in line with what was reported by participants, based on artificial intelligence methods. By this means a participant could repeatedly and at their convenience do a 24-h recall or report typical intake over the past week with verbal or online prompts that help find correct food codes and pointed questions to help improve the quality of the information obtained.

One mobile application is called PIQNIQ and was evaluated in a randomized clinical trial

that compared simultaneous entry of provided foods, photo-assisted recall of the foods, or 24-h recalls of the foods [28]. Most nutrients, except added sugar and calcium, were within 30% of the known consumed intake. Accuracy of food intake was not reported.

There is increasing development of technological tools such as wearables and sensors for the collection of dietary data [29]. Many opportunities and challenges in the development of such tools have been reviewed, according to challenges for researchers, users, and developers. Issues include aspects such as enhancing portion size estimation, simplifying, yet maximizing, food lists, minimizing user reactivity, improving convenience, wearability, comfort, and acceptability, improving image-based methods, and preserving privacy in public.

A requisite for exploiting this type of ambitious scheme would be correspondingly simple-to-use programs to extract nutrients, foods, food groups, and food group-specific nutrients. The researcher would require package programs to assemble the data, to formulate and reformulate food groups, and to compute nutrient values. As new information comes along, it could be added to the food table, to simplify study of novel compounds.

Willett [2] comments on another method that has promise, but also pitfalls: correlation of food intake with biomarkers. A biomarker is a chemical measured in some biological sample, commonly blood or urine, but others as well, for example, feces, hair, toenails, cheek cells, adipocytes, and skin scrapings. Minerals reside in toenails, which grow over several months; therefore, this measure represents an average intake over several months. This technique has been used in studies on the relationship between selenium status and risk of cancer [30]. Urinary nitrogen is a marker of nitrogen and therefore protein intake. Sodium and potassium intake are mirrored quite rapidly (over ~2 days) in urinary sodium and potassium. Serum carotenoids and ascorbic acid are highly responsive to both dietary and supplemental intake of the same substances. Freedman and coworkers suggested methods for combining biomarker and diet information to improve accuracy [31, 32]. Despite the undoubted value of biomarkers, they do have limitations as indicators of dietary intake. Each tissue and substance has its own half-life and metabolism. Some tissues store substances, and some utilize them rapidly. The amount of a substance in blood may not be representative of its occurrence throughout the body. The concentration of substances may be maintained homeostatically or may be partially under dietary and partially under homeostatic control. There may be changes in nutrients consumed prior to storage; for example, elongation of fatty acids. For all these reasons, biomarkers are rarely a perfect representations of intake. Furthermore, biomarkers tell us nothing about dietary behaviors. Still, biomarkers have a future in dietary assessment. Research should continue to identify and better understand biomarkers in relation to dietary intake.

What Element of Diet Should Be Studied?

As discussed in section "The Nature of Dietary Information", Willett [2] discussed the different types of substances that are found in food. The number and kind of such substances present a very complex picture. Diet can also be described in terms of food, food groups, or dietary patterns. The early history of nutrition research focused primarily on single substances, with some justification according to Willett. The existence of deficiency diseases such as scurvy (ascorbic acid), rickets (vitamin D), beriberi, pellagra, and neural tube defects (B vitamins) points to one class of nutritional problems. Willett cites a model of Mertz [33] that begins with deficiency disease and death at a sufficiently low level of a nutrient; the model also allows for disease at levels that are sufficiently high. Also in the model is reduced function at modestly reduced or elevated levels of the nutrient. Willett calls this "subclinical dysfunction," a view much in line with the slow, mostly subclinical, development of diseases such as cancer and cardiovascular disease (CVD). There is also a broad plateau at highest function across a wide range of intake of the nutrient.

Willett [2] further asserts that the focus on major energy sources is justified because they are quantitatively important in the diet and manifestly vary markedly across human populations. These focus on nutrients which have led to the development of extensive tables of energy and of these dietary chemicals. Furthermore, there is a strong tendency among basic scientists toward reductionism: the belief that worthwhile knowledge consists of simple pathways linking single nutrients to bodily function and pathogenesis [34, 35], what Willett calls "linkage to our fundamental knowledge of biology." An excellent example is the protective association of folate with neural tube defects [36], as is the improvement in insulin function and metabolic control in diabetics with supplemental magnesium [37]. Much remains to be studied regarding the composition of foods. The tabulated nutrient composition of a food does not fully describe the physiological effect of that food, whether because of differential bioavailability or unknown constituents. There are thousands of untabulated or unidentified compounds in foods, including many phytochemicals.

Foods themselves should also be studied even if that does not immediately lead to additional knowledge of specific biological pathways. Foods are what people eat; and findings regarding foods are directly applicable to people's diets. Most importantly, it is quite likely that there are synergies among food constituents and between foods [38, 39]; studies of individual chemical constituents may never find the relevant pathways because they are more complex than the researchers imagined. In a non-deficiency state, despite findings that foods containing antioxidants are associated with better long-term health, consumption of isolated nutrients or chemicals does not fare so well. The most striking example is that of supplementary beta-carotene, which has been administered in several large, long-term clinical trials, with the effect of increasing disease [40]. Higher antioxidant nutrient intake was associated with more diabetic retinopathy in one study [41]. Other provocative examples from the author's observational work include that supplemental vitamin C in diabetics was associated with increased CVD [42], and that supplemental iron in association with breakfast cereal intake (which is often fortified with iron) was associated with an increased rate of distal colon cancer [43].

These findings are supportive of the concept that food synergies are critically important: the compounds in question are part of foods that appear to be healthy, but do not work outside their food matrix. The food matrix arises from a living organism consisting of thousands of compounds with checks and balances among those compounds to maintain homeostasis and life by preventing the action of any one compound from getting out of control. It is likely that some of this multiplicity of function is retained during human metabolism of the food. For example, whole grain cereals are associated with reduced risk of chronic disease [44–46], as are fruits and vegetables [14, 47], which are high in beta-carotene and vitamin C, among a wide variety of phytochemicals. The concept of food synergy is discussed at greater length in Chap. 23.

In a very simple example of food synergy, vitamin E functions as an antioxidant by accepting electrons, after which it exists in an oxidized state, that is, as a pro-oxidant. To reduce the risk that it will cause damage, it must be reduced, which is done by vitamin C. The vitamin C is then oxidized and must be reduced, and so on until the cycle reaches an end.

Jacobs and Gallaher [44] highlight an interesting historical side note related to the paradigm shift from a focus on nutrients to a focus on food synergy. The earliest study using modern epidemiologic methods of whole grain foods and coronary heart disease was carried out by Morris, Marr, and Clayton [48]. In their study of London busmen, they observed that a diet high in fiber is strongly associated with lower long-term risk of coronary heart disease. This interpretation was forced into a nutrient framework, however. The primary observation was that consumption of brown bread, a good source of whole wheat, was associated with lower risk. Sinclair brought this point to the authors' attention in a letter to the editor [49] in which he discussed the importance of whole grain as a source of essential fatty acids. He noted the botanical roles of essential fatty acids in stability of cellular membranes and

formation of prostaglandins, thromboxanes, and prostacyclin. He also mentioned antagonistic nonessential fatty acids, tocopherols, and vitamin B6. Sinclair's letter reveals how he focused on two fundamental elements of the food synergy paradigm in interpreting the London Busmen data: food (whole grain) and plant physiology. While he did not quite get to the idea of food synergy, he did emphasize the need for broader thinking related to food, rather than solely explaining nutrition in terms of simple nutrient concepts. Nevertheless, it was some years before focuses on dietary patterns and food synergy became a dominant paradigm.

A final aspect of the diet that has been successfully studied is dietary patterns. These have been discovered using factor analysis. For example, much evidence indicates that the Mediterranean dietary pattern has a protective association with CVD, cancer, and type 2 diabetes [50–52]. The association of a food pattern with incident disease is suggestive of a synergy between foods. There has been much advice about a diet that has potential to prevent chronic disease; the lower risk associated with the "prudent" pattern suggests that many people have apparently taken that advice and that the advised diets do have merit in risk reduction.

Summary

This chapter has discussed two particularly challenging issues in nutritional epidemiology. The discussion was done in an editorial fashion. Concerning how to find out what people eat, nutritional epidemiologists use variants of two basic methods. In the first, the participant records or recalls extensive detail about recent intake. The investigator then synthesizes this information into analytically usable variables. This method does not represent the typical diet well unless multiple recalls/records are obtained. In the second method, the participant synthesizes his/her dietary information by responding to general questions about diet, such as how often a particular class of foods is eaten. This method does determine the typical diet, but fails to obtain details that are necessary for many types of analysis. It is hoped that advances in technology will enable simpler and more extensive collection and processing of dietary intake data.

Concerning how to think about the effect of diet on health, I suggest that simple nutrient pathways are inadequate for a full understanding of diet. It is proposed that considerable attention be paid to the foods and food patterns that people eat, as well as to the relationships of these foods and food patterns with disease outcomes.

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3 The Nutrition Transition and the Double Burden of Malnutrition

Malek Batal, Ana Deaconu, and Lara Steinhouse

Key Points

- The nutrition transition is characterized by a dietary shift from traditional foods to modern, globalized foods marked by excessive intakes of sodium, sugar, and saturated fat.
- The latter dietary pattern is associated with obesity and chronic disease.
- An incomplete passage through the nutrition transition makes populations vulnerable to a double burden of malnutrition in which problems of nutrient deficiencies associated with traditional food systems remain unresolved or are even exacerbated, while novel problems related to nutrient excesses appear.
- Economic development, urbanization, and globalization are major drivers of these dietary shifts.
- While these can have positive impacts on diets, they also create inequalities that make certain populations more vulnerable to the double burden of malnutrition.
- The nutrition transition is now mostly observed in low- and middle-income countries.
- However, it also affects particular populations in high-income countries, such as indigenous people in Canada.
- Around the world, indigenous populations safeguard health-promoting food traditions and are key to constructing healthier food systems.

Introduction

The past few decades have witnessed a range of interrelated shifts in demographics, diets, and human health. These changes can be summarized as the demographic transition, the epidemiological transition, and the nutrition transition.

The **demographic transition** refers to the aging of populations as a result of decreased mortality coupled with trends in which families have fewer children, particularly in high-income nations [1]. By 2050, it is expected that the global number of children under 15 and adults over 60 will be nearly equal, and that people over the age of 80 will triple [2]. This aging population will herald new challenges and put added pressure on health systems, particularly given that chronic diseases disproportionately affect the elderly [2]. This evolving health landscape is related to the **epidemiologic transition**, which refers to the shift from high prevalence of infectious diseases related to environmental conditions, such as poor sanitation, to a predominance of chronic, non-

M. Batal (✉) · A. Deaconu · L. Steinhouse
Faculty of Medicine, Nutrition Department, Université de Montréal, Montréal, QC, Canada
e-mail: Malek.batal@umontreal.ca; ana.deaconu@umontreal.ca

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_3

communicable diseases. Poor diets, particularly those characterized by nutrient deficiencies, tend to aggravate infectious disease. However, when nutrient excesses predominate in the diet, they not only aggravate but are directly implicated in many chronic diseases. This latter form of malnutrition, characterized by excesses, has quickly grown in importance over recent decades [1, 3, 4]. Such a historic shift in the nature of disease is thus profoundly related to shifts in the composition of diets and nutritional intake.

The Nutrition Transition

Barry Popkin first coined the term "**nutrition transition"**in the early 1990s to describe a sequence of five nutritional and activity patterns that have emerged historically, with earlier patterns posited to still exist among certain populations [1]. Popkin's characterization of these five patterns is summarized below [1]:

Pattern 1—Collecting food: This diet is characteristic of hunter-gatherer populations and is generally high in carbohydrates and fiber, and low in saturated fat. Lifestyles are active, and obesity is rare.

Pattern 2—Famine: Shifts toward human settlements and agriculture are associated with food scarcity and diets that are much less varied, leading to a reduction in human stature. Meanwhile, social stratification increasingly governs access to nutritious foods.

Pattern 3—Receding famine: As societies progress in reducing chronic hunger, starchy staples become less important and consumption of fruits, vegetables, and animal proteins increases. Meanwhile, activity patterns shift and inactivity becomes a part of some people's lifestyles, including in the form of leisure.

Pattern 4—Chronic diseases: In most high-income societies, and increasingly in some lower-income societies, diets tend to be high in fat, cholesterol, sugar, and other refined carbohydrates, and low in fiber and polyunsaturated fatty acids. These diets, coupled with increasingly sedentary lifestyles, lead to obesity and chronic disease.

Pattern 5—Behavioral change: The desire to prevent disease and prolong health motivates positive changes to diets.

The term nutrition transition originally described the entirety of these five patterns. However, the speed with which many populations are currently undergoing shifts from Pattern 3 to Pattern 4 and the resultant public health imperatives have led the term nutrition transition to essentially be synonymous with the transition between these two stages [5]. In short, it is now used primarily to describe societal shifts from "traditional" food systems with diets characterized by nutritional deficiencies, toward "modern" food systems with diets characterized by nutritional excesses [2]. Although these food systems vary widely across localities, many predominantly traditional food systems feature rural, subsistence smallholder farming, high labor-intensive occupations such as farming and mining, a predominance of home cooking, and dietary diversity dependent largely on the local production of foods. Meanwhile, many predominantly modern food systems are characterized by urban living or by living in well-connected small towns, infrastructure for recreational physical activity, eating out or otherwise consuming pre-prepared meals, and access to a wide diversity of foods that are disconnected from the local agricultural ecosystem [2].

Because high-income countries have already mostly shifted toward modern food systems, the nutrition transition is now observed most broadly in low- and middle-income countries (LMICs). LMICs are also undergoing the nutrition transition much more rapidly than their high-income predecessors, with many notable changes to food systems observed over a matter of years rather than decades. Case Study 1 provides an example in an LMIC context, with emphasis on the unfolding of the transition in farming communities. However, the nutrition transition also continues to be relevant among certain populations in high-income countries. Case Study 2 exemplifies this through its attention to First Nations in Canada.

Drivers and Consequences of the Nutrition Transition

Obesity and Chronic Disease

In 1975, the global prevalence of underweight was twice that of obesity, and obesity was largely viewed as a problem of high-income societies. Since then, the predominant shape of malnutrition has shifted, with obesity now more common than underweight across most of the globe [6]. Between 1975 and 2016, the global obesity prevalence tripled, resulting in 39% of the world's adults being classified as overweight and 13% as obese [7]. In both middle-income and high-income countries, obesity disproportionately affects the poor, contradicting long-held perceptions that problems of nutrient excess are problems of unrestrained privilege [8]. It is only in certain lowest-income countries, such as Haiti, Mali, Nigeria, and Niger, that obesity remains concentrated among people with the highest socioeconomic status [9].

This rise in body mass index (BMI) is coupled with increase in diet-related chronic diseases (also commonly referred to as noncommunicable diseases), such as cardiovascular diseases and type 2 diabetes. Chronic diseases are now responsible for two-thirds of annual deaths worldwide [10]. Much of the astronomical rise in obesity has occurred in low- and middle-income countries [2]; consequently, 80% of deaths related to chronic disease occur in LMICs [10]. In sub-Saharan Africa, for example, cardiovascular diseases have become the leading cause of death, overtaking HIV/AIDs, lower respiratory infections, diarrheal disease, infectious diseases, and malaria [11]. Across the world, the prevalence of diabetes has risen from 4.7% in 1980 to an alarming 8.5% in 2014, with LMICs harboring most of the rise in prevalence of the past decade [12].

The Double Burden of Malnutrition and Its Consequences

Unfortunately, the encroachment of obesity and chronic diseases in countries and communities where it was previously uncommon does not come with a commensurate eradication of undernutrition or of infectious diseases. Many communities find themselves in an uncomfortable limbo between stages of both the epidemiological transition and the nutrition transition: they simultaneously face the public health problems of infectious and chronic disease, and food systems that harbor both under- and overnutrition [2]. Consequently, they experience a "double burden of malnutrition," wherein problems of nutrient excess, such as obesity, coexist with problems of nutrient deficiencies, such as stunting in children and anemia in adults.

This double burden can exist at different levels and take on diverse forms. At a national level, problems of nutrient excess and nutrient deficiency are simultaneously present as severe health concerns for an estimated 44% of the world's countries [13]. At the household level, the double burden exists when some members of the household are overweight or obese while others are underweight, stunted, anemic, or experience nutrient deficiencies. By the turn of the millennium, the proportion of households that had both overweight and underweight was reported as 8% in China, 8% in Russia, and 11% in Brazil [14]. More recently, Guatemalan national nutrition data revealed that an overweight or obese mother lived with a stunted child in 20% of the country's households [15]. Finally, the double burden of malnutrition can exist at the level of the individual; this refers to the situation where an individual experiences the health problems related to both nutrient excesses and deficiencies. For example, in urban areas of Central Africa, 22% of women of child-bearing age are simultaneously overweight (or obese) and anemic [16].

Diet-related chronic diseases are most proximately related to obesity and other issues of nutrient excess, such as excess sugar, sodium, and saturated fat. However, a growing body of evidence also points to a role for undernutrition in aggravating risk for chronic disease [7]. Specifically, people who were undernourished during the prenatal environment or in their first few years of life are more

likely to become overweight as adults, and are also more likely to experience greater severity of metabolic disorders, including diabetes, high blood pressure, and harmful lipid profiles [17–19]. Moreover, people who were undernourished during early life are also more likely to experience chronic disease than counterparts who had the same BMI but had never been undernourished [18, 20]. This exemplifies how the long-term health consequences of the double burden of malnutrition are worse than the sum of its two parts.

Economic Development, Urbanization, and Globalization

The double burden of malnutrition is recognized as the product of an "incomplete" passage through the nutrition transition. In turn, the principal forces driving this are commonly identified as economic development, urbanization, and globalization. Much of both the positive and negative shifts in populations' dietary patterns have been attributed to these three interlinked forces [2]. For example, increased incomes are often accompanied by increase in food purchasing power, thereby expanding food choices and modifying people's dietary preferences. This shift gives people greater access to many of the nutritious foods of their traditional food environment, such as legumes, fruits, leafy vegetables, and animal-source foods (e.g., meat, eggs, and dairy). However, it also provides economic access to foods that are high in fat, sodium, and caloric sweeteners (e.g., sugar, high-fructose corn syrup) and introduces the possibility of excessive animal-source food consumption [2, 21].

These dietary changes tend to first occur in urban centers before they radiate to increasingly rural and remote areas. Because the global population has become increasingly urbanized, more people also find themselves at the heart of urban food environments. Urban centers offer exposure to new foods that can allow people to diversify their diets and adopt new dietary practices. While such abundance can be positive, it can also include exposure to cheap, energy-dense, and micronutrient-poor foods in the retail environment, or through street food and fast food outlets [21]. One of the first such major changes in the food environments of LMICs was the increased availability of cheap vegetable oils, obtained through either import or domestic production. On the heels of this change came steep increase in the availability of sugar-sweetened beverages and packaged foods containing caloric sweeteners (e.g., sugar, high-fructose corn syrup). Finally, LMIC populations are also consuming greater quantities of animal-source foods [21]. While these foods can enable vulnerable populations to meet their nutrient needs—and indeed, they remain out of reach for many of the poorest people and communities—overconsumption brings a new set of health and environmental problems [2].

Economic development and urbanization are inextricable from globalization, and particularly from the global expansion of trade liberalization—that is, policies to promote and facilitate international trade, such as the reduction or elimination of tariffs, protective regulations, and other barriers to free exchange. Trade liberalization, or "free trade," is often credited for improving nutrition and food security, such as by creating employment, increasing household incomes, reducing food prices, and increasing food availability. However, it has now come under a critical reappraisal as free trade can also undermine access to foods and food varieties that are integral parts of people's traditional diets and often replaces them with less nutritious alternatives. For example, when Mexico signed the North American Free Trade Agreement (NAFTA) with the USA and Canada, cheap and largely homogenous yellow corn from the USA flooded into Mexico, pushing many smallholder corn farmers into poverty and undercutting the agricultural systems that maintain the immense diversity of traditional corn varieties—many of which are more nutritious than U.S.-grown yellow corn. Then, when U.S. corn prices rose, Mexico could no longer afford U.S. corn, and could also no longer meet its demand through its own production. This triggered the 2007 Mexican tortilla crisis, wherein a large sector of the population could not access its staple food [22].

Moreover, free trade increases the availability and affordability of the energy-dense, nutrient-poor foods that contribute to obesity. Many of these foods are sold by quickly expanding transnational food corporations, such as fast-food chains and supermarkets. In fact, the globalized food system is marked by an increased concentration of corporate ownership across the entirety of the food supply chain, from production, to processing and supply, and finally to retailing. Backed by powerful marketing strategies these corporations expedite the consumption of the same or very similar products around the world, supplanting the diversity of local foods and cuisines that has evolved over generations [23] and in some cases, even inserting cheap transnational products into local notions of social prestige [24]. Unfortunately, this concentration of power and homogenization of products is deteriorating people's food sovereignty, meaning that they are losing control over the foods they eat, as well as how, where, and from whom they obtain them [25].

Predominance of Ultra-Processed Foods

One of the most emblematic tendencies of the nutrition transition, and perhaps the poster child of modern food, is the increased availability and consumption of processed and ultra-processed foods. In turn, food processing has garnered rapidly growing attention in recent years for its role in affecting nutrition and public health [26, 27]. Traditional food processing in the form of cooking, fermenting, and smoking has long served and continues to serve, human populations in preserving foods and increasing palatability [28]. The history of food processing notwithstanding, in today's increasingly industrialized food system, the term generally refers to "all methods and techniques used by industry to turn whole fresh foods into food products" [29]. At the beginning of the twentieth century, widespread industrial adoption of processes such as pasteurization, canning, and fortifying foods with nutrients improved food safety and reduced food insecurity. But over the ensuing decades, the focus turned away from food safety and turned instead to an in increased interest in convenience and palatability [30]. By the beginning of the 1980s, advances in food science fomented an abundance of cheap convenience foods, high in refined carbohydrates and fat [28].

This evolution of industrial food processing brought a need to distinguish between different forms of food processing for understanding their role in public health and nutrition. Hence, the term "ultra-processed" foods emerged to describe food products that are mostly or entirely formulated from substances that are derived from whole, unprocessed foods, as well as additives. Ultra-processed foods are distinguished from other processed foods because they also include components not normally used in culinary preparations [27]—that is, ingredients whose names and uses are unfamiliar to most consumers, or that consumers would not be able to recognize if they saw them. Carlos Monteiro, a pioneer in research on nutrition and food processing, explains: "These are not modified foods, but formulations mostly of cheap industrial sources of dietary energy and nutrients plus additives, using a series of processes (hence 'ultra-processed')" [27].

Ultra-processed foods are designed to maximize palatability and attractiveness, generally have long shelf lives, and are usually easy to consume on the go. Meanwhile, their sales are supported by aggressive marketing strategies that often promote overconsumption. As a result, ultra-processed foods now dominate food supplies in many high-income countries, and their presence in LMICs is similarly becoming pervasive, supplanting minimally processed foods and freshly prepared dishes [27]. In both the United States and the United Kingdom, for example, recent national dietary data observed that ultra-processed foods make up nearly 60% of individuals' daily caloric intake [31, 32], and in Canada, they make up 47% of intake [33]. In Mexico, Chile, and Brazil, which are middle-income countries, these foods make up 30%, 29%, and 22% of caloric intake, respectively, and their sales in Latin American countries are expanding rapidly [27].

The detrimental impact of ultra-processed foods on public health is increasingly understood as they are associated with obesity and chronic diseases, including diabetes, hypertension, dyslipidemia, and metabolic syndrome in multiple country settings [21, 27, 34]. The problem with ultra-processed foods appears to be less in the processing itself but rather that the food products created have overwhelmingly unhealthy nutrient profiles: they tend to be energy-dense, are high in unhealthy types of fats, refined carbohydrates, free sugars, and sodium, and tend to be low in protein, dietary fiber, and micronutrients. Dietary studies from the United States, the United Kingdom, Mexico, Brazil, Chile, and elsewhere have unambiguously identified associations between higher consumption of ultra-processed foods and unhealthy nutrient consumption patterns, marked by both harmful excesses and deficiencies. As such, high consumption of ultra-processed foods can exacerbate the double burden of malnutrition [27].

Loss of Traditional food Practices

The transition toward new, "modern" foods, such as ultra-processed foods, as well as changes in food-related practices come with a commensurate loss of traditional foods and practices. For example, culinary and mealtime traditions that developed slowly over generations are being quickly displaced by new products and preparations, just as people's ways of eating their foods are being transformed by a changing retail environment, fast food establishments, screens, and changing social practices (e.g., eating alone) [35]. Many of these departures from food traditions come at a nutritional cost. For example, people who consume home-cooked meals less often as well as those who watch screens more often while eating are more likely to be obese [36]. Similarly, pre-prepared meals have been documented to be less nutritious than home-cooked meals [37].

Yet the shift away from traditional food practices is perhaps most striking among Indigenous People, who are quickly losing access to their traditional products, culinary preparations, cultural traditions around food, and ways of obtaining food (e.g., fishing, hunting, gathering, and traditional agricultural practices) [38]. The continued need to eat forces many Indigenous People to consume from a food environment with limited options and that is often suddenly saturated with unhealthy foods due to external economic and political policies or interests [38]. The confluence of the nutrition transition with deeply rooted socioeconomic inequalities and other forms of historic and ongoing marginalization makes Indigenous People disproportionately vulnerable to the double burden of malnutrition in both high-income and low-income country settings [15, 38–40].

On the other hand, retaining stronger traditional food practices—such as consuming traditional products and culinary preparations or obtaining foods through more traditional agricultural practices—has been associated with healthier outcomes both in terms of meeting key nutrient needs and maintaining a healthy body weight [38, 41–43]. Although people who continue to operate in more traditional food systems can also be vulnerable to nutrient deficiencies or even disruptions, such as famines, the documented health-promoting aspects of traditional foods and practices underline the need to better understand and support traditional food systems in an evolving global food context.

Case Study 1 Ecuador

Like many other low- and middle-income countries, Ecuador finds itself at a challenging crossroads: because it has not made a complete passage through the nutrition transition from traditional to globalized foods, it is vulnerable to the nutritional disadvantages of both patterns. Although the country has made remarkable progress in reducing hunger over the past two decades—from affecting one fifth of the population in 2000 to half of that in 2019 [44], pressing deficiencies persist. A nationally representative study conducted in 2012 identified inadequate intake of iron, vitamin A, and zinc among 83%, 77%, and 42% of the population, respectively [45]. Deficiencies of these micronutrients are impli-

cated in the developmental disruptions that are responsible for stunting among 25% of the nation's children under 5 years of age [45]. Meanwhile, two-thirds of the country's adults are overweight or obese, and the top four causes of death are heart disease, type 2 diabetes, cerebrovascular disease, and hypertensive disease [46]. These problems often coexist in close proximity, with 13% of the nation's households sheltering both an overweight or obese mother and a stunted child [45].

This double burden of malnutrition occurs in a dietary context in which the top five contributors to energy intake are rice, bread, chicken, palm oil, and sugar [45]. This underlines the heavy consumption of energy-dense, micronutrient-poor, starchy staples and simple sugars, as well as excessive intake of foods high in saturated fat. Moreover, a shifting food retail environment is driving increased consumption of sugar-sweetened beverages and other processed and ultra-processed foods, which contribute to high intakes of energy, sodium, and unhealthy fats [45]. By 2013, Ecuadorians purchased, on average, 88 kg of processed and ultra-processed foods per year. While this was lower than the Latin American regional average (130 kg) and much lower when compared to Canada (230 kg) or the United States (307 kg), it nevertheless represented an alarming 20% increase over a period of only 3 years [34]. Consumption of such products is likely to further accelerate, given recent years' political enthusiasm for neoliberal trade policies that may broaden the country's aperture for foreign products in its food environment [47].

Nutrition Transition in the Rural Sector

The nutrition transition is apparent in Ecuador at a national level; however, it is far from uniform. In urban sectors, it is mostly characterized by the rapidly increasing consumption of processed and ultra-processed foods, such as snack foods, fast foods, processed meats, and sugar-sweetened beverages, which are readily available [48]. At first glance, the nutrition transition is less evident in rural communities, which maintain many healthful aspects of traditional diets, including using numerous traditional fruits, vegetables, grains, and legumes, and consuming primarily home-cooked meals made from fresh ingredients [49, 50]. Even though most ultra-processed foods do not yet form a substantial part of rural diets, processed foods in the form of culinary ingredients, such as sugars and edible oils, are used in high quantities in home cooking [51]. Home cooking is generally recognized as a healthy dietary practice [52] and is characteristic of earlier stages of the nutrition transition, preceding the emergence of widespread nutrient excesses tied to overweight and obesity. Nevertheless, rural diets in Ecuador depict how heavy use of modern, store-bought ingredients undermine the nutritional advantages of home cooking by adding harmful nutrient excesses to otherwise healthy meals.

Subsistence Farming During the Nutrition Transition

Evidence from rural Ecuador also suggests that smallholder farmers who rely more heavily on foods from their own production are likely to have diets that are more diverse, richer in micronutrients, and with fewer problematic nutrient excesses than the diets of farmers who rely more heavily on market purchases [53]. This adds nuance to the understanding of the nutrition transition, which generally posits that subsistence farming (i.e., producing for own consumption) is associated with diets that are less diverse and poorer in micronutrients than transitioning, market-based diets [54]. While this may be the tendency at a macro scale, it is not the case for this population in the present day. Farmers in Ecuador, who navigate their diets at the crossroads of traditional and modern food systems, show that subsistence farming can play a role in supporting healthy diets in the face of the double burden of malnutrition. Their example also underlines the need to understand how each population is distinct and has a unique trajectory in its path through the nutrition transition.

Case Study 2 Indigenous Peoples in Canada

In Canada, Indigenous People are recognized as belonging to three cultural groups: First Nations, Métis, and Inuit. Traditionally, and prior to European contact, these Indigenous People based their diet on the local resources available in their immediate environment and on exchanges from other neighboring food systems. They lived from hunting, fishing, and gathering, and some also depended on agriculture and livestock. The traditional diet of Indigenous People was thus based entirely on a variety of fresh or minimally processed foods, conserved through processes such as drying, smoking, and freezing. Traditional foods include game meat (e.g., caribou and moose), birds (e.g., goose and duck), fish (e.g., salmon and walleye), and other marine animals, various varieties of squash, beans, and corn, and wild berries [55].

Today, the diet of Indigenous People in Canada is characterized by a variable mix of traditional and commercial foods. Some commercial foods such as flour, sugar, and bread were introduced into the diet at the time of first contact with Europeans. Other foods or beverages have emerged over the course of the twentieth century (soft drinks, snack foods, and frozen meals), particularly in recent decades as the Canadian food supply has changed [56].

Overall, it can be argued that the nutrition transition among Indigenous People is marked by a gradual shift away from traditional foods to commercial foods. There is still very little longitudinal data on the nutrition transition and changes in eating practices among Indigenous People. However, in the Inuit populations of Inuvialuit, Nunatsiavut, and Nunavut, it has been estimated that energy intake from traditional foods among women declined from 40 to 29% of total energy intake between 1999 and 2008 [57]. Among First Nations people living on-reserve in the ten Canadian provinces, current consumption of traditional foods averages between 43 and 98 g per person per day [58].

There are multiple reasons for the abandonment of traditional food by Indigenous People:

- the decline in financial resources allocated to hunting and fishing
- the high cost of hunting and fishing equipment
- the absence of a hunter in the household
- concern about contaminants
- adverse effects of climate change on animal migration and access to marine species
- government restrictions on hunting zoning
- procedures related to meat processing
- negative influence of local industries (especially forestry) on the hunting area
- projects with environmental impacts (mines, dams, etc.)
- a loss of knowledge transfer from elders to younger people [58–60].

On the other hand, paid employment may limit the time and energy spent on traditional subsistence activities, leading to a greater reliance on commercial foods. Finally, the remoteness and geographic isolation of some communities may make it easier or more difficult to rely on traditional foods [58–61]. Indeed, accessibility and convenience are the main advantages reported by First Nations members regarding commercial foods, despite their low nutritional value [58].

Today, traditional foods are mostly consumed and preferred by older Indigenous People, while youth consume more commercial foods [58]. There seems to be a generational effect here where youth are more exposed to a commercial culture that values these foods, which have become even more available in recent years [55].

Nutritional Transition and Impact on Diet Quality

The shift from traditional foods to commercial foods has had a significant impact on the quality of Indigenous diets. Numerous studies in Canada have consistently shown that, taken as a whole, traditional foods are of higher nutritional quality than commercial foods taken as a whole and that

the quality of Indigenous diets is higher on days when traditional foods are consumed [54, 60–63].

The significant differences in nutritional quality between traditional foods and commercial foods may be explained by the fact that most commercial foods available and purchased by Indigenous People today are ultra-processed. Of these, the most commonly consumed foods are sweetened beverages, salty snack foods, industrial breads, and some convenience foods. Such foods contribute significantly to increased intake of sugar, sodium, and energy [62].

Indigenous Health and the Nutrition Transition

The 2008–2018 First Nations Food, Nutrition and Environment Study (FNFNES) [63] revealed major health issues and significant health disparities with the general Canadian population. Indeed, the prevalence of obesity among First Nations persons is as high as 50% in men and 60% in women in some Canadian provinces. Type 2 diabetes affects an average of 21% of First Nations people in Manitoba and 24% of those on-reserve in Ontario (compared to 8.7% in the general Canadian population), leading some to speak of a growing epidemic [64]. It should also be noted that food insecurity affects an average of 48% of First Nations households on-reserve compared to 12% of non-Indigenous households in Canada [65].

Options for Improving the Quality of Nutrition for Indigenous People

Several local, regional, and provincial initiatives have been developed to promote healthy eating [66, 67]. Some of these initiatives are designed and implemented by the communities themselves, while others are developed by government authorities in collaboration with local teams. A glowing example comes from the Syilx Okanagan Nation in the interior of British Columbia where community efforts spanning over a decade managed to bring back the salmon, one of the four food "chiefs" as understood through the captik (oral teaching) of the Nation. Restoration efforts of the Syilx Okanagan Nation— including undamming of waterways, monitoring of water quality, and release of fish fry—emanated from a strong desire to bring back this culturally and spiritually defining food. The newly found salmon abundance was able to support food, social, and ceremonial needs, as well as a transition to a commercial fishery. It was found that the initiative was positively associated with well-being and cultural connectedness [66, 67].

Integrated Responses to the Nutrition Transition

Global evidence on the nutrition transition suggests that it is speeding up, placing more people in the limbo of the double burden of malnutrition [5]. Responding to this double burden, the World Health Organization proposes "double duty" actions which aim to simultaneously address all forms of undernutrition (including wasting, stunting, and micronutrient deficiency) as well as overnutrition (including overweight, obesity, and diet-related chronic diseases). This double duty approach is grounded in the growing understanding that under- and overnutrition do not represent opposite problem-scapes but are instead united by shared drivers. The common roots of these two nutritional problems thus provide an opportunity for integrated solutions, brought to action through interventions, programs, and policies [68]. Recognizing that diet quality is part of a complex food system, others have built on this and call for a "triple duty" approach, in which double duty actions also support other development objectives, such as those related to the environment and social end economic justice [69]. For example, supporting diversity in agricultural production can provide access to a variety of nutrient-rich foods and prevent diet-related chronic disease, as well as support ecosystem health in the agricultural landscape and, if structured properly, empower women farmers. Meanwhile, school meal programs can be designed to prevent both undernutrition and obesity risk among

children while also providing income to farmers [69]. Through such actions, it is possible to safeguard certain practices that may persist from traditional food systems and that have potential to confer health benefits (e.g., supporting agricultural production diversity), as well as to innovate within the evolving modern food system to create positive impacts on dietary health (e.g., well-designed school meal programs). Because it is not feasible to turn back the clock on the nutrition transition, it is critical to alter it trajectory to create a healthier food system.

Summary

This chapter has provided an overview of the nutrition transition, beginning with its original conceptualization and extending to the current understanding of its relevance, particularly in low- and middle-income countries. It explained linkages between the nutrition transition and obesity and chronic disease, as well as with the double burden of malnutrition. It further examined how economic development, urbanization, and globalization generate dietary shifts, including the loss of traditional food practices and the problematic emergence of ultra-processed foods. Finally, two case studies show how the nutrition transition can operate differently in distinct environments: the first case study highlights how the nutrition transition has made harmful inroads in Ecuadorian farming communities that otherwise maintain many aspects of more traditional diets; the second turns to Indigenous People in Canada to exemplify how the nutrition transition can also affect populations within high-income countries. The chapter concluded by summarizing leading ideas for mitigating the consequences of the nutrition transition.

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Part II

Nutritional Control and Prevention of Chronic Diseases

4 Prenatal and Childhood Stressors Promote Chronic Disease in Later Life

Kent L. R. Thornburg

Key Points

- There is a pandemic of chronic disease that is widespread across the globe.
- Low birthweight, as a result of slow fetal growth, is associated with increased rates of coronary heart disease and related disorders including stroke, hypertension, obesity, and type 2 diabetes. These associations extend across the entire range of birthweight.
- People who were small at birth have elevated risks for later disease because they have reduced functional capacity in specific organs, altered settings of hormones and metabolism, or harmful responses to adverse influences in the postnatal environment.
- People born at the high end of the birthweight scale who put on weight rapidly during infancy and early childhood also have elevated risks for chronic disease.
- The most common chronic diseases are the consequences of developmental plasticity, the biological process by which one genotype can give rise to a range of different physiological or morphological phenotypes in response to environmental stressors during development. This is often referred to as programming.
- Slow growth in infancy and rapid weight gain after the age of one year further increase the risk of later disease.
- Slow fetal growth is the product of the mother's body composition and diet before and during pregnancy, together with her metabolism.
- The placenta is complicit in the growth of the fetus and hence in the programing of disease.
- The vulnerability for adult-onset chronic disease can be firmly entrenched during prenatal stages but can also arise independently during childhood when individuals remain plastic, providing the underpinnings for harm from adverse childhood experiences that progress to chronic conditions and mental disorders.

Introduction

In addition to the pandemic caused by SARS-CoV-2, the twenty-first century has seen a separate insidious pandemic of chronic disease the likes of which have not been previously experienced in human history. The chronic disease pandemic has its roots in global changes in environmental conditions which affect human development over the last 3 or 4 generations.

K. L. R. Thornburg (✉)
Knight Cardiovascular Institute, Center for Developmental Health, School of Medicine, Oregon Health and Science University, Portland, OR, USA

Bob and Charlee Moore Institute for Nutrition and Wellness, School of Medicine, Oregon Health and Science University, Portland, OR, USA
e-mail: thornbur@ohsu.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_4

People most severely affected by Covid-19 have underlying conditions that arise in early life.

Over the past 30 years, many of the mechanisms underlying the developmental origins of chronic disease have come to light. It is now clear that chronic diseases arise from structural and epigenetic responses to stressors that bear on developmental processes during gametogenesis, embryo and fetal development, and postnatal stages through childhood. The genetic mechanisms that underlie mammalian development accommodate stress by allowing modifications of organ growth and epigenetic patterning throughout prenatal life and childhood. Thus, the process known as developmental plasticity links environmental conditions in the womb and childhood with risks for lethal conditions that arise over the life course.

Impact of Growth in Fetal Life and Childhood on Risk for Chronic Disease in Later Life

In the county of Hertfordshire, UK, from 1911 onwards, women delivered their babies attended by a midwife who recorded the birthweight. A health visitor went to the baby's home at intervals throughout infancy, and the weight at one year was recorded. These data have been studied in relation to groups of men and women in middle or late life. Among the first studies, which were carried out three decades ago, were those in 10,636 men born during 1911–1930 [1, 2]. Standardized mortality ratios for coronary heart disease (CHD) fell with increasing birthweight. There were stronger trends with weight at one year. A subsequent study confirmed a similar trend with birthweight among women [2]. Studies from this cohort showed that the percentage of men with impaired glucose tolerance or type 2 diabetes fell steeply with increasing birthweight and with weight at one year (Fig. 4.1). There were similar trends with birthweight among women. The striking conclusion from these studies is that the risk for insulin resistance or type 2 diabetes was some 7–8 times higher for men born at the low end of the birthweight scale compared to those in the normal weight range.

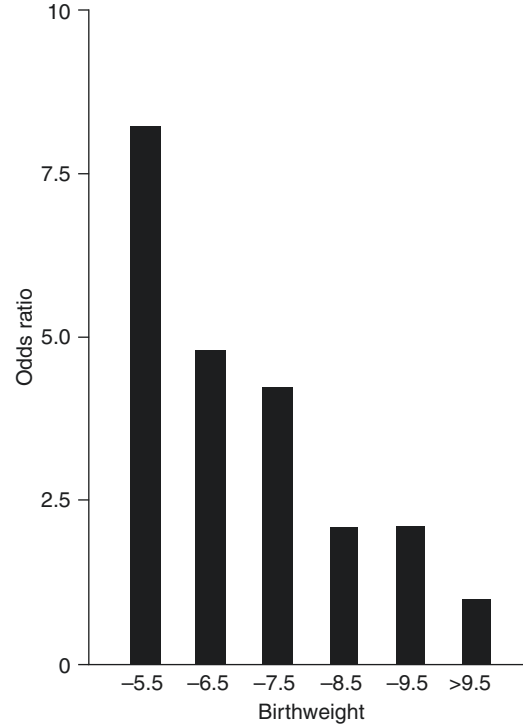

Fig. 4.1 Odds ratios for impaired glucose intolerance or type 2 diabetes according to birthweight among 370 men age 64 years born in Hertfordshire (adjusted for body mass index) [3]

The association between low birthweight and CHD has now been replicated among men and women in Europe, North America, and India [4–10]. The association between low weight gain in infancy and CHD in men has been confirmed in Helsinki, Finland [11]. Low birthweight has been shown to predict altered glucose tolerance in studies around the world [12–16].

The discovery that people who develop CHD grew differently compared to other people during fetal life and childhood points to early life causes for this chronic disease [1, 17]. Recent studies have consistently shown that babies born at the high end of the birthweight scale or who acquired excess fat during early childhood also have elevated risks for obesity, metabolic disease, and heart disease as shown in Fig. 4.2 [20]. Thus, the relationship between birthweight and cardio-

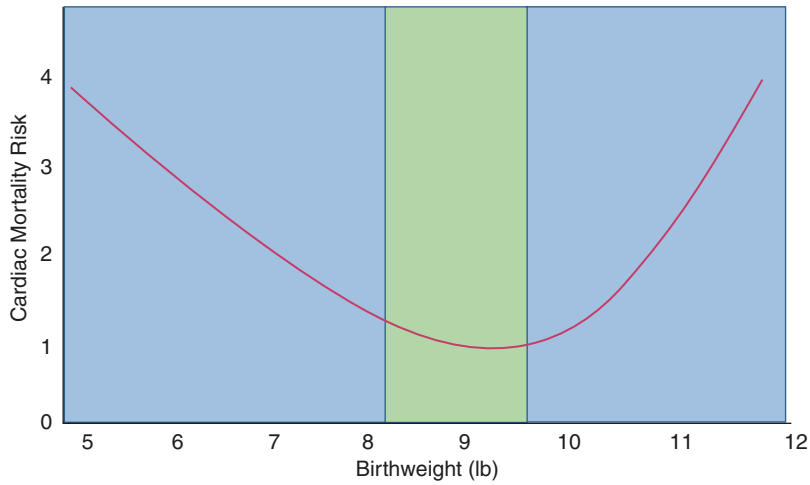

Fig. 4.2 Standard Mortality Ratio for ischemic heart disease in men and women of Hertfordshire, UK. Babies born in the green zone had the lowest risk for mortality related to heart disease [1, 18, 19]

metabolic disease is "U" shaped which reflects the fact that extreme growth patterns before birth alter the structure and physiology of offspring in such a way that they are at high risk for a chronic disease as adults [18, 21].

Possible Importance of Confounding Variables

These findings suggest that early growth influences have an important effect on the risk of CHD and type 2 diabetes. In a number of studies, data were collected on lifestyle, including smoking habits, employment, alcohol consumption, and exercise. In the Nurses' Health Study in the USA, allowance for these influences had little effect on the association between birthweight and CHD [6]. Similar results came from Sweden and the UK [3, 8]. In studies of type 2 diabetes and blood pressure, the associations with size at birth were independent of social class, cigarette smoking, and alcohol consumption. Adult lifestyle, however, adds to the effects of early life: for example, the prevalence of impaired glucose tolerance is highest in people who had low birthweight but became obese as adults [3, 12–16]. As described later in this chapter, slow fetal growth may also heighten the body's response to socioeconomic influences in later life. Associations between low birthweight and altered glucose tolerance and raised blood pressure have been found in numerous studies of children, which is a further argument against these associations being the product of confounding variables in adult life.

Early life stressors can lead to profound elevation of disease risk for the remainder of one's lifetime. However, it is becoming increasingly clear that over the life course this risk can be elevated or ameliorated by lifestyle choices [22] but not to the degree found in early life. Regardless of risk modifications made during adult life, one point is clear, a person's vulnerability for acquiring and dying of a chronic disease is most strongly influenced by stress exposure in early life. Strategies for significantly improving the health of any given population are bound to fail without taking this fact into account.

Adverse Childhood Experiences

There is no doubt that developmental plasticity is very sensitive to environmental stressors in the embryo and fetus. The early designation as the fetal origins of adult disease was expanded to the

1000 days concept that included stress from conception onward through infancy. This concept continues to be important [23]. However, both human and animal data show that vulnerability for disease due to detrimental alterations in structural and epigenetic regulation remain after birth and in childhood but gradually subside through life as plasticity wanes. The detrimental outcomes of childhood trauma represent links between the adverse experiences and elevated risk for many of the same conditions associated with the extremes of birthweight. There is now a large body of literature that associates adverse childhood experiences (ACEs) with risk for chronic diseases, including psychiatric disorders in later life [24]. What is missing from the ACEs discussion is nutritional stress during childhood which can lead to similar outcomes.

Biological Basis

Developmental plasticity is evident when one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development [25]. The fetal heart is a good example of developmental plasticity. If a sheep fetus becomes anemic for even a few days, the heart responds by increasing the diameter but not the density of its capillaries. Flow conductance then doubles in the fetus and lasts into adulthood [26]. Developmental features that predispose an individual for disease risk in later life are the essence of developmental plasticity: a critical period when a system is plastic and sensitive to the environment, followed by loss of plasticity with maturation and a fixed functional capacity. For most organs and systems, the majority of critical periods occurs in utero but some last well into childhood.

There are good reasons why it may be advantageous, in evolutionary terms, for the body to remain plastic during development. It enables the production of phenotypes that are better matched to their environment than would be possible if the same phenotype was produced in all environments. Plasticity during intrauterine life enables animals, and humans, to receive a "weather forecast" from their mothers that prepares them for the type of world in which they will live [27]. If the mother is poorly nourished, she signals to her unborn baby that the nutritional environment it is about to enter is likely to be harsh. The baby responds to these signals by adaptations, such as reduced body size and altered metabolism, which help it to survive a shortage of food before and after birth. Thus, there may be immediate and long-term survival value in the biological adaptations to adverse conditions, both before and after birth. In this way, plasticity gives a species the ability to make short-term adaptations, within one generation, in addition to the long-term genetic adaptations that come from natural selection. The price for survival adaptations may be a heightened propensity for disease and a shorter life span.

As Mellanby noted many years ago, the ability of a human mother to nourish her baby is partly determined when she herself was in utero, and by her childhood growth. The human fetus is continuously receiving environmental signals based not only on conditions at the time of the pregnancy but also on conditions a number of decades before [28, 29]. This may be advantageous in populations which frequently experience periodic food shortages.

The different sizes of newborn human babies exemplify plasticity. The growth of babies has to be constrained by the size of the mother, otherwise normal birth could not occur. In pregnancies after ovum donation, smaller women tend to have smaller babies even if the woman donating the original ovum was large [30]. Babies may be small because their growth is constrained in this way or because they lack the nutrients for growth. As McCance wrote long ago, "The size attained in utero depends on the services which the mother is able to supply. These are mainly food and accommodation" [31]. Since the mother's height or pelvic dimensions are generally not found to be important predictors of the baby's long-term health, research into the developmental origins of disease has focused on the nutrient supply to the baby, while recognizing that other influences, such as hypoxia, toxic chemicals, maternal conditions, and stress, also influence fetal growth. This focus on fetal nutrition

has been endorsed by nutrition scientists [32]. The National Institutes of Health in the USA has included the role of nutrition in the developmental origins of health and disease as one of its top research priorities [33–35].

Fetal Life and Responses to Stressors

There are five categories of stress that are associated with "developmental programming" in offspring during pregnancy, namely: (1) nutritional stress, (2) accumulated social stress burden, (3) exposure to toxic chemicals, (4) hypoxia, and (5) specific maternal medical conditions that compromise fetal development. Many babies are born having been exposed to several of these stressors simultaneously.

One might ask, *Why should fetal responses to undernutrition lead to disease in later life?* The general answer is clear: "*life history theory*," which embraces all living things and states that during development, increased allocation of energy to one trait, such as brain development, necessarily reduces allocation to one or more other traits, such as tissue repair processes. This must be true for human development because energy allocation to the growing fetus is finite. Smaller babies, who have had a lesser allocation of energy, must incur higher costs and these, it seems, include disease risk in later life. In this case, the price of survival in the womb may be a shorter lifespan. A specific answer to the question, however, is that people who were small at birth are vulnerable to later disease through three kinds of processes.

First, they have fewer cells in key organs, such as the kidney.

Second, slow fetal growth may be linked to later disease in the setting of hormones and metabolism.

Third, there is a link between low birthweight and later disease in that people who were small at birth are more vulnerable to adverse environmental influences in childhood and in later life.

Thus, further severe stresses in later life more easily lead to type 2 diabetes, hypertension, and CHD. Observations on animals show that the environment during development permanently changes not only the body's structure and function but also its responses to environmental influences encountered in later life [27]. Table 4.1 shows the effect of low income in adult life on CHD among men in Helsinki [36]. As expected, men who had a low income had higher rates of the disease. There is no agreed explanation for this, but the association between poverty and CHD is a major component of the social inequalities in health in many Western countries and exemplify the importance of the social determinants of health. Among the men in Helsinki the association was confined to men who had slow fetal growth and were thin at birth, defined by a ponderal index (birthweight/length [4]) of less than 26 kg/m^3 (see Table 4.1). Men who were not thin at birth showed no association between CHD and income, suggesting that they were resilient to the biological effects of low income.

One explanation for these findings is based on the psychosocial consequences of a low position in the social hierarchy, as indicated by low income and social class, suggesting that perceptions of low social status and lack of success lead to changes in neuroendocrine pathways and hence to disease [37]. The findings in Helsinki seem consistent with this. People who were small at birth are known to have persisting alterations in responses to stress, including raised serum cortisol concentrations [38]. It is suggested that persisting small elevations of cortisol concentrations over many years may have effects similar to those seen when tumors lead to more sudden,

Table 4.1 Hazard ratios (95% CI) for CHD among 3676 men in Helsinki according to ponderal index at birth (birthweight/length^3) and taxable income in adult life [36]

Household income in pounds sterling/year	Hazard ratios	
	Ponderal index ≤26.0 kg/m^3 (n = 1475)	Ponderal index >26.0 kg/m^3 (n = 2154)
>15,700	1.00	1.19 (0.65–2.19)
15,700	1.54 (0.83–2.87)	1.42 (0.78–2.57)
12,400	1.07 (0.51–2.22)	1.66 (0.90–3.07)
10,700	2.07 (1.13–3.79)	1.44 (0.79–2.62)
≤8400	2.58 (1.45–4.60)	1.37 (0.75–2.51)
P for trend	<0.001	0.75

large increase in glucocorticoid concentrations. People with Cushing's syndrome caused by an over-active adrenal cortex tend to be insulin resistant and have raised blood pressure, both of which predispose to CHD.

It is now clear that toxic social stress during pregnancy (allostatic load) leads to changes in placental function and fetal growth. Mothers with high cortisol levels have smaller offspring who are more likely to have a chronic condition as adults. Toxic stress does not refer to the normal day-to-day stressors of ordinary life during pregnancy. Rather, it refers to severe circumstances like racism, intimate partner abuse, low socioeconomic status, housing insecurity, unemployment, and fear related to personal safety. These conditions affect placental health [39] and often occur in women who also have poor diets. The relationship between maternal stress and placental form and function has been little studied but is believed to be an important process by which fetal health is compromised.

Childhood Growth and Coronary Heart Disease

The growth of 357 men who were either admitted to hospital with CHD or died from it is shown in Fig. 4.3 [19]. They belong to a cohort of 4630 men who were born in Helsinki. Their mean height, weight, and body mass index (BMI, weight/height [2]) at each month from birth to 2 years, and at each year from ages 2 to 11, are expressed as standard deviations (z-scores). The mean z-score for the cohort is set at 0 and a boy maintaining a steady position as tall or short, or fat or thin, in relation to other boys would follow a horizontal path on the figure. The mean body size of the boys who later had CHD was approximately 0.2 standard deviations below the average and they were thin. Between birth and 2 years, mean z-scores for each measurement fell so that at 2 years the boys were thin and short. After 2 years, their z-scores for BMI began to increase and continued to do so. In a simultaneous regression, both low BMI at 2 years and high BMI at age 11 were associated with later coronary events ($p < 0.001$ and $p = 0.05$, respectively). When BMI at birth was added to the model, the measurements of body size at each of the three ages were associated with later coronary events ($p = 0.04$ for low BMI at birth, $p = 0.001$ for low BMI at 2 years, and $p = 0.03$ for high BMI at 11 years).

As with the boys, the mean body size of the 87 girls who later had coronary events was below the average. They tended to be short at birth rather than thin, but their mean z-scores for BMI fell progressively after birth so that, like the boys, they were thin at age 2 years. After age 4, the z-scores began to increase and continued to do so, exceeding the average at approximately 6 years. Similarly to the boys, in a simultaneous regression body size at each of the three ages was associated with later coronary events ($p = 0.02$ for short length at birth, $p = 0.002$ for low BMI at 2 years, and $p = 0.02$ for high BMI at 11 years).

Hazard ratios for CHD according to birthweight and fourths of BMI at age 11 among 13,517 men and women in Helsinki born during 1924–1944 are shown in Table 4.2 [40]. The risk of the disease fell with increasing birthweight and rose with increasing BMI at age 11. The pattern was similar in both sexes.

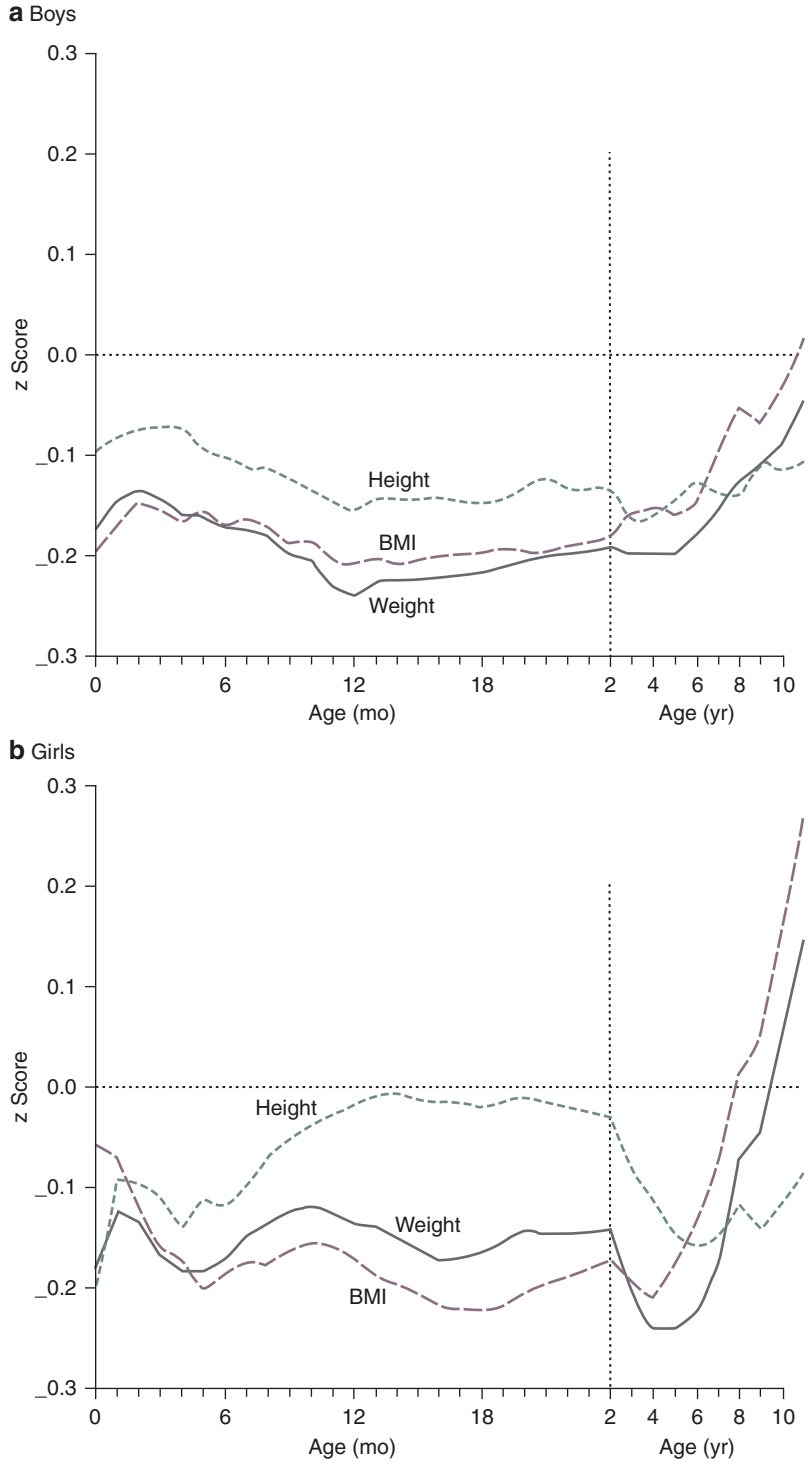

Fig. 4.3 Height, weight, and body mass index (BMI) in the first 11 years after birth among boys and girls who had coronary heart disease as adults. The mean values for all boys and all girls are set at 0, with deviations from the mean expressed as standard deviations (*z*-scores). Figure "a" represents the growth patterns of boys who later acquired coronary artery disease as adults. Affected boys stayed thin throughout infancy; the steady increase in BMI in childhood is characteristic for that risk. Figure "b" represents the growth patterns of girls who had coronary artery disease as adults. Note the steep rise in BMI that began at age 4 years

Table 4.2 Hazard ratios for coronary heart disease according to birthweight and body mass index (BMI) at age 11 years among 13,517 men and women in Helsinki

	BMI at age 11			
Birthweight (kg)	<15.7	−16.6	−17.6	>17.6
Hospital admissions and deaths (1235 cases)				
<3.0	1.4	1.6	1.8	2.1
−3.5	1.3	1.5	1.5	1.6
−4.0	1.3	1.4	1.3	1.4
>4.0	1.0	1.2	1.1	1.0
Deaths (480 cases)				
<3.0	1.4	1.8	2.1	3.0
−3.5	1.4	1.9	2.2	2.7
−4.0	1.9	1.8	1.7	1.6
>4.0	1.0	1.4	1.6	1.3

Type 2 Diabetes and Hypertension

People who at birth were small or very large remain biologically different from people who were average sized; these differences include an increased susceptibility to type 2 diabetes and hypertension. Table 4.3 is based on the same cohort of men and women shown in Table 4.2, and shows odds ratios for type 2 diabetes and hypertension according to birthweight and fourths of BMI at age 11 years. The two disorders are associated with the same general pattern of growth as CHD [40]. Risk of disease falls with increasing birthweight and rises with increasing BMI.

Associations between low birthweight and type 2 diabetes have been found in other studies [3, 12–16]. The association with hypertension has also been found elsewhere [41]. There is a substantial literature showing that birthweight is associated with differences in blood pressure and insulin sensitivity within the normal range [3, 12, 16, 42]. These differences are found in children but they tend to be small. A 1-kg difference in birthweight is associated with around 3 mmHg difference in systolic pressure. The contrast between this small effect and the large effect on adult hypertension (see Table 4.3) suggests that abnormalities that accompany poor fetal growth and tend to elevate blood pressure, and which may include a reduced number of glomeruli, have a small influence on blood pressure within the normal range; this is because counter-regulatory mechanisms maintain normal blood pressure levels. As the abnormalities worsen through, for example, hyper-filtration of the reduced number of glomeruli and consequent glomerulosclerosis, these mechanisms are no longer able to maintain homeostasis and, as a result, blood pressure rises. The rise in blood pressure results in progression of lesions and further rises in blood pressure [35, 43, 44]. Direct evidence in support of this has come from a study of the kidneys of people killed in road accidents. Those being treated for hypertension had fewer, but larger, glomeruli [45]. Evidence to support the development of self-perpetuating cycles comes from a study of elderly people in Helsinki among whom the effect of birthweight on blood pressure was confined to those being treated for hypertension

Table 4.3 Odds ratios (95% confidence intervals) for type 2 diabetes and hypertension according to birthweight and BMI at age 11 years among 13,517 men and women in Helsinki

Birthweight	BMI at age 11 year			
(kg)	<15.7	−16.6	−17.6	>17.6
Type 2 diabetes (698 cases)				
<3.0	1.3 (0.6–2.8)[a]	1.3 (0.6–2.8)	1.5 (0.7–3.4)	2.5 (1.2–5.5)
−3.5	1.0 (0.5–2.1)	1.0 (0.5–2.1)	1.5 (0.7–3.2)	1.7 (0.8–3.5)
−4.0	1.0 (0.5–2.2)	0.9 (0.4–1.9)	0.9 (0.4–2.0)	1.7 (0.8–3.6)
>4.0	1.0	1.1 (0.4–2.7)	0.7 (0.3–1.7)	1.2 (0.5–2.7)
Hypertension (2997 cases)				
<3.0	2.0 (1.3–3.2)	1.9 (1.2–3.1)	1.9 (1.2–3.0)	2.3 (1.5–3.8)
−3.5	1.7 (1.1–2.6)	1.9 (1.2–2.9)	1.9 (1.2–3.0)	2.2 (1.4–3.4)
−4.0	1.7 (1.0–2.6)	1.7 (1.1–2.6)	1.5 (1.0–2.4)	1.9 (1.2–2.9)
>4.0	1.0	1.9 (1.1–3.1)	1.0 (0.6–1.7)	1.7 (1.1–2.8)

[a]Odds ratios adjusted for sex and year of birth

[46]. Despite their treatment, the blood pressures of those who had low birthweight were markedly higher, whereas among normotensive subjects, birthweight was unrelated to blood pressure. Whether measured in the clinic or by ambulatory methods, there was >20 mmHg difference in systolic pressure between those who weighed <2500 g (5.5 lb) at birth and those who weighed >4000 g (8.8 lb). An inference is that by the time they reach old age most of the people with propensities acquired in utero have developed clinical hypertension. Studies in South Carolina bear on this issue. They show that among 3236 hypertensive patients, blood pressures of those with low birthweight tended to be more difficult to control with medication [47]. Investigations of the role of nephrons on disease will benefit as new methods to evaluate nephron number become available [48].

The growth of boys and girls who later developed type 2 diabetes is shown in Fig. 4.4. They had below average body size at birth and at 1 year, after which their weight and BMI rose progressively to exceed the average [50]. Table 4.6 shows the relation between age at "adiposity rebound" and later type 2 diabetes. After the age of 2 years, the degree of obesity of young children, as measured by BMI, decreases to a minimum around 6 years of age before increasing again—the so-called adiposity rebound. The age at adiposity rebound ranges from around 3 to 8 years or more. The early adiposity rebound is strongly related to a high BMI in later childhood, as has previously been shown [49] and is evident in Table 4.4. It also predicts an increased incidence of type 2 diabetes in later life. This new observation has been replicated in a longitudinal study in Delhi, India [51]. In both studies, an early adiposity rebound was also associated with thinness at birth and at one year [50, 51]. It is not therefore the young child who is overweight that is at the greatest risk of type 2 diabetes but the one who is thin but subsequently gains weight rapidly. There is, however, another path of growth that leads to type 2 diabetes: babies born to mothers with severe obesity or gestational diabetes are heavy at birth and become overweight or obese as children.

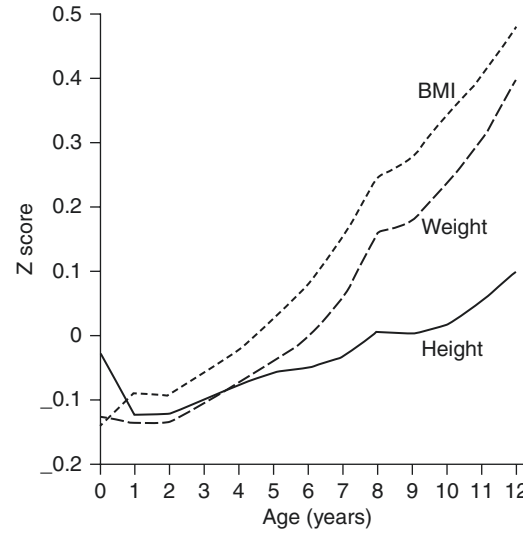

Fig. 4.4 Mean standard deviation scores (z-scores) for height, weight, and BMI during childhood in 290 boys and girls who later developed type 2 diabetes within a cohort of 8760 children. At any age, the mean z-score for the cohort is set at 0 while the standard deviation is set at 1 [49]

Table 4.4 BMI at age 11 years and cumulative incidence of type 2 diabetes according to age at adiposity rebound in 8760 men and women in Helsinki

Age at adiposity rebound (year)	Mean BMI at age 11	Cumulative incidence of diabetes % (n)		
	All	Men	Women	All
≤4	19.7	8.1 (86)	8.9 (112)	8.6 (198)
5	17.6	6.2 (904)	2.5 (864)	4.4 (1768)
6	17.0	3.7 (1861)	2.5 (1456)	3.2 (3317)
7	16.8	2.4 (249)	2.1 (243)	2.2 (492)
≥8	16.7	3.0 (135)	0.7 (150)	1.8 (285)
p for trend	<0.001	<0.001	0.002	<0.001

Compensatory Growth

When undernutrition during early development is followed by improved nutrition, many animals and plants stage accelerated or "compensatory" growth [40]. This growth pattern has costs, however, which in animals include reduced lifespan

[52]. A recent paper from Helsinki describes how compensatory growth among boys is associated with increased mortality from all causes and therefore a reduced lifespan [53]. There are a number of processes by which, in humans, undernutrition and small size at birth followed by rapid childhood growth could lead to cardiovascular disease and type 2 diabetes in later life [11, 14]. Rapid growth may be associated with persisting hormonal and metabolic changes. Larger body size may increase the demand on functional capacity that has been reduced by slow early growth—fewer glomeruli, for example. Rapid weight gain may lead to an unfavorable body composition. Babies that are small and thin at birth lack muscle, a deficiency that will persist as the critical period for muscle growth occurs in utero and there is little cell replication after birth [54]. If they develop a high body mass during later childhood, they may have a disproportionately high fat mass in relation to lean body mass, which will lead to insulin resistance [55]. The biological propensity for small babies to experience "catch-up" or compensatory growth offers a dilemma for pediatricians. Many physicians are now adhering to a healthy moderate growth trajectory for small infants in order ameliorate the adverse effects of putting on excess fat [56].

Pathways to Disease

New studies, especially the Helsinki studies with their detailed information on child growth and socioeconomic circumstances, increasingly suggest that the pathogenesis of CHD and the disorders related to it depend on a series of interactions occurring at different stages of development. One important interaction relates to genes acquired at conception. In a study of 476 elderly people in Helsinki [57] mean fasting plasma insulin concentrations were grouped according to two polymorphisms of the peroxisome proliferator-activated receptor gene (PPAR-γ). The Pro12Ala polymorphism was associated with insulin resistance. However, insulin resistance occurred only among subjects who had low birthweight. Conversely, low birthweight has been consistently linked to later insulin resistance [16], but this effect occurred only among people with the Pro12Ala polymorphism. As birthweight serves as a marker of fetal nutrition [32], this gene–birthweight interaction may reflect a gene–nutrient interaction during development. It is becoming increasingly recognized that aging and disease risk are related to genotype as well as to epigenotype [58]. The mechanisms by which gene sequences interact with epigenetic modifications require additional research.

The effects of the intrauterine environment on later disease are conditioned not only by events at conception but by events after birth. Table 4.5 shows how the effects of low birthweight on later hypertension are conditioned by living conditions in childhood, indicated by the occupational status of the father [59]. Among both men and women, low birthweight was associated with an increased incidence of hypertension, as has been shown before [41]. This association, however, was present only among those who were born into families where the father was a laborer or of lower middle class.

It seems that the pathogenesis of cardiovascular disease and type 2 diabetes cannot be completely explained by a linear model in which risks associated with adverse influences at different stages of life add to each other [60]. Disease can also arise as the product of branching paths of development. The environment triggers the branchings, and these determine the vulnerability of each individual to what lies ahead. The pathway to CHD can originate either in slow fetal growth as a consequence of undernutrition or in

Table 4.5 Cumulative incidence % of hypertension according to birthweight and father's social class in 8760 men and women in Helsinki

	Father's social class			
Birthweight (g)	Laborer	Lower middle class	Upper middle class	*p* for trend
<3000	22.2	20.2	10.5	0.002
−3500	18.8	15.2	10.6	<0.001
−4000	14.5	12.5	10.3	0.04
>4000	11.1	15.6	15.7	0.11
p for trend	<0.001	0.05	0.79	

poor infant growth as a consequence of poor living conditions.

Strength of Effects

The effects of slow fetal growth and low birthweight, and the effects of postnatal development, depend on the environmental influences and paths of development that precede and follow them. Low birthweight, or any other single influence, does not have "an" effect that is best estimated by a pooled estimate from all published studies. *Low birthweight, though a convenient marker in epidemiological studies, is an inadequate description of the phenotypic characteristics of a baby that determine its long-term health.* The wartime famine in the Netherlands produced lifelong insulin resistance in babies who were in utero at the time, but there was little alteration in birthweight [61]. In neonates, as in children, slowing of growth is a response to a poor environment, especially undernutrition, but body weight at birth does not adequately describe the long-term morphological and physiological consequences of undernutrition. The same birthweight can be attained by many different paths of fetal growth and each is likely to be accompanied by different gene–environment interactions and different epigenetic patterns [32]. Nevertheless, birthweight provides a basis for estimating the magnitude of the effects of the fetal phase of development on later disease, though it is likely to underestimate them.

Because the risk of cardiovascular disease is influenced both by small body size at birth and during infancy and by rapid weight gain in childhood, estimation of the risk of disease attributable to early development requires data on fetal, infant, and childhood growth. Currently, the Helsinki studies are the main source of this information [40]. Men and women who had birthweights >4 kg (8.8 lb) and whose prepubertal BMI was in the lowest fourth had around half the risk of CHD when compared with people who had birthweights <3 kg (6.6 lb) but whose BMI at age 11 years was in the highest fourth (Table 4.2). The hazard ratios for hospital admissions and deaths were 0.80 (95% CI 0.72–0.90) for each kilogram increase in birthweight and 1.06 (1.03–1.10) for each kg/m^2 increase in BMI at age 11. The hazard ratios for deaths alone were 0.83 (0.69–0.99) and 1.10 (1.04–1.16), respectively.

Other findings are presented in Table 4.6. Subjects were divided according to thirds of body size at birth and the decrease or increase in standard deviation score for BMI between ages 3 and 11 years. In both men and women, the highest incidence of CHD was seen in those who were in the lowest third of birthweight and whose stan-

Table 4.6 Cumulative incidence % of CHD according to body size at birth and change in standard deviation score for BMI between ages 3 and 11 years among 6345 men and women in Helsinki

Birth size	Change in standard deviation score for BMI between ages 3 and 11	
	Decrease	Increase
Men		
Birthweight (kg)		
<3.2	8.8 (512)	9.0 (476)[a]
−3.6	6.9 (662)	11.3 (512)
>3.6	5.9 (740)	8.6 (521)
Ponderal index (kg/m^3)		
<25	8.0 (411)	11.7 (394)
−27	7.6 (649)	10.8 (556)
>27	6.2 (838)	7.2 (539)
Women		
Birthweight (kg)		
<3.2	1.6 (563)	3.8 (604)
−3.6	1.5 (612)	2.5 (438)
>3.6	0.7 (450)	3.6 (334)
Birth length (cm)		
<49	1.5 (543)	4.2 (520)
−50	1.5 (452)	3.3 (338)
>50	0.8 (609)	2.6 (496)

[a]Cumulative incidence, % (*n*) of coronary heart disease (hospital admissions and deaths). There were 279 cases in men and 66 in women

Table 4.7 Cumulative incidence % (number of subjects) of type 2 diabetes and hypertension according to birthweight and change in standard deviation score for BMI between ages 3 and 11 years among 6424 men and women in Helsinki

Birthweight (kg)	Change in standard deviation score for BMI between ages 3 and 11	
	Decrease	Increase
Type 2 diabetes (227 cases)		
<3.2	3.1 (1075)	5.5 (1080)
−3.6	2.4 (1274)	4.3 (950)
>3.6	1.5 (1190)	5.4 (855)
Hypertension (1036 cases)		
<3.2	15.9 (1075)	21.3 (1080)
−3.6	14.8 (1274)	19.4 (950)
>3.6	12.0 (1190)	13.9 (855)

dard deviation score for BMI increased between 3 and 11. Among men ponderal index at birth was more strongly related to CHD than birthweight, while among women length at birth was stronger. From these data, it can be calculated that if each man in the cohort had been in the highest third of ponderal index at birth, and each woman in the highest third of birth length, and if each man or woman had decreased their BMI score between ages 3 and 11, the incidence of CHD would have been reduced by 25% in men and 63% in women [40].

Similar findings were seen for type 2 diabetes and hypertension. Men and women who had high birthweights >4 kg and whose prepubertal BMI was in the lowest fourth had around half the risk for these conditions when compared with people who had birthweights <3 kg but whose BMI was in the highest fourth (Table 4.5). The odds ratio for type 2 diabetes was 0.67 (95% CI 0.58–0.79) for each kilogram increase in birthweight and 1.18 (CI 1.13–1.23) for each kg/m^2 increase in BMI at age 11 years. The corresponding figures for hypertension were 0.77 (CI 0.71–0.84) and 1.07 (CI 1.04–1.09), respectively.

Subjects were again divided into six groups according to thirds of birthweight and whether their standard deviation score for BMI decreased or increased between ages 3 and 11 years (Table 4.7). For both type 2 diabetes and hypertension, there were independent effects of birthweight and change in BMI score. The patterns of odds ratios and incidence shown in Tables 4.3 and 4.7 were similar in the two sexes. If each individual in the cohort had been in the highest third of birthweight and had decreased their standard deviation score for BMI between ages 3 and 11, the incidence of type 2 diabetes and hypertension would have been reduced by 52% and 25%, respectively [40].

Maternal Influences on Fetal Nutrition

Size at birth is the product of the fetus's trajectory of growth, which is set at an early stage in development, and the materno-placental capacity to supply sufficient nutrients to maintain that trajectory. In Western communities, randomized controlled trials of maternal macronutrient supplementation have indicated relatively small effects on birthweight [62]. This has led to the view that regulatory mechanisms in the maternal and placental systems act to ensure that human fetal growth and development are little influenced by normal variations in maternal nutrient intake, and that there is a simple relationship between a woman's body composition and the growth of her fetus.

Recent experimental studies in animals and observational data in humans challenge these concepts [63]. They suggest that a mother's own fetal growth and her dietary intakes and body composition can exert major effects on the balance between the fetal demand for nutrients and the materno-placental capacity to meet that demand. Specific issues that have not yet been adequately addressed include: (1) maternal effects on the trajectory of fetal growth; (2) intergenerational effects; (3) paradoxical effects on placental growth; and (4) the importance of the mother's body composition and the balance of macronutrients in her diet.

The role of nutrition in supporting pregnancy has finally become an important topic across

the globe. Outstanding reports from Europe and the US have recently provided strong evidence for the importance of robust nutrition before and during pregnancy and during lactation [64–70]. Especially heartening is the new Dietary Guidelines for Americans, 2020–2025, from the US Department of Agriculture which have for the first time included recommendations for children and people who are pregnant and lactating. In addition, one group of nutrition experts has documented the scientific underpinnings of recommendations related to dietary requirements during pregnancy [71].

The Fetal Growth Trajectory

A rapid trajectory of growth increases the demand of the fetus for nutrients. This demand is greatest late in pregnancy but the trajectory is thought to be primarily determined by genetic and environmental effects in early gestation. Experimental studies of pregnant ewes have shown that, although a fast growth trajectory is generally associated with larger fetal size and improved neonatal survival, it renders the fetus more vulnerable to a reduced materno-placental supply of nutrients in late gestation. Thus, maternal undernutrition during the last trimester adversely affects the development of rapidly growing fetuses with high requirements, while having little effect on those growing more slowly [72]. Rapidly growing fetuses were found to make a series of adaptations in order to survive, including placental oxidation of fetal amino acids to maintain lactate output to the fetus [63]. Experiments in animals have shown that alterations in the maternal diet around the time of conception can change the fetal growth trajectory. In a recent study, rats were fed a 9% casein low-protein diet in the periconceptional period. This led to structural changes at the blastocyst stage of embryonic development, reduced fetal growth rates, small size at birth, and raised blood pressure in the offspring during adult life [73].

The sensitivity of the human embryo to its environment is being increasingly recognized with the increasing clinical use of assisted reproductive technology [74]. The trajectory of fetal growth is thought to increase with improvements in periconceptional nutrition and is faster in male fetuses. The consequent greater vulnerability of male fetuses to undernutrition may contribute to the shorter lives of men [75].

Intergenerational Effects

One clear transgenerational effect is the nourishment of primary follicles in the ovaries of a female fetus. During fetal life, the ovaries, uterus, and other reproductive organs are nourished by nutrients from the mother. If maternal nutritional supplies are inadequate for optimal growth of the fetus, the offspring will have compromised uteri and ovaries which will be smaller than found in normally grown girls. This situation provides the opportunity for the affected follicles, that will someday give rise to ova, that may be biochemically or epigenetically compromised. Thus, when such a girl becomes mature and pregnant, an affected fertilized egg will form her offspring. Her baby will have been affected by the provision of nutrients by her grandmother. From the time that a follicle in the ovary is made to the time that epigenetic influences may give rise to disease risk in offspring can be up to a century. For this reason, the transgenerational effect is sometimes called “the 100-year effect.”

Experimental studies in animals have shown that undernutrition can have effects on reproductive performance which may persist for several generations. Among rats fed a protein-deficient diet over 12 generations, there was a progressive fall in fetal growth rates. When restored to a normal diet, it took three generations before growth and development were normalized [76].

Epigenetic Influences

The role of maternal nutrition in determining risks for late onset disease could not be appropriately addressed without including epigenetic changes that are associated with maternal preconception and postconception diets [77–79].

Epigenetic changes are those that influence the mechanisms regulating transcription and translation of genes and include the methylation of specific nucleotides, the modification of histone tails that regulate access to regions of DNA, and non-coding RNAs that play a variety of roles in gene product regulation. Developmental epigenetics is affected by all the prenatal stressors that are associated with elevated disease risks in offspring. Various nutrients within the diet are associated with epigenetic changes that can be passed on to future generations [77, 80].

Strong evidence for major intergenerational effects in humans has come from studies showing that a woman's birthweight influences the birthweight of her offspring [81]. A study in the UK showed that whereas low birthweight mothers tended to have thin infants with a low ponderal index, the father's birthweight was unrelated to ponderal index at birth [82]. The effect of maternal birthweight on thinness at birth is consistent with the hypothesis that in low birthweight mothers the fetal supply line is compromised and unable to meet fetal nutrient demand. Potential mechanisms underlying this effect include alterations in the uterine or systemic vasculature, changes in maternal metabolism, and impaired placentation.

The roles of compromised sperm and egg are becoming more clearly defined in both animals and humans. Egg health affects the health of offspring and it is generally recognized that the health of an oocyte is an important factor in determining the health of an embryo when using assisted reproductive technology. Many factors influence the health of an oocyte including nutritional and oxidative stresses [83, 84]. These factors are an extension of the usual considerations for maternally derived fetal programming. In addition, it is becoming increasingly recognized that sperm quality is a key factor regulating embryo and offspring health. Both the egg and sperm can be directly affected by the nutritional and oxidative stress environments. These and other factors may alter gene expression patterns in later life through an epigenetic mechanism including modification of promoter regions of genes, histone modifications, and changes in non-coding RNAs that affect gene translation or post-translational modifications.

Maternal Diet and Body Composition

Direct evidence supporting a long-term effect on the fetus of levels of maternal nutrient intake during pregnancy has come from a follow-up study in Argentina of children whose mothers took part in a randomized controlled trial of calcium supplementation in pregnancy [85]. Supplementation was associated with lowering of the offspring's blood pressure in childhood, even though it was not associated with any change in birthweight. Follow-up studies after the Dutch famine of 1944–1945 found that severe maternal caloric restriction at different stages of pregnancy was variously associated with obesity, dyslipidemia, and insulin resistance in the offspring, and there is preliminary evidence of an increased risk of CHD [61, 86, 87]. Again, these effects were largely independent of size at birth.

In the Dutch studies, famine exposure per se was not associated with raised blood pressure in the offspring, but there was an effect of macronutrient balance. Maternal rations with a low-protein density were associated with raised blood pressure in the adult offspring [88]. This adds to the findings of studies in Aberdeen, UK, which show that maternal diets with either a low or a high ratio of animal protein to carbohydrate were associated with raised blood pressure in the offspring during adult life [89].

The fetus does not live on the mother's diet alone: that would be too dangerous a strategy. It also lives off stored nutrients and the turnover of protein and fat in the mother's tissues [90]. Maternal size and body composition account for up to 20% of the variability in birthweight [91]. Gestational diabetes is known to be associated with adverse long-term outcomes in the offspring [92]. More recently, studies in Europe and India have shown that high maternal weight and adiposity are associated with adult development of insulin deficiency, type 2 diabetes, and CHD in the offspring [7, 14, 93]. Of great importance is an increasing body of consistent evidence show-

Table 4.8 Mean 2-h plasma glucose and insulin concentrations according to maternal BMI in late pregnancy in 584 Chinese men and women

	Maternal BMI at 38 weeks of pregnancy				
	≤23	−24.5	−26	>26	*p* for trend
2-h glucose (mmol/L)	7.6	6.6	6.7	5.7	0.003
2-h insulin (pmol/L)	304	277	282	177	0.007

ing strong links between low maternal weight or BMI and insulin resistance in the adult offspring [61, 94, 95]. One study investigated plasma glucose and insulin concentrations in Chinese men and women aged around 45 years following a standard oral glucose challenge [95]. As shown in Table 4.8, the findings revealed that low maternal BMI at 38 weeks of pregnancy was associated with raised plasma glucose and insulin concentrations. Results for maternal BMI in early pregnancy, around gestational week 15, were stronger. In contrast to these associations between maternal BMI and insulin resistance, thin maternal skinfold thicknesses, and low pregnancy weight gain have been consistently associated with raised blood pressure in the offspring [96–99]. One of the metabolic links between maternal body composition and birth size is protein synthesis. Women with a greater lean body mass have higher rates of protein synthesis in pregnancy [100]. Variation in rates of maternal protein synthesis explains around a quarter of the variability in birth length.

Placental Transfer

A baby's birthweight depends on the placenta's ability to transport nutrients to it from its mother. The placenta seems to act as a nutrient sensor regulating the transfer of nutrients to the fetus according to the mother's ability to deliver them and the demands of the fetus for them [101]. The size, weight, and shape of the placenta are all subject to wide variations [102]. Its size reflects its ability to transfer nutrients [92]. Small babies generally have small placentas but, in some circumstances, an undernourished baby can expand its placental surface to extract more nutrients from the mother [103].

In the last century, the surface of the placenta was described as being either "oval" or "round" [104]. In order to describe the extent to which the surface was more oval than round, two so-called diameters of the surface were routinely recorded in some hospitals, a maximal diameter (the length of the surface), and a lesser one bisecting it at right angles (the width or breadth) [105].

Preeclampsia is associated with reduced placental surface area. One apparent cause of abnormal placentation is impaired invasion of the maternal spiral arteries by the trophoblast at implantation [106]. In the Helsinki Birth Cohort, placentas from pregnancies complicated by preeclampsia had a more oval surface than those from normotensive pregnancies because of a disproportionate reduction in the width [107], leading to a more oval shape. The relation with the width was graded: the shorter the width, the greater the risk for, and severity of, preeclampsia. This led to the conclusion that placental growth is polarized from the time of implantation, so that growth along the major axis, the length, is qualitatively different to growth along the width. One possibility is that growth along the major axis is aligned with the rostro-caudal axis of the embryo, while tissue growth along the minor axis may arise from other influences.

Low placental weight is associated with an increased risk of hypertension in later life [108]. However, a study of men and women born in a maternity hospital in Preston, UK, showed that high placental weight in relation to birthweight is also associated with later hypertension [109]. At any placental weight, lower birthweight was associated with higher systolic pressure (Table 4.9); but at any birthweight, higher placental weight was associated with higher systolic pressure. The highest systolic pressure was in people who had

Table 4.9 Mean systolic blood pressure mmHg among men and women aged 50, born at term

	Placental weight (lb)			
Birthweight (lb)	≤1.0	−1.25	−1.5	>1.5
≤6.5	149	152	151	167
−7.5	139	148	146	159
>7.5	131	143	148	153

the lowest birthweights but the highest placental weights. This observation has been replicated, and high placental weight in relation to birthweight has also been shown to predict CHD [110]. Observations in sheep show that in response to undernutrition in mid-gestation, the fetus is able to extend the area of the placenta by expanding its individual cotyledons [103]. This increases the area available for nutrient and oxygen exchange, and results in a larger lamb than there would otherwise have been. This is profitable for the farmer, and manipulation of placental size by changing the pasture of pregnant ewes is a common practice in sheep farming. There is evidence for a similar phenomenon in humans [105].

It is becoming apparent that the shape and size of the placental surface at birth are a new marker for chronic disease in later life. The predictions of later disease depend on the combination of placental size/shape and mother's body size. Particular combinations have been shown to predict hypertension [105], chronic heart failure [111], CHD [112], and certain forms of cancer [113]. The intrauterine origins of cancer are being explored [113–115]. Several cancers are related to placental size and shape.

Research Challenges

Further research has to address the following overarching questions.

Environmental Influences

What are the environmental influences which, acting through the mother, or directly on the infant and young child, alter gene expression and thereby permanently change the body's structure and function? Research on maternal influences will need to address: (1) effects on the fetal growth trajectory; (2) effects on placental growth; (3) intergenerational effects; (4) maternal dietary pattern during the periconception period; and (5) exposure to toxic chemicals.

To what degree do fetal accommodations to maternal stress predispose children to adult-onset disease when faced with adverse childhood experiences?

Pathogenesis

How do gene–environment interactions during development translate into chronic disease? Through a combination of clinical and experimental studies, progress is being made in understanding the developmental origins of altered glucose, insulin, and lipid metabolism, stress responses, blood pressure, and renal function. The role played by epigenetic responses to early life stresses needs to be investigated.

Disease Prevention

It is unlikely that the current chronic disease pandemic can be reversed without urgent attention to the environmental stresses that occur in the early stages of life. Strategies which target infants and young children may give the most immediate benefit but improving the intrauterine environment is an important long-term goal. Despite current levels of nutrition in Western countries, the nutrition of many fetuses and infants remains suboptimal because their mothers' diets are unbalanced or because their delivery is constrained by maternal metabolism or inadequate placental development. There is sufficient knowledge to implement preventive programs now. More research is needed, however, to increase the effectiveness of these programs.

Mother:

- An optimal diet begins before pregnancy. In developing countries, micronutrients in the diet may be limiting factors in fetal growth, whereas in Western countries macronutrient

balance, especially between protein and carbohydrate, is likely more important.
- Women require an optimal body composition before pregnancy, with avoidance of excessive thinness or overweight.
- It is not known whether the greatest benefits for the next generation will come from improving the nutrition of adult women, adolescent girls, or girl children. Any rational policy needs to address all three.

Infant:

- The growth in weight and length during the first year after birth needs to be protected by good infant feeding practices, including breastfeeding, nutritious foods, and avoidance of recurrent infections.

Child:

- Young children who were small or thin at birth should not increase their centile score for BMI after the age of 2 years. A healthy balanced diet is important for optimal childhood growth. Boys and girls need to be studied together to determine sex differences.

Adult:

- People who were small or large at birth are more vulnerable to adverse influences acting in adult life.

Basic and Preclinical Research

There are a host of unknowns in the field of developmental programing that need attention by the medical community. Of these, some are especially urgent because they underlie disease processes that could be reversed. Urgent questions that arise in this field include:

- To what degree is it possible to use epigenetic markers in blood as an indicator of disease risk? Can such markers be used to follow therapy?
- To what degree are immune cells affected by an adverse environment in people born at the extremes of the birthweight scale?
- What are common and disparate pathways of disease that arise from prenatal and childhood adverse stresses and trauma?
- What are the epigenetic responses to toxic chemical exposure in the womb?
- To what degree can stress-induced disease risk be mitigated at specific stages of development?

Conclusions

Low birthweight and high birthweight are associated with increased rates of CHD and the related disorders, namely stroke, hypertension, and type 2 diabetes. These associations have been extensively replicated in studies in different countries and are not the result of confounding variables. They extend across the full range of birthweight. Low birthweight effects depend on birthweights in relation to the duration of gestation rather than the effects of premature birth. The associations are thought to be consequences of developmental plasticity, the phenomenon by which one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development. Recent observations have shown that impaired growth in infancy and rapid childhood weight gain exacerbate the effects of impaired prenatal growth. CHD and the disorders related to it arise through a series of interactions between environmental influences and the pathways of development that preceded them. These diseases are the product of branching pathways of development in which the branchings are triggered by the environment before and after birth.

Variations in the normal processes of early human development have implications for health throughout life. This may be because these variations affect key processes that determine vulnerability to disease, including the quality of stem cells, antioxidant defenses, tissue repair, immune competence, and chronic inflammation. Impetus has been added to this reevaluation by recent findings showing that a woman's dietary

balance and body composition in pregnancy are related to levels of cardiovascular risk factors and the risk of CHD in her offspring in adult life without necessarily affecting size at birth. These observations challenge the view that the fetus is little affected by variations in maternal nutrition, except in the extreme circumstance of famine. There is an increasing body of evidence that a woman's own fetal growth, and her diet and body composition through childhood up to the time of her pregnancy, play a major role in determining the future health of her children. A new vision of optimal early human development is emerging which takes account of both short- and long-term outcomes.

Acknowledgments The author would like to recognize the enormous contributions of David J. P. Barker, MD, PhD, FRS, CBE, FMedSci (1938–2013) MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, UK, to the field of fetal programming, his passion. This chapter is based on his previous writings which he presented in the third edition of this book, some of which were carried directly to this version. Were he to have lived until now, we would have written this chapter together. This chapter honors our years of collaboration and friendship and the role of his wife, Jan, in bringing this field to the fore.

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5 Nutritional Principles in the Treatment of Diabetes

Roeland J. W. Middelbeek, Samar Hafida, and Anna Groysman

Key Points

- Medical nutrition therapy is an essential component of diabetes self-management and education, and should be individualized, flexible, and involve shared decision-making between persons with diabetes and their healthcare teams.
- Medical nutrition therapy involves delivering tools and support for adopting and maintaining healthy eating patterns focused on goal-specific outcomes with attention to promoting sustained behavioral changes over time.
- Medical nutrition therapy has been shown to be an effective method to manage weight loss, diabetes, high blood pressure, and high cholesterol levels.
- Numerous eating patterns varying in macronutrient composition have shown beneficial effects on glycemic control and weight management in people with diabetes.

Introduction

The incidence and prevalence of diabetes have skyrocketed during the last decades, posing a significant threat to worldwide communities, with currently nearly half a billion people living with diabetes [1]. The International Diabetes Federation estimates that the prevalence will reach staggering numbers by 2045, affecting 700 million individuals globally. In the United States, the estimated prevalence of diabetes is 10.5%, affecting over 34 million people, with 7.3 million who are unaware of their diagnosis [2]. Diabetes care is a complex challenge and requires a multidisciplinary approach involving a myriad of professional services. Medical nutrition therapy is a fundamental pillar in the treatment of people with diabetes and has the potential to prevent progression and alleviate its burden.

R. J. W. Middelbeek (✉)
Joslin Diabetes Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA
e-mail: roeland.middelbeek@joslin.harvard.edu

S. Hafida
Joslin Diabetes Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Boston Medical Center, Boston, USA
e-mail: samar.hafida@bmc.org

A. Groysman
Joslin Diabetes Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Atrius Health, Boston, USA
e-mail: anna_groysman@atriushealth.org

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_5

Medical Nutrition Therapy (MNT) for Diabetes

Definition of MNT

The Academy of Nutrition and Dietetics defines MNT as a "specific application of the Nutrition Care Process in clinical settings that is focused on the management of diseases," a definition distinct from nutrition counseling which is the process of supporting individuals to establish unique goals based on their priorities, in order to foster a routine of self-care, centered around healthful eating [3]. The legal definition of MNT is the evidence-based application of nutrition care delivered by Registered Dietitian Nutritionists (RDN), where a face-to-face assessment of an intervention is conducted in accordance with nationally accepted protocols. In order to fulfill the components of MNT, an assessment, nutrition-based diagnosis, intervention, and plan for monitoring must be conducted (Fig. 5.1).

Goals of MNT

The American Diabetes Association (ADA) outlines four main goals of MNT (Table 5.1). These include encouraging healthful eating, personalizing nutrition needs, providing evidence-based food-related messaging, and offering practical tools to help with meal planning.

Diabetes Prevention

Reducing the risk for type 2 diabetes involves maintaining a healthy weight, as overweight and obesity are key risk factors for the development of the disease. Cereal fiber and magnesium, both components of whole grains, and fruit and green leafy vegetable intake are consistently associated with lower risk of developing type 2 diabetes [5–7] with a possible protective role for low-fat dairy foods [8]. Numerous studies have shown that increasing and maintaining physical activity are clearly associated with reduced risk for the devel-

Table 5.1 Goals of MNT

Encourage healthful eating	**Personalize nutrition needs**
1. Adopt appropriate portions 2. Choose foods dense in nutrients 3. Achieve and maintain goals related to: • Body weight • Hemoglobin A1c • Blood pressure • Serum cholesterol • Prevention of diabetes complications	1. To support personal and cultural food preferences 2. Consider barriers to food access 3. Assess readiness to embrace change
Provide evidence-based food-related messaging	**Offer practical tools**
1. To maintain the pleasure of eating 2. Promote healthy relationship with food	1. To help with daily planning of meals

Adapted from Nutrition therapy for adults with diabetes or prediabetes: a consensus report [4]

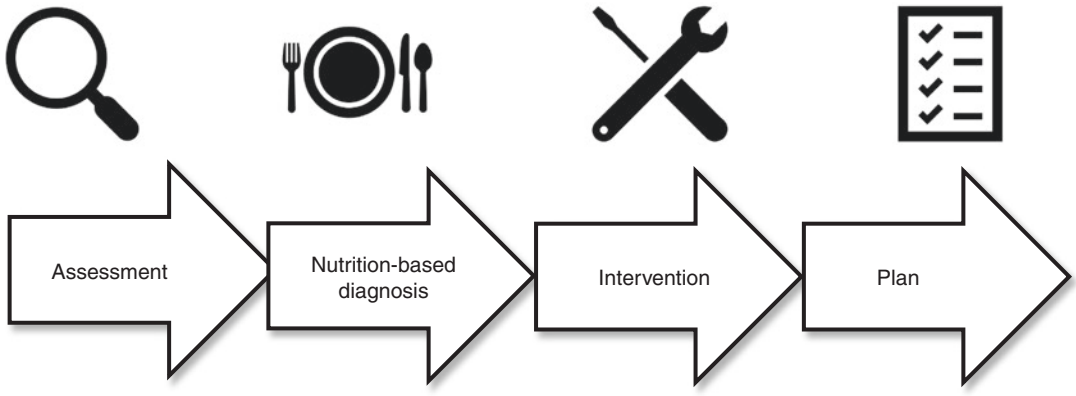

Fig. 5.1 Process of medical nutrition therapy

Table 5.2 Domains where MNT is effective in the management of diabetes

Glycemic control			**Cardiovascular risk factor mitigation**				
↓ HbA1c		**↓ FPG mg/dL**	**↓ Total Chol mg/dL**	**↓ LDL-C mg/dL**	**↑ HDL-C mg/dL**	**↓ TG mg/dL**	**↓ SBP/DBP mmHg**
T2D	0.3–2%[a]	18–61	8–28	8–22	2.4–6	15–153	3.2–9/2.5–5.3
T1D	1–1.9%[b]						
Medication use			**Weight management**				
			↓ Weight (kg)	**↓ BMI kg/m²**	**↓ Waist circumference (cm)**		
↓ Total daily dose of insulin, medication dosages, and number of medications taken for diabetes management			2.4–6.2	0.3–2.1	1.0–5.5		

Data are observed means (see text paragraph 2.5 and 2.6),↓ Reduction,↑ Increase, *HbA1c* glycated hemoglobin, *FPG* fasting plasma glucose, *T2D* type 2 diabetes, *T1D* type 1 diabetes, *Total Chol* total cholesterol, *C* cholesterol, *LDL* Low-density lipoprotein, *HDL* High-density lipoprotein, *TG* triglycerides, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index

[a]MNT resulted in lowering HbA1C in people with T2D in 13 study arms from 11 studies at 3 months after intervention [3]

[b]MNT using carbohydrate counting in people with T1D to determine pre-meal insulin dosing resulted in lowering HbA1C at 6 months and up to 1 year after intervention [14]

opment of type 2 diabetes. Another recommendation is to interrupt sitting, as sedentary time is associated with an increased risk of developing type 2 diabetes [9]. A number of risk factors, both non-modifiable (genetics and aging) and modifiable (central obesity, sedentary lifestyle, and diet), have been identified as contributing to insulin resistance, a common factor in the development of diabetes and cardiovascular disease. A recent prospective cohort study examining incident cardiovascular disease (CVD) in young adults over a 32-year period found that long-term consumption of a high-quality plant-centered diet was associated with a 52% lower risk of CVD [10]). Large clinical trials have demonstrated the role of nutrition therapy, leading to modest weight loss, combined with increased physical activity in the prevention or delay of type 2 diabetes. Examples of larger and well-designed trials include the Finnish Diabetes Prevention Study [11] and the Diabetes Prevention Program (DPP) [12].

Effectiveness of MNT in the Management of Diabetes

The Academy of Nutrition and Dietetics published evidence-based guidelines endorsed by the ADA for the management of adults with type 1 and type 2 diabetes [3, 13]. Review of the literature identified 30 diabetes-targeted nutrition practice guidelines which demonstrated effectiveness in the following domains: glycemic control, cardiovascular risk factor mitigation, medication use, weight management, diabetes prevention, and quality of life (Table 5.2).

MNT and Glycemic Control

Intervention studies involving MNT delivered by RDNs in a series of encounters with subjects who have type 2 diabetes have shown significant improvements in hemoglobin A1c (a marker of glucose control over a 3-month period) with a decrease from 0.3 to 2% [15–17]. HbA1c reductions were more pronounced in those who were newly diagnosed with type 2 diabetes and with higher baseline HbA1c of >8%. Similar HbA1c reductions were also seen in people with type 1 diabetes, who received MNT using carbohydrate counting to calculate mealtime insulin doses, resulting in clinically important mean HbA1c reductions of 1–1.9% over a period of 6 months [14]. Mean fasting blood glucose levels also showed decreased range between 18 and 61 mg/dL in people with type 1 and type 2 diabetes [3].

Cardiovascular Risk Factor Mitigation

Several studies assessing total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) levels in adults with type 2 diabetes who received MNT reported mixed effects. This is likely due in part to the use of lipid lowering agents by the participants during the study period, which can significantly alter lipid profiles and may obscure MNT-related lipid panel changes. However, a number of other studies did result in improvements in LDL, HDL, and TG levels [4]. For blood pressure control, mixed results were also reported in several randomized controlled studies and cohort studies of adults with type 1 and 2 diabetes where MNT was a component of the intervention. Six studies demonstrated a significant lowering of systolic and diastolic blood pressure. It is worth noting that 50–70% of the subjects were taking medications to lower blood pressure, and most had near-normal blood pressure at the time of study entry [3, 16, 18].

Medication Use

MNT delivered by RDNs in regular intervals was associated with significant decrease in doses and number of medications for type 2 diabetes. The favorable effect of MNT persisted for 2 years in The United Kingdom Prospective Diabetes Study (UKPDS), after which participants required escalation of therapy due to the natural progression of type 2 diabetes. MNT in the form of carbohydrate counting resulted in improvement of HbA1c in adults with type 1 diabetes, without an increase in the total dose of insulin. Furthermore, MNT alleviated or prevented weight gain associated with initiation of basal insulin in people with type 2 diabetes [19] and insulin pump therapy in people with type 1 diabetes [20].

Quality of Life

In six studies where MNT was incorporated, adults with either type 1 or type 2 diabetes reported an improved quality of life. These studies included a number of RDN encounters followed by long-term follow-up with RDN visits. The improvements in quality of life included self-perception of health status, knowledge and motivation, treatment satisfaction, and psychological well-being [3].

Medical and Surgical Weight Loss

Medical Weight Management and Impact on Type 2 Diabetes

Intervention with MNT in several studies involving participants with either type 1 or type 2 diabetes demonstrated mixed results with regard to changes in body weight, body mass index (BMI), and waist circumference. Some outcomes showed no change while others reported 2.4–6.2 kg weight loss and decrease in waist circumference by 1–5.5 cm [3]. Pharmacotherapy for weight management can be used in appropriate patients as an adjunct to MNT and is indicated for people with Class 1 obesity or those with a BMI ≥27 kg/m2 plus one or more weight-related comorbidities such as type 2 diabetes. Most FDA-approved medications for weight management have demonstrated beneficial effects on glucose control and their use has been associated with delaying the progression of type 2 diabetes [21]. Table 5.3 shows a comparison among the current FDA-approved medications for weight management and their effects on glycemic control.

Incretin-based medications for type 2 diabetes have been shown to promote a greater weight loss than the aforementioned FDA-approved weight-loss medications. In a recent study examining the effect of semaglutide 2.4 mg weekly compared to semaglutide 1 mg weekly and placebo, participants lost 9.6% of their baseline weight and two-thirds of participants with type 2 diabetes achieved an HbA1c <6.5%. The weight loss with semaglutide 2.4 mg was greater than that seen with liraglutide and other approved anti-obesity medications. Adverse events occurred more frequently with semaglutide 2.4 mg (87.6% of patients) and 1.0 mg (81.8%) than with placebo (76.9%). The most common adverse events were gastrointesti-

Table 5.3 FDA-approved medications for weight management studied in people with type 2 diabetes

Medication	HbA1c change medication vs. control	Duration of treatment	Weight change medication vs. control (% of baseline weight)
Orlistat [22]	−0.9% vs. −0.6%; $P = 0.014$	1 year	−4.6% vs. −1.7%; $P \leq 0.001$
Naltrexone-bupropion [23]	−0.6% vs. −0.1%; $P < 0.001$	1 year	−5.0% vs. −1.8%; $P \leq 0.001$
Phentermine/topiramate (15/92 mg) [24]	−1.6% vs. −1.2%; $P = 0.038$	1 year	−9.4% vs. −2.7%; $P \leq 0.0001$
Liraglutide 3.0 mg [25]	−1.1% vs. −0.6%; $P < 0.001$	1 year	−5.8% vs. −1.5%; $P < 0.0001$
Semaglutide [26]	−1.55% vs. −0.02%; $P < 0.0001$	30 weeks	−4.53% vs. −0.98%; $P < 0.0001$
Semaglutide 2.4 mg [27]	−1.6% vs. −0.4%; $P < 0.0001$	68 weeks	−9.6% vs. −3.4%; $P \leq 0.0001$

nal, which were mild to moderate [27]. In a randomized control trial using tirzepatide compared to semaglutide 1 mg weekly in people with type 2 diabetes, individuals receiving tirzepatide 15 mg had a reduction of HbA1c of 2.5% and body weight of 12.4 kg after 40 weeks [28].

Surgical Weight Management and Impact on Type 2 Diabetes

Bariatric or weight-loss surgery has been repositioned as metabolic surgery, due to its effectiveness on obesity and related comorbidities [29]. The benefits of bariatric surgery on type 2 diabetes have been demonstrated in prospective clinical trials spanning over a decade showing a favorable effect on both the incidence and progression of diabetes, independent of pre-operative BMI [30]. Several randomized control trials using one or more surgical procedures have corroborated the benefits seen in observational trials, with metabolic surgery showing superior outcomes on glycemic control, the need for medications to manage diabetes, and in some cases diabetes remission compared to intensive lifestyle interventions for weight management [31]. The American Diabetes Association has endorsed metabolic surgery as an intervention for type 2 diabetes management. The ADA recommends its use in appropriate candidates with type 2 diabetes with BMI ≥40 kg/m^2 (BMI ≥ 37.5 kg/m^2 in Asian Americans) and in adults with BMI 35.0–39.9 kg/m^2 (32.5–37.4 kg/m^2 in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities with nonsurgical methods. Metabolic surgery may be considered as an option to treat type 2 diabetes in adults with BMI 30.0–34.9 kg/m^2 (27.5–32.4 kg/m^2 in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods [32]. Procedures used in the intervention studies included adjustable gastric banding (laparoscopic banding) (AGB), Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD) with duodenal switch, and sleeve gastrectomy (SG). Since 2012, the number of sleeve gastrectomy procedures has superseded other interventions [33] although the procedure remains underused [34]. Among the various procedures, the rates of type 2 diabetes remission are highest after BPD, followed by RYGB and SG (no difference between both), and lowest after AGB. Factors that predict remission of type 2 diabetes include short duration of living with diabetes (<5 years) and absence of the use of insulin. The amount of weight-loss predicted remission only at one year but not thereafter [35, 36].

Recommendations for MNT Referrals and Encounters

Who Should Be Referred?

MNT is effective in improving medical outcomes, quality of life, and is cost-effective [37, 38]. Anyone who is newly diagnosed with prediabetes and/or diabetes or has comorbidities, such as overweight or obesity, a history of disordered eating, hypertension, hyperlipidemia, and diabetic nephropathy, should also be referred to a RDN for MNT. There are four critical times in which a person with diabetes should be referred to a RDN for nutrition: (1) at diagnosis, (2) annually, (3) when a new diabetes complication occurs, or (4) when a transition in care occurs [39].

Frequency of Encounters

It is recommended that there can be a series of three to four encounters with an RDN, lasting from 45 to 90 min, starting at diagnosis of diabetes. The referral should be completed within 3–6 months after a diagnosis of diabetes. Follow-up appointments are recommended at least annually for ongoing monitoring and evaluation [37].

Assessment During Encounters and Follow-Up

The RDN will assess usual food intake, level of physical activity, current medications, current laboratory values, and anthropometric measurements, in addition to glycemic control. The goal of nutrition therapy is to promote healthy eating patterns that emphasize a variety of nutrient-dense foods and appropriate portion sizes rather than the individual micro/macronutrients or single foods. Teaching individuals how to make appropriate food choices (including by means of carbohydrate counting) and using data from glucose monitoring to evaluate short-term effectiveness are important components of successful MNT for type 2 diabetes.

The plate method is a general guideline for healthy food distribution and emphasizes healthy portions and food choices. Persons with diabetes can benefit from basic information about carbohydrates—what foods contain carbohydrates and how many servings to select for meals (and snacks if desired). They should learn what types of carbohydrate foods have the biggest impact on glucose levels. The carbohydrate list is composed of starches, fruits, milk, and sweets; one serving or carbohydrate exchange is the amount of food that contains 15 g of carbohydrate. During the initial assessment, the RDN will guide the person with diabetes in choosing the appropriate amounts of carbohydrate servings per meal and snack. In addition, the RDN will help clarify how other macronutrients (proteins and fats) play a role in health and diabetes management.

Successful self-management of diabetes is an ongoing process of problem solving, adjustment, and support. Support from family and friends is important, in addition to continuing education and support from professionals. Structured programs with consistent follow-up contact assist individuals to achieve lifestyle goals and to maintain what are often challenging lifestyle changes. Technology is a helpful tool for education and diabetes management. Some apps provide data logging functions and food databases. These help validate the successful achievement of someone's nutrition and physical activity goals. There are hundreds of mobile apps available for download, some free and some requiring a small fee. Examples include Calorie King, My Fitness Pal, Fitbit, Garmin wearables, and the Body Weight Planner.

MNT Intervention

Macronutrients

Carbohydrate

Carbohydrates are addressed first as it is the balance between carbohydrate intake and available insulin in the body that determines the postprandial glucose response, and because carbohydrate

is the major determinant of mealtime insulin dose. Foods containing carbohydrates—grains, fruits, vegetables, legumes, milk, and yogurt—are important components of a healthy diet and should be included in the food/meal plan of persons with diabetes. A number of studies have reported that when subjects are allowed to choose from a variety of starches and sugars, the glycemic response is similar, as long as the total amount of carbohydrate is the same. Consistency in carbohydrate intake is also associated with good glycemic control [4].

Research does not support any ideal percentage of energy from macronutrients for persons with diabetes [4] and it is unlikely that one such combination of macronutrients exists [15]. Macronutrient intake should be based on the Dietary Reference Intakes (DRI) for healthy adults. It is important to tailor carbohydrate recommendations based on the person's needs, preferences, and impact on glucose level.

The ideal amount of carbohydrates recommended for healthy adults to maintain well-being is unknown. This also applies to people with diabetes where the quality of carbohydrates outweighs the significance of quantity. High-quality carbohydrates include those rich in fiber, vitamins, and minerals. Processed carbohydrates should ideally be low in sodium and added sugars.

Although different carbohydrates produce different glycemic indexes (GI), there is limited evidence to show long-term glycemic benefit when low-GI diets versus high-GI diets are implemented. Benefits of a low-GI diet are complicated by differing definitions of "high-GI" or "low-GI" foods or diets. Systematic reviews related to GI in people with diabetes have shown no effect on HbA1c and limited effects on fasting glucose [4].

Protein

There is no solid evidence that usual intake of protein (15–20% of energy intake) be changed in people who do not have renal disease [4, 37]. Although protein has an acute effect on insulin secretion, usual protein intake in long-term studies has minimal effects on glucose, lipids, and insulin concentrations.

Protein is probably the most misunderstood macronutrient with inaccurate advice frequently given to persons with diabetes. Although people with diabetes are often told that 50–60% of protein becomes glucose and enters the bloodstream 3–4 h after it is eaten, research documents the inaccuracy of this statement. Although nonessential amino acids undergo gluconeogenesis in subjects with controlled diabetes, the glucose produced does not enter the general circulation [40]. If differing amounts of protein are added to meals or snacks, the peak glucose response may be affected by the addition of protein as there may be delayed glycemic excursions [41]. However, including protein with meals and snacks can help the individual feel more satiated thereby potentially eating less overall. Protein intake may increase the insulin response to carbohydrates and thus carbohydrate sources with a high protein content (e.g., nuts and milk) are generally not recommended to treat hypoglycemia [4, 42].

Dietary Fat

Cardioprotective nutrition interventions recommended by the "Standards of Medical Care in Diabetes" include reduction in saturated and trans fatty acids, as well as increase in plant sterols/stanols and *n*–3 fatty acids [40, 41]. It is still important to be aware that foods high in cholesterol tend to have a higher saturated fat content [42].

Nutrition goals for persons with diabetes are the same as for persons with pre-existing cardiovascular disease. This includes saturated fats <7% of total energy, minimal intake of trans fatty acids, and cholesterol intake <200 mg/day [3]. Two or more servings of fish per week (with the exception of commercially fried fish fillets) are recommended. In persons with type 2 diabetes, intake of ~2 g/day of plant sterols and stanols has been shown to lower total and LDL cholesterol. If products containing plant sterols are used, they should displace, rather than be added to, the diet to avoid weight gain.

A number of eating patterns consisting of variations in the components of macronutrients have been evaluated in terms of effects on diabetes management, weight control, and other variables. An overview is presented in Table 5.4.

Table 5.4 Impact of eating patterns on diabetes prevention, treatment, and additional benefits on weight and other variables

Eating pattern	Description	Effect on diabetes management/ prevention	Effect on weight and other variables
USDA Dietary Guidelines for Americans (DGA) [43–45]	• Focus on nutrient-dense foods and beverages (vegetables, fruits, whole grains, eggs, beans, nuts, low-fat dairy, lean meats) • Encourages a mainly plant-based source of foods, fewer sugars, saturated fat, sodium, and drinking water over milk	• Helps lower diabetes risk • Higher DQI[a] score associated with increased insulin resistance and diabetes risk among African-Americans adults	• Higher DQI associated with weight loss for whites, but not blacks • Higher DQI associated with higher HDL and improved blood pressure
Mediterranean diet [46–48]	• Focuses on intake of plant-based food, fish, other seafood • Olive oil is main source of dietary fat • Low to moderate amount of dairy products • Reduced intake of red meat, wine, and rare intake of sugar and processed food	• Reduced risk of diabetes • Improved glycemic control • Reduced or delayed need for glucose lowering medications • Protects against insulin resistance	• Improved blood pressure • Increase in HDL, decrease in total cholesterol and triglycerides • Improved quality of life • Weight loss • Protects against metabolic syndrome • Reduced mortality risk and mortality from cardiovascular disease
Dietary Approaches to Stop Hypertension (DASH) [49, 50]	• A "combination diet" that focuses on vegetables, fruits, low-fat dairy • Includes some whole grains, lean protein, nuts • Reduced saturated fat, red meat, added sugars, sodium, and fat	• Reduced risk of diabetes • Variable improvement in glycemic control	• Weight loss • Improved blood pressure • Increased HDL, reduced LDL
Low carbohydrate [51–53]	• Avoids starchy and sugary foods • No consistent definition of "low" carbohydrate; often defined as 26–45% of total calories	• Improved glycemic control (HbA1c reduction) • Reduced need for antihyperglycemic agents	• Weight loss • Improved blood pressure • Increased HDL cholesterol and lower triglycerides
Very low carbohydrate: Ketogenic diet [51–53]	• Often 20–50 g of non-fiber carbohydrates per day to induce nutritional ketosis • Often reduces carbohydrates to <26% of total calories • Meals usually derived from >50% of calories from fat	• Improved glycemic control (HbA1c reduction) • Reduced risk of diabetes • Reduced need for antihyperglycemic agents • Can cause swift reduction in blood glucose, requires consultation with knowledgeable practitioner	• Weight loss • Improved blood pressure • Inflammation decreased • Some evidence for improved biomarkers of cardiovascular disease risk
Vegetarian or vegan [10, 54–56]	• Vegetarian: plant-based diet but includes eggs and/or dairy products • Vegan: same as vegetarian but excludes any animal-derived products	• Reduced risk of diabetes • Improved glycemic control (HbA1c reduction)	• Weight loss • Reduced LDL and HDL cholesterol

Table 5.4 (continued)

Eating pattern	Description	Effect on diabetes management/ prevention	Effect on weight and other variables
Low fat [57, 58]	• Total fat intake ≤30% of total calories • Saturated fat intake ≤10% of total calories	• Inconsistent improvement in glycemic control	• Weight loss observed, in combination with caloric reduction
Very low fat: Ornish and Pritikin patterns [56, 59, 60]	• Total fat intake 10% of total calories • 70–77% carbohydrate (includes 60 g fiber), 13–20% protein of total calories • Whole-foods, plant-based eating plan	• May improve glucose levels	• Weight loss • Improved blood pressure • Improved HDL
Paleolithic ("Old Stone Age") diet [61–63]	• Diet based on lean meat, fish, fruits, vegetables, root vegetables, eggs, nuts • Avoids grains, dairy, salt, refined fats, sugar	• Mixed results for effect on glycemic control (some evidence for reduced HbA1c, improved glucose tolerance, insulin sensitivity) • Most research studies are small, lasting up to 3 months, with inconclusive evidence	• Mixed results (some evidence for weight loss and increased HDL) • Inconclusive evidence
Intermittent fasting[b] [64–66]	• Focuses on consuming all daily calories in set hours during the day • Includes set times for eating and fasting (i.e., restricted intake for x hours per day, alternate-day fasting, severe calorie restriction for several consecutive days)	• Limited research evidence (no significant improvement in HbA1c, some evidence for improved fasting glucose) • Some evidence for increased rate of hypoglycemia for patients on hypoglycemic agents	• Variable results. Need further research (some evidence for weight loss, improved blood pressure, improved quality of life)

[a]DQI (diet quality index). Higher score associated with increased adherence to Dietary Guidelines for Americans (DGA)
[b]Not an eating pattern by definition, however, included due to increased interest from the diabetes community

Micronutrients

There is no evidence of benefit from vitamin or mineral supplementation in persons with diabetes who do not have underlying deficiencies [4]. It is recommended that health professionals focus on nutrition counseling for acquiring vitamin and mineral requirements from natural foods and a balanced diet rather than from supplements. Research including long-term trials is needed to assess the safety and potentially beneficial role of chromium, magnesium, and antioxidant supplements, and other complementary therapies in the management of diabetes. In select groups such as the elderly, pregnant or lactating women, strict vegetarians, or those on calorie-restricted diets, a multi-vitamin supplement may be needed. Routine supplementation with antioxidants, such as vitamins E and C and carotene, has not proven beneficial and is not advised because of concerns related to long-term safety [4].

Other Nutritional Considerations

Non-nutritive Sweeteners

Non-nutritive sweeteners (NNS) can be used as an alternative for products sweetened by sugar, thereby allowing for a reduced intake of carbohydrates and calories. The use of NNS is controversial, however, since the health outcomes associated with NNS are unknown. Lohner et al.

performed a meta-analysis of nine randomized controlled trials to assess the effects of NNS compared with sugar, placebo, or nutritive low-calorie sweetener consumption in people with diabetes. There was inconclusive evidence on clinically relevant benefit or harm for HbA1c, body weight, and adverse events in people with type 1 or type 2 diabetes. There was no data on factors such as diabetes complications, all-cause mortality, health-related quality of life [67]. Given these concerns, it is preferred to replace sugar-sweetened beverages (SSB) with water. Drinking water as a replacement of sugar and without compensation for reduced caloric intake may help reduce weight [68, 69]. People should be recommended to abstain from consuming additional calories from other foods when sugar substitutes are used with the goal of reducing caloric intake. SSB may have putative negative effects, including negatively modifying hunger sensation [69].

Caffeine and green tea catechins have both been associated with increased satiety and improving sensation of fullness. Several studies have looked at additional beneficial effects of moderate caffeine consumption by humans and noted increased energy availability, daily energy expenditure, and physical performance. They also noted decreased energy intake and fatigue. Therefore, these beverages can be considered as alternatives to SSB [70].

Fiber

Recommendations for fiber intake for people with diabetes are similar to the recommendations for the general public (DRI: 14 g/1000 kcal). Diets containing 44–50 g fiber daily are reported to improve glycemia, but more usual fiber intakes (up to 24 g/day) have not shown beneficial effects on glycemia. It is unknown whether free-living individuals can sustain daily consumption of the amount of fiber needed to improve glycemia. However, some research suggests that viscous fiber can decrease postprandial glucose and HbA1c [71]. In addition, diets high in total and viscous fiber, as part of cardioprotective nutrition therapy, have been shown to reduce total cholesterol by 2–3% and LDL cholesterol by up to 7% [4]. Therefore, foods containing 25–30 g/day of fiber, with special emphasis on viscous fiber sources (7–13 g), are to be encouraged.

Alcohol

Recommendations for alcohol intake are similar to those for the general public. If individuals with diabetes choose to use alcohol, daily intake should be limited to one drink per day or less for women and two drinks per day or less for men [41]. One drink is defined as a 12 oz beer, 5 oz wine, or 1.5 oz of distilled spirits, each of which contains about 14 g alcohol. Moderate amounts of alcohol when ingested with food have minimal, if any, effect on blood glucose and insulin concentrations. The type of beverage consumed does not appear to make a difference. However, the effect of alcohol on persons with diabetes is individualized. For individuals using insulin or insulin secretagogues, if alcohol is consumed, it should be consumed with food to prevent hypoglycemia. Moderate alcohol consumption is associated with a decreased incidence of heart disease in persons with diabetes [41, 72]. However, chronic excessive ingestion of alcohol (>3 drinks/day) can cause deterioration of glucose control with the effects from excess alcohol being reversed after abstinence for 3 days. In epidemiological studies, moderate alcohol intake is associated with favorable changes in lipids, including triglycerides. Because the available evidence is primarily observational, it does not support recommending alcohol consumption to persons who do not currently drink. Occasional use of alcoholic beverages can be considered an addition to the regular meal plan, and no food should be omitted.

Diabetes-Related Comorbidities

Diabetic Kidney Disease

The recommendations for nutrition, in particular protein intake, for patients with diabetic kidney disease have changed over time. While previously low-protein diets were advised with the goal of reducing albuminuria and reducing the progression of kidney disease, it was found that this did not significantly alter the progression of

diabetic kidney disease [4]. Moreover, there may be increased risk of malnutrition if protein is restricted, therefore there is no recommendation to restrict protein intake in persons with diabetes and kidney disease. In persons with diabetic nephropathy, a protein intake of 1 g or less per kg body weight per day is recommended.

Gastroparesis

It is advisable to refer patients with gastroparesis to consult a RDN with experience in gastroparesis. An important aspect is the selection of foods of smaller particle sizes and/or consume smaller, more frequent meals as this can help facilitate the transfer of food through the digestive tract [73]. In addition, it would be helpful to recommend foods that do not delay gastric emptying such as lower fiber and lower fat foods. Liquid foods may be preferred over solid foods. Acute hyperglycemia could negatively affect gastric emptying and should ideally be minimized. In people with gastroparesis, timing of insulin administration can be difficult. Continuous glucose monitoring may aid in optimizing insulin administration, and some people with type 1 diabetes or insulin-treatment in type 2 diabetes may see benefit from treatment with an insulin pump [73, 74].

Cardiovascular Disease

The incidence of cardiovascular disease (CVD) in people with type 1 and type 2 diabetes is high. Thus, there is particular interest in mitigating the risk of CVD in diabetes. Many of the nutrition recommendations for CVD reduction in the general population also apply for people with diabetes. MNT that improves blood glucose control, blood pressure, and lipid profiles is a cornerstone element in the management of diabetes. This has been shown to lower the risk of CVD including stroke [4]. Data from clinical trials support the role of nutrition therapy for reaching glycemic targets and decreasing markers of CVD risk [4]. People with diabetes are encouraged to reduce the amount of saturated fat and replace this with unsaturated fats where possible. This has been shown to reduce total cholesterol and LDL-C and can improve cardiovascular risk factors. In a study, which included close to 50% of people with diabetes, intakes of monounsaturated and polyunsaturated fats were associated with a lower CVD risk and death, whereas intakes of saturated fat and trans fat were associated with a higher CVD risk. Replacing saturated and trans fats with monounsaturated or polyunsaturated fats in food was inversely associated with CVD. In general, replacing saturated fat with unsaturated fats, especially polyunsaturated fat, significantly reduces both total cholesterol and LDL-C, and replacement with monounsaturated fat from plant sources, such as olive oil and nuts, reduces CVD risk. However, the association between saturated fat intake and risk of CVD remains controversial. Consumption of *n*–3 fatty acids from fish but also from supplements has been suggested to reduce adverse cardiovascular outcomes [4], although the evidence that *n*–3 fatty acids from supplements n3 fats from supplements reduces risk of CVD remains weak [75].

Trans fats should be avoided as they have been associated with all-cause mortality and CVD mortality [76]. Trans fats have now been almost eliminated from food in the United States. Reducing sodium to the general recommendation of 2300 mg/day demonstrates beneficial effects on blood pressure [4].

Summary and Conclusions

Over the past decades, there have been major developments in the field of medical nutrition therapy for the management of diabetes. Medical nutrition therapy (MNT) is an essential pillar of diabetes management that involves an ongoing approach to deliver effective recommendations tailored to the individual needs of the person with diabetes. Monitoring of glucose, HbA1c, lipids, and blood pressure is crucial to assess the outcomes of nutrition therapy interventions and/or to determine if changes in medications are necessary. It is important that all healthcare providers understand the fundamentals of evidence-based nutrition therapy to safely guide recommendations that promote adoption of healthful lifestyle practices and support each individual's unique needs and wishes.

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6 Obesity: A Disease of Overnutrition

George A. Bray and Catherine M. Champagne

Key Points

- Obesity is a serious worldwide problem that is increasing in prevalence.
- Obesity results from increased energy intake from food exceeding what is needed for daily energy expenditure over a considerable period of time.
- Obesity predicts the risk for many diseases, including diabetes, liver and gall bladder disease, infectious diseases such as SARSCov-19, and heart disease, among others.
- Treatments for obesity include diet, exercise, behavioral therapy, medications, and surgery.

Introduction

The title of this chapter was selected to highlight two aspects of obesity: first, obesity predicts the development of many diseases; and second, obesity results from ingesting more energy from food calories over an extended period of time than are expended in daily living. We will deal with several questions designed to focus the discussion:

1. How do we define and measure obesity?
2. Who becomes obese?
3. How does obesity develop? OR What causes obesity?
4. Why is obesity called a chronic relapsing disease process?
5. What problems does obesity produce?
6. What can we do to prevent obesity?
7. How effective are treatments for obesity?

How Do We Define and Measure Obesity?

Obesity means too much body fat. Body fat and its distribution around the body can be measured with considerable accuracy by several methods, including anthropometric methods such as skinfold thickness; and assessment of body density by the Archimedes principle of water displacement when an individual is weighed underwater

G. A. Bray (✉)
Pennington Biomedical Research Center, Baton Rouge, LA, USA

Walnut Creek, CA, USA
e-mail: George.bray@pbrc.edu

C. M. Champagne
Pennington Biomedical Research Center, Baton Rouge, LA, USA
e-mail: Catherine.chamapgne@pbrc.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_6

and then out of water, since fat is lighter than water and other components of the body. Air displacement can be used instead of water in an instrument called a Bod Pod. Another method is to measure body water by bioelectric impedance analysis (BIA), a technique that assesses body water by resistance of current flow and allows calculation of body fat. The most specific method and also the most expensive involves dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and computed tomographic scans (CT) [1].

Once body fat has been measured, how do we define desirable levels of fat? Because the proportion of body fat varies between males and females and changes with age, widely accepted levels of body fat have not been defined. In general, adult women have about 12% more fat than adult men, but there is a considerable range of values depending on age, level of physical activity, and ethnic background.

Body fat increases with body weight and thus measurement of body weight has become a surrogate for body fat. Tables of desirable body weight for men and women were initially developed by the insurance industry (Metropolitan Tables of Acceptable Weight) and have been widely used. For children and adolescents, the Centers for Disease Control and Prevention (CDC) have developed charts for determining the appropriate range of weights for a given height. Healthy children gain weight at a predictable rate. Positive deviation from this trajectory can be a sign of obesity and future disease risk and indicates a need for preventive efforts.

For adults, the body weight is usually adjusted for height, as it is in children, and currently the most widely used surrogate for body fat in adults is the body mass index (BMI). This measure, developed over 100 years ago by Quetelet, is the body weight divided by the square of height in meters [wt (kg)/(height in m)^2]. BMI is widely used in studies of obesity in populations and is a useful starting point for evaluating individuals with possible obesity. However, BMI is not a precise measure of body fat but can be a useful indicator of the need for further evaluation of an individual patient. BMI is an insufficient criterion on its own for the diagnosis of "obesity." In the 2013 AHA/ACC/TOS Guidelines for the Management of Overweight and Obesity in Adults, there is an algorithm showing how BMI is used as a starting point in the evaluation of the patient with obesity [2]. Body weight rises with age until about 60 years of age in both men and women as shown in Fig. 6.1. After age 60 most people eat less, due in part to changes in taste and smell, which reduces the pleasure of eating. The decline also reflects the gradual loss of muscle mass that occurs with aging.

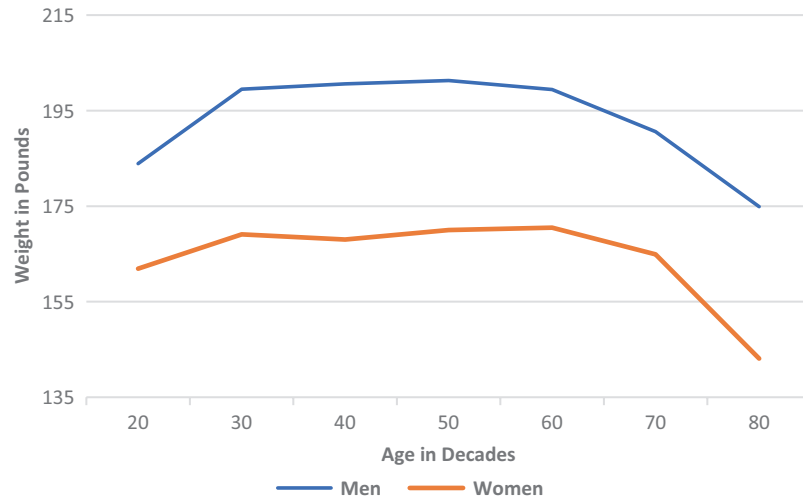

Fig. 6.1 Weight Change from Age 20 to 80 in Men and Women [3]

In addition to the BMI, which provides a single number for assessing weight status, there is also interest in where fat is located. This is because fat located in some areas of the body carries greater risk for future disease than fat in other regions. In particular, central adiposity, that is fat located primarily intraabdominally in so-called visceral fat deposits, carries greater risk of disease. By contrast, fat located on the lower extremities may actually be protective, but at least fat in this location carries less risk for future disease. Measurement of central fat can be done by several techniques, including waist circumference, computed tomography (CT), and MRI scans. For clinical purposes, the waist circumference is most widely used. Like the BMI, standards for central fat are ethnically specific. For Americans, a waist circumference (WC) of >40 inches (102 cm) in men and >35 inches (89 cm) in women is defined as high risk for future disease. In many other countries, a WC of >90 cm in men and >80 cm in women is defined as the cut-point for establishing risk from central adiposity. The patterns of central fat are commonly called "apple-shaped" and "pear-shaped" to refer to whether the fat is mainly visceral (apple-shaped) or more distally located (pear-shaped).

Who Becomes Obese?

To provide some guidance on whom we should label as "obese," cut-points have been developed along the bell-shaped curve of BMI. Since there are ethnic differences between populations, these cut-points also differ between ethnic groups. For Americans and most Europeans, a BMI between 20 and 25 kg/m^2 is normal, a BMI between 25 and 30 is defined as overweight, and a BMI >30 is defined as obesity. Among those with obesity, there are additional BMI subdivisions at 35 and 40 to define further increases in risk and for use in initial assessment for certain types of treatment for individuals with obesity.

The prevalence of obesity varies by ethnicity and from country to country. In 2015, there were an estimated 1.9 billion people globally who were overweight and 609 million who were obese. Obesity is a worldwide epidemic. In 1980, 26.5% of the world's population were overweight and 7% obese. By 2015, this had risen to 39.0% who were overweight and 12% who were obese [4]. Figure 6.2 shows the rising BMI for several sub-groups in the American population from 1960 to 2000. All groups began to gain weight around 1975 and contin-

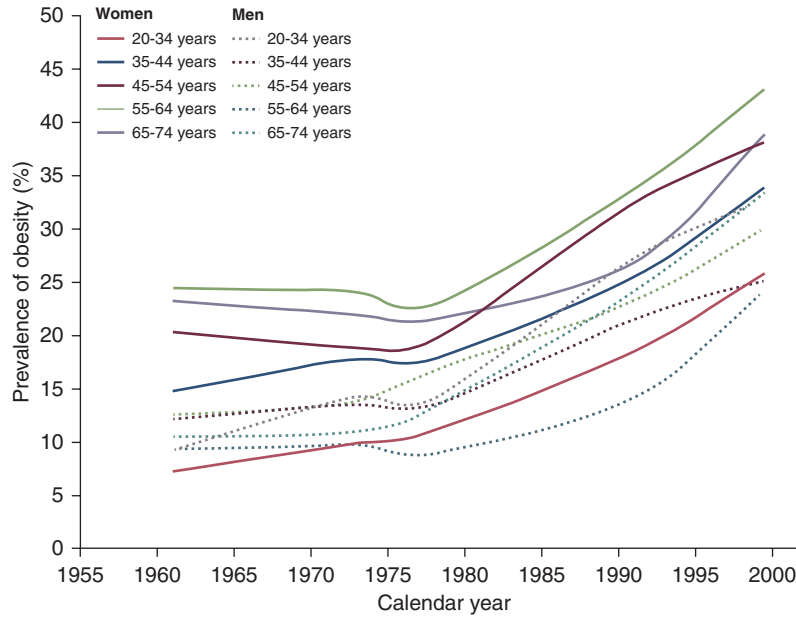

Fig. 6.2 Prevalence of obesity by age and sex in the United States, 1962–2000

Table 6.1 Prevalence of obesity in the United States

Prevalence of obesity (BMI ≥30 kg/m^2)			
	Total (%)	Male (%)	Female (%)
Non-Hispanic White	42.2	44.7	39.8
Non-Hispanic Black	49.6	41.1	56.9
Hispanic	44.8	45.7	43.7
Asian	17.4	17.5	17.2

https://www.cdc.gov/obesity/data/prevalence-maps.html. Accessed 15 April 2021 [6]

ued in parallel for the next 25 years. The data suggest that a number of ideas about the cause of obesity may be untenable, including genetic changes, changes in exercise patterns, changes in willpower, and lifestyle factors; the suggestion is rather that some factor in the environment, possibly the food supply, changed about 1970 [5].

Ethnicity affects the prevalence of obesity as shown in Table 6.1. Asians of both sexes have the lowest prevalence of obesity. Non-Hispanic Blacks, and particularly Black women, bring up the other end of the continuum.

What Causes Obesity?

As noted above, obesity is a disease of overnutrition. It develops because an individual consumes more energy from the food they eat over an extended period of time than is needed for daily energy expenditure. The increase in body weight is usually gradual, about 0.5 kg/year (Fig. 6.3).

As people grow older, their food intake tends to remain constant over time while their physical activity declines slowly. Over one year, an adult will eat nearly 800,000 calories. Storage of only 3000 kcal in fat would increase body fat by about 0.5 kg per year [7].

Estimating an individual's energy needs is an important first step in treating obesity. It is also important to consider an individual's physical activity levels, along with several other factors. The Estimated Energy Requirement (EER), which was defined by the Dietary Reference Intakes (DRIs), includes calculations that account for energy intake and expenditure, age, sex, height, and weight, and level of physical activity [8]. The Mifflin-St. Jeor Equation is one of the most widely used and is the one we suggest. It was developed to provide a more valid estimate of resting metabolic rate (RMR) and had the highest performance for agreement measures and bias in a whole cohort of patients with obesity [9, 10].

This imbalance between intake and expenditure is influenced by many factors. People who sleep less are more likely to be obese. People with longer times for consuming food over the daytime tend to be heavier. Body weight varies with the season, with weight gain in the winter. There is also a sex difference—men tend to be heavier than women (Fig. 6.1). For obesity, the principal lifestyle factors are food and physical inactivity. Other agents include drugs, toxins, viruses, and the microbiome (Table 6.2).

Around the world, tasty, inexpensive, and convenient foods, which are usually high in fat, are abundant and easy to overeat. These foods, often called "ultra-processed foods," are hard to put down and easily lead to overeating. Energy-dense foods, those with more fat and less water, also tend to be overeaten. Portion sizes have increased, providing more energy to people with each portion, and people tend to eat more when larger portions are provided. The microbiome may also play a role in harvesting energy from

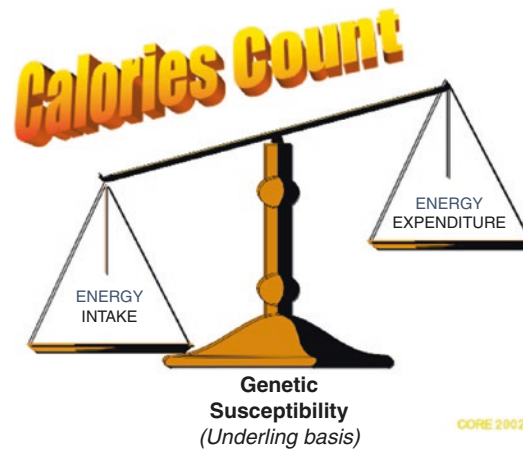

Fig. 6.3 A balance beam illustrates the effect of energy intake and expenditure on body weight: calories do count

foods and thus in obesity [12]. Obesogens, a group of chemical agents used in various products such as plastics, can produce obesity in animals and are of concern. Certain viruses are known to produce obesity in animals, and their potential role in obesity in humans needs to be studied further. Some people have genes that in the current "toxic" food environment may become more manifest. The genetic effect can be summarized this way: "Genetic variability loads the gun; environment pulls the trigger; bullets do the damage!" [13].

Several intrauterine events influence postnatal weight and lifetime weight gain [14]. These include maternal smoking and consumption of sugary beverages which should be eliminated during pregnancy. The presence of maternal diabetes can produce large and fat infants at birth. Intrauterine undernutrition and maternal weight gain should be avoided and can be treated. All of these factors heighten the risk for increased body weight and diabetes later in life.

Our medicated society now produces some medications that cause weight gain. The health professional can use this knowledge to intervene on some occasions by replacing medications that cause weight gain with ones that do not. Table 6.3

Table 6.2 Factors that affect food intake

Food abundance, particularly ultra-processed food
Exercise and time in sedentariness
Temperature
Medications that produce weight gain
Infective agents—COVID-19
Smoking
Intrauterine environment
Maternal age
Duration of time sleeping

Adapted by McAllister et al. Crit Rev Food Sci Nutr 2009 [11]

Table 6.3 Medications that produce weight gain and possible alternatives

Category	Drugs that may cause weight gain	Possible alternatives
Antipsychotics	Thioridazine; olanzapine; quetiapine; risperidone; haloperidol; perphenazine; clozapine	Molindone Ziprasidone
Antidepressants; Tricyclic antidepressants; Monoamine oxidase inhibitors; Selective serotonin Reuptake inhibitors	Amitriptyline; nortriptyline Imipramine; trimipramine Mirtazapine Paroxetine Doxepin	Protriptyline Bupropion Nefazodone Fluoxetine (short-term) Sertraline (<1 year)
Anticonvulsants	Valproate Carbamazepine Gabapentin	Topiramate Lamotrigine Zonisamide
Antidiabetic drugs	Insulin Sulfonylureas Glinides Thiazolidinediones	Acarbose Miglitol Metformin Pramlintide Exenatide; liraglutide SGLT-2 inhibitors
Antiserotonin	Pizotifen	Topiramate
Antihistamines	Cyproheptadine	Inhalers Decongestants
β-Adrenergic blockers α-Adrenergic blockers	Propranolol Terazosin	ACE inhibitors Calcium channel blockers
Steroids for chronic inflammatory disease	Glucocorticoids	Nonsteroidal anti-inflammatory agents. Disease modifying anti-rheumatic drugs
Contraceptives	Progestational steroids	Barrier methods
Endometriosis	Depot Leuprolide acetate	Surgical intervention

From: Bray and Champagne, Nutrition Guide for Physicians and Healthcare Professionals [15]

is a list of some of these medications and alternative treatments that can be used to avoid the weight gain.

Many aspects of diet contribute to obesity. Sugary drinks are one. The sugar in soft drinks and fruit drinks is partly "invisible" to the body. Thus, individuals don't "compensate" effectively after drinking them, and they are best avoided [16]. Gestational diabetes also significantly increases the risk of diabetes later in life. Diet quality is another factor. Increasing the intake of healthy foods is associated with more weight loss [17, 18].

Infancy and early childhood are also timepoints where the healthcare professional may be able to intervene and help prevent obesity. Infants who are breastfed for more than 3 months may have a reduced risk of future obesity. Children who sleep less have a higher risk for weight gain during school years.

Why Is Obesity Called a Chronic Relapsing Disease Process?

Two aspects of body fat help explain the way that obesity damages the body. The first is through the increased weight or mass of fat, which allows obesity to be easily recognized and thus stigmatized. Extra weight can also damage weight-bearing joints. The second way that fat produces disease in the body is through the increased secretion of adipokines by the enlarged fat cells that in turn act on distant organs after traveling through the blood (Fig. 6.4).

The products released from the fat cell in turn modify the metabolic and inflammatory processes in other organs in the body. Among the products released by fat cells are adipokines which may play a role in the susceptibility of people with obesity to the coronavirus (COVID-19). For the susceptible host, these metabolic and inflammatory changes increase circulating levels of fatty acids and enhance the production of estrogens in adipose tissue leading to a variety of other processes, including hyperinsulinemia, atherosclerosis, hypertension, and physical stress on bones and joints and increased risk of female cancers [19].

Calling obesity a disease goes back centuries. Indeed, Hippocrates, the Father of Modern Medicine in some minds, noted over 2000 years ago that heavier people were at higher risk of dying. For much of the twentieth century, the argument about whether obesity should be called a disease or simply a "condition" has gone on and on. Finally in 2013, the American Medical Association voted to call obesity a disease. World Obesity, an association of national obesity societies carrying out research in obesity, also called obesity a chronic relapsing stigmatized disease process [20]. The American Association of Clinical Endocrinology echoed this by calling it an adiposity-based chronic disease (ABCD)

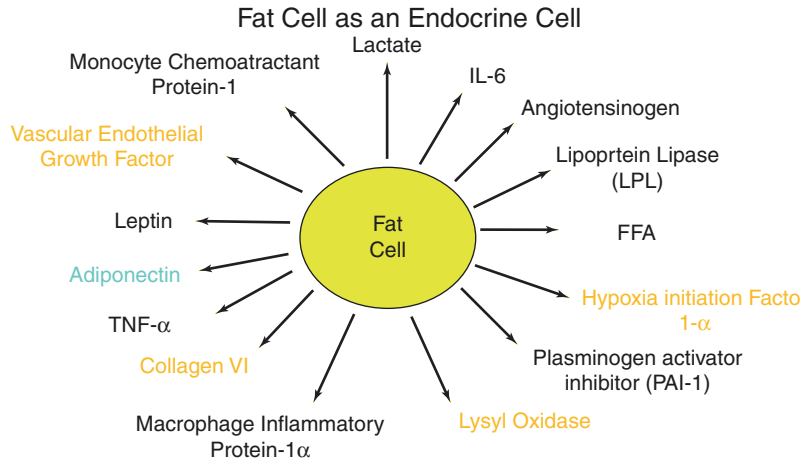

Fig. 6.4 The fat cell is an endocrine cell that produces many secretory products called adipokines

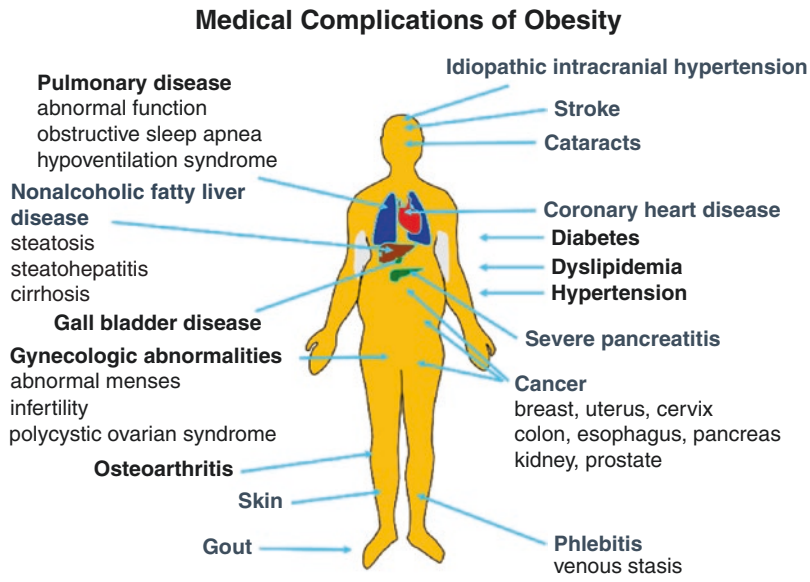

Fig. 6.5 Medical complications associated with obesity

which focuses attention on the important role that adipokines produced in the adipose tissue have on patients with obesity. Obesity causes many diseases, and these are shown graphically in Fig. 6.5.

What Can We Do to Prevent Obesity?

Findings from epidemiological investigations on obesity indicate that pregnancy, early childhood, and young adulthood represent key periods to intervene and hopefully ward off future weight gain. Pre-pregnant weight and weight gain during pregnancy increase the likelihood of early onset obesity. Early care in educational settings and schools provide multiple opportunities for prevention in these younger age groups.

Studies of children have shown that exercise and nutritional quality can be improved by lifestyle intervention. However, impacting body weight change is more difficult and often not achieved. Reducing the intake of sugar-sweetened beverages and replacing them by drinking water is a potentially useful strategy. Studies aimed at preventing weight gain in adults as a group and in special subsets of adults have been less consistent—an area where more work is needed.

How Effective Are Treatments for Obesity?

To decide on effectiveness of treatment, we need a criterion for success [21]. How much weight loss is needed to reduce risk and improve health in people with obesity? It is not necessary for patients to achieve an ideal body weight or even a body mass index <30 kg/m^2 to reap significant health benefits. Modest weight loss of 5–10% improves glycemia, blood pressure, blood lipids, the need for some medications, as well as mobility and quality of life.

While improvements in glycemia and triglycerides begin at 3% weight loss, and improvements in lipids and blood pressure begin at a weight loss of 5%, larger weight losses may be needed to produce benefits in some conditions such as obstructive sleep apnea and non-alcoholic steatohepatitis [22]. The loss of fat in critical ectopic fat deposits, such as visceral fat and hepatic fat, is disproportionately greater than weight loss. The message to healthcare professionals is that significant improvements in health can occur with a modest weight loss of 5% or so, while some patients may need a larger weight loss of 10% or more. Significant weight loss may also reduce mortality. In the Look AHEAD trial, individuals who lost >10% of their body weight

had a significant 20% reduction in the cardiovascular endpoint for the study [23]. For US adults, those who lost enough weight to move from the obese category to the overweight category in middle age had a 54% reduced mortality compared to those who remained obese.

With all treatments for obesity, there is gradual slowing of weight loss, followed by a high frequency of weight regain when treatment is slowed or stopped [14]. There is also considerable variability in the amount of weight lost along with variability in patient satisfaction with their weight loss. By the end of the first year in the large clinical study called Look AHEAD, weight loss after one year was below 3% in a quarter (25%) of the participants, but over 12% in the larger losers. Moreover, all but the top 90th percentile had stopped losing weight and were approaching a plateau in body weight. The conclusion from these studies is that a well-designed lifestyle program can provide individuals with the tools they need to lose an average of 8% of their weight and for some to lose more than 15% of their weight; this is a very satisfactory outcome. At the other end, however, are an equal number of people who receive little or no benefit in terms of weight loss from this intensive therapy.

Diets are tools that are used by many people to lose weight [24]. A key message from comparison of weight loss diets is that all diets work, if followed. In one metanalysis, the Mediterranean Diet and the DASH Diet were significantly better than comparison diets. There are other aspects of diet besides weight loss that should be considered, such as reduced cardiovascular risk. The DASH diet, for instance, significantly reduces blood pressure. The Mediterranean Diet reduced the risk of cardiovascular disease in a randomized controlled trial, reinforcing the concept that diet quality is an important consideration, especially for those with increased cardiovascular risk.

Medications can supplement weight loss produced by diet alone [25]. There are several medications approved by the US FDA for treatment of the patient with obesity, and these are summarized in Table 6.4.

Currently, the personalized choice of a medication, if used, is determined by what the patient's insurance coverage allows, whether a drug might pose a safety issue, and the patient preference. This choice is generally made as a shared decision by the prescriber and patient. Labeling for all drugs recommends stopping at 12–16 weeks if a 4–5% weight loss has not been achieved. Identification of craving and binge eating may aid in selecting treatments. Some acute food intake studies demonstrate that semaglutide is associated with reduced craving. In the longer-term STEP trials, average weight losses of more than 15% were reported with over 30% of patients losing more than 20% of their body weight. This makes semaglutide comparable to surgery in the magnitude of weight loss [26]. The combination drug naltrexone/bupropion produced greater control of cravings which were associated with greater weight loss. Three drugs (lisdexamfetamine, topiramate, and second-generation antidepressants such as citalopram, fluoxetine, and sertraline) have been shown to reduce bingeing and to produce weight loss. None of these drugs produces weight loss that exceeds 10%, in contrast to semaglutide which reduces weight by more than 10% and also significantly reduces cardiovascular risk in patients with obesity and type 2 diabetes [27]. Setmelanotide was approved in 2020 for a narrow group of genetically inherited forms of obesity [28].

Surgical treatment of obesity produces by far the largest weight losses and best maintenance of weight loss of any currently available treatment. There are four main operations in current use: Sleeve gastrectomy, Roux-en-Y gastric bypass, laparoscopically placed band or LAPBAND, and the biliary pancreatic diversion. In the Longitudinal Study of Bariatric Surgery (LABS), funded by the NIH, the median weight loss of 1513 patients who were followed for 3 years who underwent a Roux-en-Y gastric bypass (RYGB) was 31.5% (IQR: 24.6–38.4%); in the 509 patients who underwent laparoscopic adjustable gastric banding (LAGB) weight loss was about half as much or 16.0% (IQR: 8.1–23.1%) [29]. Weight loss with bariatric surgery exceeded the weight loss produced by lifestyle, by diets, and

Table 6.4 Drugs approved by the U.S. Food and Drug Administration for the Management of Obesity*

Drug and mechanism of action	Trade name(s)	Dosage	Comments
Gastrointestinal fiber			
Gelesis 100 (2019) (not scheduled)	Plenity	3 capsules 20 min before lunch & dinner with 16 oz of water	No DEA schedule; Approved for BMI 25–40; Composed of cellulose and citric acid
Pancreatic lipase inhibitor approved for long-term use orally			
Orlistat (1999) (not scheduled)	Xenical Alli	1120 mg tid before meals OR 660 mg tid before meals (over-the-counter)	GI side effects including steatorrhea, oily spotting, flatulence, fecal urgency, fecal urgency, and/or incontinence
Glucagon-like receptor-1 agonist approved for long-term use by injection			
Liraglutide (2015) (not scheduled)	Saxenda	33.0 mg/day—dose-escalation over 5 weeks from 0.6 mg/day to 3.0 mg/day	**Boxed Warning**: Thyroid C-cell tumors in mice. Nausea with some vomiting are principal side effects; acute pancreatitis or gallbladder disease can occur; hypoglycemia with some antidiabetic drugs
Semaglutide (not scheduled) Approved for type 2 DM (by DM injection in 2017; orally in 2019) Approved in 2021 as injection for obesity	Ozempic Rybelsus Wegovy	00.5 or 1.0 mg 77 pr 14 mg 22.4 mg May need dose-escalation	Approved for type 2 diabetes and obesity. Reduces CVD risk in high-risk patients Contraindicated in medullary thyroid cancer or MEN2
Melanocortin-4 receptor agonist approved for special cases			
Setmelanotide (2020) (not scheduled)	Imcivree	11, 2 or 3 mg injection each day	For use in patients with leptin receptor deficiency, pro-opiomelanocortin (POMC) defect or PCSK1 defect
Combination of two drugs approved for long-term use orally			
Phentermine/Topiramate extended release (2012) DEA Schedule IV (Combination of sympathomimetic and anticonvulsant)	Qsymia	3.75 mg/23 mg, first week; 7.5 mg/46 mg thereafter; can increase to 15 mg/92 mg for inadequate response	Contraindicated in pregnancy; Fetal toxicity with monthly pregnancy test suggested; Paresthesias and change in taste (dysgeusia); Acute myopia (rare) Metabolic acidosis and glaucoma are rare; Do not use within 14 days of a MAOI anti-depressant
Naltrexone SR/Bupropion SR (2014) (not scheduled) (Naltrexone acts as an opioid receptor antagonist and bupropion as a dopamine & norepinephrine reuptake inhibitor)	Contrave (US) Mysimba (Europe)	32 mg/360 mg tabs; take 2 twice daily after dose- escalation	**Boxed Warning:** Suicide risk in depression; Contraindicated in pregnancy, in seizures, with uncontrolled hypertension & glaucoma. Nausea, constipation, headache; Avoid in patients receiving opioids, MAOI, antidepressants, and with history of seizure disorder
Noradrenergic drugs approved for short-term use			
Diethylpropion (1959) DEA Schedule IV	Tenuate Tepanil	25 mg tid	Dizziness, dry mouth, insomnia, constipation, irritability. Cardiostimulatory
	Tenuate Dospan	75 mg q AM	
Phentermine (1959) DEA Schedule IV	Adipex Fastin	15–37.5 mg/day	Dizziness, dry mouth, insomnia, constipation, irritability Cardiostimulatory

(continued)

Table 6.4 (continued)

Drug and mechanism of action	Trade name(s)	Dosage	Comments
	Oby-Cap Ionamin slow release	15–30 mg/day	
Benzphetamine (1960) DEA Schedule III	Didrex	25–50 mg tid	Dizziness, dry mouth, insomnia, constipation, irritability. Cardiostimulatory
Phendimetrazine (1959) DEA Schedule IV	Bontril Plegine Prelu-2 X-Trozine	17.5–70 mg tid 105 mg qd	Dizziness, dry mouth, insomnia, constipation, irritability Cardiostimulatory

From: Bray and Champagne, Nutrition Guide for Physicians and Related Healthcare Professionals [15]

by pharmacotherapy, a finding which led Mueller et al. to suggest that bariatric surgery was a "benchmark for efficacy" in the management of obesity. Bariatric surgery can also produce significant health benefits. In addition to weight loss, these operations significantly reduce the risk for developing diabetes, reduce the likelihood of myocardial infarction, lower cancer risk in women, and lower all-cause mortality. The challenge for the future is to find ever safer ways of obtaining these results.

This chapter has shown that obesity is a serious worldwide problem that is increasing in prevalence. Obesity develops because food exceeds what is needed for daily energy expenditure. There are increased risks for many diseases that result from obesity, including diabetes, liver and gall bladder disease, infectious diseases such as SARSCov-19, and heart disease, among others. Strategies for managing the patient with obesity include diet, exercise, behavioral therapy, medications, and surgery all, of which have been briefly reviewed.

Summary

Obesity is defined as an increase in body fat but is usually estimated from measures of height and weight such as the body mass index – Weight (kg)/[Height (m)]^2. Obesity develops, over time, as food intake exceeds energy expenditure due to either ingestion of more food or decreased energy expenditure. Obesity is labeled a chronic disease process because it tends to recur after efforts to lose weight, and because the excess weight along with hormones and other signals released from the enlarging fat cells affect the function of other organ systems. Obesity is associated with a number of health problems, including diabetes, liver and gall bladder disease, chronic kidney disease, heart disease, increased risk of mortality and severity from COVID-19 infection, and earlier death than in people who are of normal weight. Attempts to prevent obesity need to begin with pregnant women and continue in childhood among children showing excessive weight gain, and needs to continue through adult life, but the challenges are significant. For the pregnant woman, smoking, ingestion of sugary beverages, and diabetes all increase the risk that their offspring will become obese. Treatment of obesity can involve use of diets, exercise, behavioral strategies, medications, and surgery. The magnitude of response varies with each of these therapies, and there is substantial variation in the response of individuals to each of these treatments. The challenge of obesity as a nutritional disease is still far from being solved.

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7 Effects of Nutrients on the Control of Blood Lipids

Philip A. Sapp, Kristina S. Petersen, and Penny M. Kris-Etherton

Key Points

- Lipids and lipoproteins play a central role in the development of atherosclerotic cardiovascular disease (ASCVD).
- Dietary fatty acids and refined and simple carbohydrates (CHO) affect the risk of developing ASCVD by modulating circulating lipids and lipoproteins.
- Replacing saturated fatty acids (SFA) with polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), and complex CHO lowers total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C).
- Viscous fiber and plant sterols/stanols decrease TC and LDL-C.
- Dietary cholesterol increases TC and LDL-C, but less so compared to SFA.
- Added sugars, refined CHO, and alcohol increase triglycerides (TG).
- A healthy dietary pattern that meets nutrient recommendations favorably affects lipids and lipoproteins and lowers ASCVD risk.

P. A. Sapp · P. M. Kris-Etherton (✉)
Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA
e-mail: philip.sapp@psu.edu

K. S. Petersen
Department of Nutritional Sciences, Texas Tech University, Lubbock, TX, USA
e-mail: kristina.petersen@ttu.edu

Introduction

The 2021 American Heart Association (AHA) Dietary Guidance to Improve Cardiovascular Health recommends a healthy dietary pattern to promote cardiometabolic health, and the 2019 American College of Cardiology (ACC)/AHA Guideline on the Primary Prevention of Cardiovascular Disease recommends following a healthy lifestyle (e.g., healthy diet, exercise, smoking cessation) throughout life [1, 2]. Circulating lipid and lipoprotein concentrations are a primary target for atherosclerotic cardiovascular disease (ASCVD) risk reduction [3]. Convincing clinical and epidemiological evidence demonstrates that elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and non-high density lipoprotein cholesterol (non-HDL-C) increase ASCVD risk [4, 5]. Additionally, increasing high-density-lipoprotein cholesterol (HDL-C) may have cardioprotective effects [6]. Thus, higher non-HDL-C and TC to HDL-C (TC: HDL-C) ratio increases ASCVD risk. Furthermore, evidence from observational studies and clinical trials shows that nutrient intake modulates lipids and lipoproteins [7, 8].

This chapter focuses on clinical and epidemiological studies that have evaluated the role of nutrients on circulating lipids and lipoproteins. Research has focused on the effect of dietary fatty acids, cholesterol, soluble fiber,

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_7

plant sterols/stanols (although not a nutrient they are naturally occurring compounds found in plants), dietary carbohydrates (CHO) (including refined and simple carbohydrates), and alcohol on lipids and lipoproteins. Saturated fatty acids (SFA) and dietary cholesterol adversely impact circulating blood lipid/lipoprotein levels (principally total cholesterol and LDL-C), whereas unsaturated fatty acids (monounsaturated [MUFA] and polyunsaturated fatty acids [PUFA]) when substituted for SFA, soluble fiber, and plant sterols/stanols improve lipids and lipoproteins. Refined CHO, added sugars, and alcohol in excess have adverse effects on blood lipids (i.e., TG and TG rich lipoproteins). Understanding the role that nutrients play in altering lipids and lipoproteins is important for the implementation of dietary strategies to reduce ASCVD risk.

Fatty Acids and Blood Lipids/ Lipoproteins

The pioneering epidemiological Seven Countries Study conducted in the United States, Finland, Netherlands, Italy, Yugoslavia, Greece, and Japan showed a significant positive association between SFA intake and TC levels and the incidence of coronary heart disease (CHD) [9, 10]. The Seven Countries Study also demonstrated positive associations between individual SFAs and TC. Specifically, intakes of lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0) were positively associated with TC ($r = 0.84, 0.81, 0.62, 0.60$, respectively) [9]. Subsequent epidemiological studies have confirmed these findings.

The findings of these early observational studies led to population-based interventions being conducted to evaluate the effect of lowering SFA on CHD morbidity and mortality. In Finland, a country with the highest rates of CHD mortality globally in the 1960s, a community-based intervention aimed at reducing cholesterol levels, blood pressure, and smoking led to significant reductions in CHD mortality [11]. CHD mortality decreased 80% between 1972 and 2007, with improvements in CHD risk factors explaining 60% of the mortality reduction [11]. Significant dietary changes including marked decreases in SFA intake contributed to the decrease in CHD. SFA intake in Finland was 22% of energy in 1972 and was reduced to 13% by 2007 [11]. The change in dietary SFA was due to a reduction in butter and whole milk and an increase in vegetable oils. These reductions in SFA led to marked decrease in TC (~37.4 mg/dL or ~15%), which played an important role in reducing CHD incidence.

While reducing SFA intake is a cornerstone of CHD risk reduction, the replacement nutrient impacts the direction and magnitude of CHD risk reduction. Consistent epidemiological evidence demonstrates that CHD risk is decreased when SFA is replaced with PUFA [12]. Replacing SFA with MUFA, particularly plant-based sources, is also associated with reduced CHD risk [12]. In addition, replacement of SFA with CHO, specifically complex CHO or whole grains, is associated with lower risk of CHD. However, replacement of SFA with refined grains is not associated with CHD risk reduction, suggesting that both SFA and refined grains are similarly adversely related to CHD risk [12]. Consequently, when SFA is lowered, the replacement nutrient is important for CHD risk reduction.

Epidemiological studies that have assessed the relationship between SFA intake and CHD risk without taking into account nutrient substitutions have yielded inconsistent findings. In a systematic review and meta-analysis of 16 epidemiological studies, only six studies showed a positive relationship between SFA intake and CHD [13]. The authors concluded that SFA was not associated with increased risk of CHD (RR 1.07 [95% CI: 0.96, 1.19]). Importantly, Siri-Tarino et al. did not evaluate nutrient substitutions for SFA, which likely explains the non-significant findings. Between-study heterogeneity in the replacement nutrients was likely present and attenuated the result toward the null. A more recent systematic review and meta-analysis of prospective cohort studies conducted by Mazidi et al. demonstrated that SFA was associated with CHD [14]. This meta-analysis of 19 trials including 29

cohorts with 1,164,029 subjects and a mean follow-up of 13.3 years showed a significant association between SFA intake and CHD mortality (HR 1.10 [95% CI: 1.01, 1.21]). Although this study did not assess nutrient substitutions, the direction of the results suggests that unsaturated fats or whole grains replaced SFA intake in low-SFA consumers (as has been shown in the majority of subsequent studies).

The findings of studies that have evaluated the relationship between SFA and CHD with consideration of the replacement nutrient are more consistent. Jakobsen et al. published a pooled-analysis of prospective cohort studies from the United States and Europe and reported that substituting SFA with PUFA (5% of energy) reduced the risk of CHD events (HR 0.87 [95% CI: 0.77, 0.97]) and CHD death (HR 0.74 [95% CI: 0.61, 0.89]) [15]. Additionally, the authors showed that replacement of 5% of energy from SFA with MUFA or CHO was associated with increased risk of coronary events (HR 1.19 [95% CI: 1.00, 1.42] and HR 1.07 [95% CI: 1.01, 1.14], respectively). Importantly, no differentiation was made between the CHO or MUFA sources, which likely explains these results. Findings from the Nurses' Health Study and the Health Professionals Follow-up Study, both prospective cohort studies including 127,536 men and women showed that replacement of SFA with refined grains did not affect CHD risk, but replacing 5% of energy from SFA with whole grains reduced CHD risk (HR 0.91 [95% CI: 0.85, 0.98]) [16]. Additionally, replacing 5% of energy from SFA with PUFA and MUFA was associated with 25% and 15% lower CHD risk, respectively. In another analysis of the Nurses' Health Study and the Health Professionals Follow-up Study, when MUFA from plant sources replaced SFA (5% of energy), the risk of CHD was decreased (HR 0.83 [95% CI: 0.68, 1.00]), whereas when SFA was replaced with MUFA from animal sources, CHD risk was not decreased (HR 1.04 [95% CI: 0.79, 1.38]) [17]. Collectively, these findings show that replacement of SFA with PUFA, plant-based MUFA, or whole grains is associated with lower risk of CVD. The CVD benefits reported in these epidemiological studies are in part due to lipid and lipoprotein improvements (e.g., reductions in TC, LDL-C, and TG) when SFA is replaced with PUFA, MUFA, or whole grains.

Replacement of SFA

Polyunsaturated Fatty Acids

Seminal clinical trials show that diets high in PUFA (13–21% of energy) and low in SFA significantly reduce TC and CHD events [18–21]. In a meta-analysis of four of these clinical trials that met criteria to increase the likelihood of causative findings (controlled dietary intake, ≥2-years duration, adherence measured by biomarkers, and collection of validated CVD event data), CHD risk was reduced by almost 30% (RR 0.71 [95%CI: 0.62, 0.81]) when SFA was replaced with PUFA from liquid vegetable oils high in PUFA [22]. In these trials, TC levels were reduced by 13–16%. These findings demonstrate the significant CHD benefits of replacing SFA with PUFA.

The CHD benefits observed in clinical trials of low-SFA and high PUFA diets are largely attributed to improvements in lipids and lipoproteins, a primary target for ASCVD risk reduction. In a systematic review and meta-regression analysis of 84 randomized controlled trials (RCTs) (≥13-days; n = 2353; mean pre-study LDL-C: 197.2 mg/dL), Mensink et al. showed that replacing 1% of energy from SFA with PUFA lowered TC, LDL-C, HDL-C, and TG (Table 7.1) [23]. There are two types of PUFA,

Table 7.1 Effects of replacing 1% of SFA with MUFA or PUFA [23]

Lipid or lipoprotein	1% replacement of SFA for MUFA	1% replacement of SFA for PUFA
Total cholesterol, mg/dL	−1.8 (95% CI: −2.0, −1.5)	−2.5 (95% CI: −2.7, −2.2)
LDL-C, mg/dL	−1.6 (95% CI: −1.8, −1.4)	−2.1 (95% CI: −2.4, −1.9)
HDL-C, mg/dL	−0.1 (95% CI: −0.2, 0)	−0.2 (95% CI: −0.2, −0.1)
Triglyceride, mg/dL	−0.4 (95% CI: −0.6, −0.1)	−0.9 (95% CI: −1.2, −0.6)

n-3 and n-6 PUFA, which have differential effects on lipids and lipoproteins (discussed below).

n-6 Fatty Acids

Omega-6, or n-6, PUFA fatty acids have been extensively studied. The most commonly consumed n-6 PUFA is linoleic acid (LA). A Cochrane review which included 19 RCTs (≥12 months) reported that higher vs. lower intake of total n-6 PUFA (included LA, gamma-linolenic acid, dihomo-gamma-linolenic-acid, and arachidonic acid) had no significant effect on risk of CVD events or mortality [24], which is expected given heterogeneity in the replacement nutrient in the included studies (i.e., CHO, SFA, MUFA, protein, or alcohol). In 10 of the studies that assessed TC, it was significantly lower with higher n-6 PUFA (−12.8 mg/dL [95% CI: −19.3, −6.2]) compared to lower intake. Additionally, when SFA was replaced with PUFA, TC was reduced (8 trials; −14.7 mg/dL [95% CI: −21.7, −8.1]). This is consistent with the findings of a review of intervention trials that diets higher in LA significantly reduced TC 5–15% and LDL-C 10–22% compared to diets lower in LA and higher in SFA [25]. Evidence from controlled trials show clear benefits of n-6 PUFA on lipids and lipoproteins, specifically when n-6 PUFA replace SFA.

The 2009 AHA Science Advisory on Omega-6 Fatty Acids and Risk for CVD recommends that n-6 PUFA provide approximately 5–10% of energy and that any reduction in n-6 PUFA would increase CHD risk [26]. The review reported that higher intakes of n-6 PUFA appear to be safe and in combination with a low-SFA, low-cholesterol diet provide additional health benefits (on total mortality, cancer mortality, neurodegenerative mortality, and respiratory disease mortality). This is consistent with the 2020 Dietary Guidelines Advisory Committee (DGAC) conclusions that strong evidence demonstrates that replacing SFA with PUFA in adults reduces the risk of CHD events and CVD mortality. Collectively, strong and consistent evidence supports replacing SFA with n-6 PUFA for CVD risk reduction.

n-3 Fatty Acids

Clinical trials assessing omega-3, or n-3, PUFA have focused on marine long-chain n-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), although the most commonly consumed n-3 PUFA is alpha-linolenic acid (ALA). Of note, ALA is converted to EPA and DHA but the conversion efficiency is very limited (~5% of ALA is converted to EPA and <0.5% to DHA) [27, 28]. In a 2020 Cochrane review including 86 RCTs (≥12 months) higher vs. lower ALA and long-chain n-3 PUFA intake had no significant effect on CVD mortality and events, but long-chain n-3 PUFA reduced CHD events (RR: 0.91 [95% CI: 0.85, 0.97]) [29]. In 28 of the included studies that assessed TG, TG was significantly lower with higher long-chain n-3 PUFA intake vs lower intake (−21.3 mg/dL [95% CI: −27.5, −14.2]). However, higher vs. lower ALA intake had no effect on TG in the six studies evaluated. Although trials assessing marine long-chain n-3 PUFA and ALA are often combined in meta-analyses, there are differential effects of these two omega-3 fatty acids classes on lipids/lipoproteins.

Marine long-chain n-3 PUFA supplementation has potent TG lowering effects while ALA supplementation improves TG, TC, and LDL-C. A systematic review and meta-analysis of placebo-controlled trials (≥4 weeks) showed that supplementation with EPA (8 studies) and DHA (15 studies) (ranging from 0.7–4 g/day) significantly lowered TG (45.8 and 25.1 mg/dL, respectively) [30]. DHA supplementation significantly increased LDL-C (7.23 mg/dL) and also HDL-C (4.49 mg/dL) while EPA did not. In a recent systematic review and dose-response meta-analysis of 47 RCTs (≥2 weeks) assessing ALA supplementation (0.4–16 g/day), significant improvements were observed in TG (−8.9 mg/dL), TC (−5.4 mg/dL), and LDL-C (−5.1 mg/dL) versus control [31]. Every 1 g/day of ALA was associated with a 0.14, 0.3, 0.2, and 0.1 mg/dL reduction in TG, TC, LDL-C, and HDL-C, respectively. Additionally, clinical trial evidence suggests that long-chain n-3 PUFA supplementation may reduce risk of CHD events.

Several AHA Science Advisories on n-3 PUFA have been published. The 2017 AHA Science Advisory on Omega-3 PUFA (fish oil) Supplementation and the Prevention of Clinical CVD does not recommend n-3 PUFA supplementation for individuals that are not at high CVD risk, but evidence suggests benefit for secondary prevention of CHD [32]. An AHA Science Advisory on Seafood Long-Chain n-3 PUFA and CVD published in 2018 recommends 1–2 seafood meals/week for CVD benefits with greater benefits when seafood meals replace red and processed meat [33]. Lastly, an AHA Science Advisory on Omega-3 PUFA for the Management of Hypertriglyceridemia published in 2019 concluded that 4 g/day of marine-derived n-3 PUFA can lower TG by 30% and reduce risk of major CVD events by 25% in adults with hypertriglyceridemia [34]. Collectively, these 3 Science Advisories provide convincing evidence for the benefits of long-chain n-3 PUFA supplementation in high-risk populations, and in all individuals, intake of 1–2 seafood meals/week reduces CVD risk. These conclusions are congruent with those made by the 2020 DGAC report that n-3 PUFA, particularly EPA and DHA, significantly lowers TG and is associated with CVD risk reduction [35].

Monounsaturated Fatty Acids

Long-term clinical trials evaluating the effects of MUFA consumption on CVD endpoints are limited. Only one long-term (>2-years) trial, published in 1965, has assessed the effects of diets devoid of animal fat with 80 g/day of olive oil (higher in MUFA) or corn oil vs. a control diet in adults with CHD and demonstrated no effect on combined CVD events or TC [36]. Although long-term trials assessing CVD event are limited, consistent RCT evidence shows that replacing SFA with MUFA improves blood lipids and lipoproteins. Replacing 1% of energy from SFA with MUFA lowers TC, LDL-C, HDL-C, and TG by 1.8, 1.6, 0.1, and 0.4 mg/dL, respectively (Table 7.1) [23]. Together, these findings from well controlled clinical trials demonstrate that replacing dietary SFA with MUFA significantly alters TC, LDL-C, and HDL-C, but does not lower TG in adults with elevated LDL-C. Thus, replacing SFA with MUFA is a recommended strategy for ASCVD risk reduction.

Other Substances in Food

Dietary Cholesterol

An AHA Science Advisory on Cholesterol and Cardiovascular Risk published in 2020 concluded that epidemiological evidence generally does not show a significant association between dietary cholesterol and CVD risk [37]. However, evidence from intervention studies suggests that dietary cholesterol modestly increases TC and LDL-C. In a systematic review and meta-analysis of 27 controlled clinical studies, dietary cholesterol (range: 17–4800 mg/day) increased TC (mean: −30 to 115 mg/dL), although the effect was dependent upon baseline TC [38]. Individuals with the lowest baseline TC tended to have greater increases in TC when dietary cholesterol was increased while hypercholesterolemic individuals had less significant changes. In a more recent meta-regression analysis where statistical adjustment was made for fatty acid intake, a nonlinear relationship between dietary cholesterol and LDL-C was observed. LDL-C increased by 4.5 mg/dL for each 100 mg/day increase in dietary cholesterol [39]. The inconsistencies in the evidence likely reflect the co-occurrence of cholesterol with SFA in the diet and therefore the inability to isolate the independent role of dietary cholesterol.

Dietary cholesterol likely has a modest impact on blood lipids/lipoproteins, whereas SFA intake has an established strong effect on lipids/lipoprotein. Following dietary guidance to limit SFA to <10% of calories will typically restrict cholesterol intake since many sources of SFA are also sources of cholesterol. Current dietary guidelines for SFA, which concurrently restricts cholesterol intake, coupled with U.S. population cholesterol intakes that are below 300 mg/day, the previous dietary target has resulted in the removal

of numerical targets for dietary cholesterol. However, all of the recommended healthy dietary patterns have <300 mg/day of dietary cholesterol.

Soluble Fiber

Soluble/viscous dietary fibers (e.g., oats, beans, barley) have significant lipid lowering effects. The lipid lowering mechanism of soluble/viscous fiber is not completely understood but is likely due to the binding of fiber with circulating cholesterol in the small intestine, in turn, reducing the absorption of cholesterol [40, 41].

In a systematic review and meta-analysis of 67 RCTs, for each gram increase in soluble fiber (2–10 g/day), TC (−1.7 mg/dL), LDL-C (−2.2 mg/dL), and HDL-C (−0.1 mg/dL) were reduced [40]. A more recent systematic review and meta-analysis of 58 clinical trials showed higher total fiber intake (~30.9 g/day) significantly reduced TC (trials: 36; −5.8 mg/dL), LDL-C (trials: 34; −3.5 mg/dL), and TG (trials: 31; −5.3 mg/dL) compared to lower fiber intake (~18.9 g/day) [42]. Lastly, in a systematic review of 77 studies, more than 50% of the trials assessing soluble fiber reported significant reductions in LDL-C ($k = 35$) and TC ($k = 34$) compared to the control group [43]. The trials reporting the greatest lipid lowering effects of soluble fiber included subjects with hypercholesterolemia at baseline. Clinical research demonstrates soluble fiber has significant LDL-C lowering effects, but fiber rich diets that are high in both soluble and insoluble fiber have beneficial effects on lipids and lipoproteins.

The National Lipid Association (NLA) recommends 5–10 g/day of soluble fiber based on clinical data demonstrating LDL-C reductions between 4 and 10% [44]. The Adequate Intake (AI) for fiber is 14 g/1000 kcal for individuals ages 2 and older [45]. To assist with achieving the AI, the 2020–2025 Dietary Guidelines for Americans (DGA) recommends at least half of grains be whole grains; for an adult consuming 2000 kcal/day, at least 3 ounce-equivalents/day of whole grains should be consumed (one ounce-equivalent of grains is a half-cup cooked brown rice, 1 slice of whole grain bread, and 1-cup ready-to-eat whole grain cereal) [46]. Therefore, consuming a Healthy U.S.-Style Dietary Pattern that meets current recommendations for dietary fiber would be expected to reduce LDL-C.

Plant Sterols/Stanols

Plant sterols and stanols are naturally occurring in foods like beans, seeds, and lentils but in very low amounts. Consistent evidence from RCTs demonstrates that doses of 1.5–3 g/day lower TC and LDL-C >10 mg/dL [44, 47]. The NLA recommends consuming ~2 g/day of plant sterols/stanols for cholesterol lowering [44]. However, consuming this quantity from a whole food diet (without stanol/sterol fortified foods) is not feasible. For example, an individual would need to consume >400 g of sesame seeds or >1.9 kg of beans to achieve 1.5 g of plant sterols/stanols [48]. Fortified foods such as margarines and supplements are available.

Researchers began studying the effects of stanols and sterols in the 1950s. Best et al. evaluated the effects of 5–6 g/day of beta-sitosterol in nine subjects (7 with hypercholesterolemia) for approximately 12-weeks [47]. There was a 7–20% reduction in total cholesterol, which equated to a 13–224 mg/dL (mean: 53 mg/dL) reduction. Law published a systematic review of 14 double-blind trials (subjects' median baseline TC: 146.9 mg/dL) comparing the effects of polyunsaturated margarines with and without plant sterols on LDL-C and reported a dose–response relationship between plant sterol consumption (≤2 g/d) and LDL-C resulting in a ~15 mg/dL reduction in LDL-C [49]. A recent systematic review and meta-analysis of 8 RCTs showed plant sterols/stanols (1–3 g/day) lowered LDL-C by 12 mg/dL compared to placebo [50]. Based on these trials, convincing evidence shows that supplementation of plant sterols/stanols (1–2 g/day) significantly improves TC and LDL-C. Therefore, combining plant sterol/stanol enriched foods, or supplements, with a healthy dietary pattern will significantly decrease TC and LDL-C.

Added Sugars

Added sugars are defined by the U.S. Food and Drug Administration as "sugars that are added during the processing of foods (such as sucrose or dextrose), foods packaged as sweetners (such as table sugar), sugars from syrups and honeys, and sugars from concentrated fruit or vegetable juices" [51]. The most common sources of added sugars in the US diet, based on National Health and Nutrition Examination Survey (NHANES) data, are sugar-sweetened beverages (SSB) and sweet bakery products [52]. Consumption of added sugars has been extensively researched and consistently linked to chronic diseases (i.e., CVD, obesity, non-alcoholic fatty liver disease, type 2 diabetes) [53]. Moreover, there is convincing epidemiological and clinical evidence that added sugars adversely affect TG. Consequently, the ACC and NLA recommend limiting added sugars for the prevention and treatment of hypertriglyceridemia (fasting ≥150 and non-fasting ≥175 mg/dL) [44, 54].

Added sugars are adversely associated with TG and HDL-C. Epidemiological studies and clinical trials assessing increased added sugar intake demonstrate increases in TG, TC, and LDL-C. Welsh et al. conducted an analysis of NHANES data collected between 1999 and 2006 including 6113 adults and reported a positive linear relationship between added sugars intake and LDL-C, and an inverse linear relationship between added sugar intake and HDL-C [55]. In a 6-month RCT, including individuals (n = 47) who were overweight or obese with a mean baseline TG of 137 mg/dL, the intake of sucrose-sweetened beverages, aspartame-sweetened beverages, milk, and water (1 L/day) resulted in no between group differences in weight or macronutrient intake, but a significant increase in TG was observed in the sucrose-sweetened beverage group (32.7% or 31.6 mg/dL) compared to the other groups [56]. One large systematic review and meta-analysis of RCTs demonstrated increases in TC (6.2 mg/dL), LDL-C (4.6 mg/dL), and TG (9.7 mg/dL) when comparing diets higher vs lower in sugar (~80 vs ~30 g/day) [57]. Overall, data from epidemiological studies and RCTs suggest that there is a deleterious relationship between higher added sugar consumption and lipids/lipoproteins. Therefore, limiting added sugars (<10% of energy) is recommended to lower TG and may improve LDL-C, TC, and HDL-C [46].

Alcohol

Approximately 55% of US adults reported drinking alcohol in the last month based on the 2019 National Survey on Drug Use and Health [58]. Moreover, an analysis of NHANES data collected between 1999 and 2014 revealed that on drinking days ≥60% of US adults consumed more alcoholic drinks than the amount recommended by the 2015–2020 DGA (1/day for women and 2/day for men) [59]. Excess alcohol consumption is associated with many chronic diseases including CVD, type 2 diabetes, and hypertension [60]. Additionally, excess alcohol consumption is related to abnormal circulating lipids/lipoprotein levels.

Beginning in the 1960s, researchers reported an association between alcohol consumption and dyslipidemia, but many of these studies assessed large intakes of alcohol or included populations with alcoholism [61–63]. Crouse and Grundy conducted a tightly controlled trial including 12 men (mean TC 197 mg/dL and TG 252 mg/dL) and reported that consuming 24% of calories from alcohol (90 g/day alcohol or ~7 standard drinks) for 4 weeks significantly increased TC (12 mg/dL) and TG (48 mg/dL) vs. control (isocaloric diet without alcohol) [64]. Studies assessing moderate alcohol consumption (30 g or about 2 drinks/day) suggest that there may be a positive impact on HDL-C and no effect on TG [65, 66]. In a systematic review and meta-analysis of RCTs, moderate alcohol consumption compared to no alcohol consumption increased HDL-C (3.6 mg/dL) with no effect on LDL-C or TG [66]. A consensus statement for the management of ASCVD risk in patients with persistent hypertriglyceridemia from the ACC concluded that alcohol should be restricted (no more than 2 drinks/day for men and 1 drink/day for women) for

Table 7.2 Expected effects of dietary modifications on LDL-C and TG [34, 44, 67, 68]

Dietary modification	Dose	LDL-C	TG
SFA replaced by PUFA	5% of E	−9.0 mg/dL	−2.0 mg/dL
SFA replaced by MUFA	5% of E	−6.5 mg/dL	+1.0 mg/dL
CHO replaced by n-6 PUFA	5% of E	−3.8 mg/dL	−10.2 mg/dL
n-3 PUFA	3.5 g/day	0–4.3 mg/dL	−39.9 mg/dL
Plant sterols/stanols	3 g/day	−11.6 mg/dL	No effect
Dietary cholesterol	100 mg/day	1.9 mg/dL	No effect
Soluble fibers	3.5–7.0 g/day	−8.5 mg/dL	No effect
Added sugars	<10% of energy	≤−5 mg/dL	≤−10 mg/dL
Alcohol	≤2-drinks/day for men and ≤1 drink/day for women	No effect	≤70% reduction

patients with TG >150 mg/dL (fasting) to <500 mg/dL and avoided for those with TG >500 mg/dL [54]. Moreover, the authors concluded that restricting or avoiding alcohol for adults with hypertriglyceridemia may lower TG >70%. The findings from early trials along with recent reviews demonstrate that excess alcohol consumption increases TC and TG; adults with hypertriglyceridemia should limit or abstain from consuming alcohol.

Summary

CHD is the leading cause of death in the United States with a primary risk factor being dyslipidemia. A healthy dietary pattern is the first line of intervention for prevention/treatment of ASCVD. As discussed in this chapter, diet plays a key role in modulating lipids and lipoproteins (Table 7.2). Fatty acid intake has a significant effect on LDL-C levels. Replacement of SFA with MUFA, PUFA, and complex CHO decreases TC and LDL-C. n-3 PUFA significantly reduce circulating TG levels. Soluble fiber has a significant TC and LDL-C lowering effect. Plant sterols/stanols lower TC and LDL-C, but consuming doses high enough to promote meaningful reductions requires foods fortified with sterols/stanols or supplements. Added sugars and alcohol consumed in excess have an adverse effect on TG. Recommended healthy dietary patterns that meet nutrient targets discussed herein have beneficial effects on lipid and lipoprotein concentrations and, therefore, CVD risk.

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8 Coronary Heart Disease: Nutritional Interventions for Prevention and Therapy

Marina Ferrari, Jayne V. Woodside, Sarah F. Brennan, and Norman J. Temple

Key Points

- Diet plays a major role in the causation of coronary heart disease (CHD), which is a major cause of morbidity and mortality.
- Replacing saturated fat with polyunsaturated fats (PUFA) may help lower risk.
- Evidence suggests that increased consumption of fatty fish and of n-3 polyunsaturated fats (n-3 PUFA) is likely to reduce CHD risk.
- A high intake of salt, *trans* fats, processed meat, and added sugar is likely to increase CHD risk.
- Diets with a generous content of fruit, vegetables, and whole grain cereals are associated with lower risk of CHD.
- Adhering to a healthy overall dietary pattern such as the Mediterranean diet pattern reduces CHD risk.
- Maintaining a healthy weight and being physically active have each been shown to reduce CHD risk factors and actual risk of CHD.

M. Ferrari · J. V. Woodside · S. F. Brennan
Centre for Public Health, Queen's University Belfast, Belfast, UK
e-mail: mferrari02@qub.ac.uk; Sarah.Brennan@qub.ac.uk

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

Introduction

Coronary heart disease (CHD) is a major cause of morbidity and mortality in the Western world. Factors that are strongly associated with elevated risk of the disease are age, male sex, smoking, physical inactivity, hypertension, obesity, and type 2 diabetes. In addition, blood lipid levels are strong predictors of CHD risk. A pattern of blood lipids that accelerates atherosclerosis (i.e., dyslipidemia) is one where total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are elevated and high-density lipoprotein (HDL-C) is relatively low. The strongest indicator of risk is seen for the ratio of TC to HDL-C [1].

A large body of evidence collected over several decades from observational epidemiological studies and randomized controlled clinical trials (RCTs) strongly supports a major role for diet in the prevention and treatment of CHD. Observational epidemiological studies refer mainly to prospective cohort studies and case-control studies. Dietary factors that have been proposed to have a clinically important impact on the risk of CHD include saturated fats (SFA), *trans* fats (TFA), polyunsaturated fats (both n-6 and n-3 PUFA), meat, carbohydrate sources, dietary fiber, fruit, vegetables, salt, alcohol, and also the overall dietary pattern.

It is important to bear in mind that changes in diet and their associations with outcomes are complex. When a change is made to one

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_8

component of the diet, it leads to other inherent changes. For example, increasing fish intake might lead to reduced red meat intake, while reducing fat intake might lead to increased carbohydrate intake. The consequences for metabolism will also be different depending on the source of carbohydrate replacement: refined or whole grain. Since the associations may be stronger when we consider a whole diet approach, rather than the intake of individual nutrients, it may make more sense to focus on food groups and the overall diet in nutritional interventions. This may also be more relevant and interpretable for consumers.

This chapter examines how each of these diet components may affect the risk of CHD. Early studies focused on the effect of diet on blood lipids, but it is now accepted that diet affects CHD etiology through multiple mechanisms, including insulin resistance, blood pressure, endothelial function, inflammation, and thrombosis, so consideration of these will be included. The chapter also discusses the relationship between both obesity and physical activity and CHD risk, incorporating consideration of likely mechanisms.

Dietary Fat and Coronary Heart Disease

Fat Intake

For many years, it was widely believed that a relatively high intake of dietary fat (around 35–42% of energy intake) increases the risk of CHD and other chronic diseases of lifestyle. A major reason for this belief was that the populations of Westernized countries typically eat a diet relatively rich in fat and also have a high frequency of CHD. In addition, it was long believed that an increased intake of fat can lead to a positive energy balance and contribute to obesity. Because of these widely held beliefs, populations were strongly advised to reduce their fat intake. Starting in the 1980s a common recommendation was that fat intake should be "less than 30%" of energy intake. However, accumulated research has left no doubt that the type of fat consumed has a stronger association with the risk of CHD than quantity. There is no good evidence that diets with a reduced content of fat reduce mortality rates from CHD when other components of the diet are not considered. As a result of this realization, the recommendation regarding fat intake shifted in 2005 to a more liberal 20–35% of energy intake.

It must be borne in mind that when the intake of one macronutrient is reduced, the intake of other energy sources is likely to rise in compensation. There are different sources of fats and carbohydrates that will each impact on the risk of CHD. This topic is discussed further when we look at fats and carbohydrate sources.

Different fats have very different effects on blood lipid levels and this is the key mechanism that explains how fat affects risk of CHD [2]. Common dietary recommendations for fat intake are shown in Table 8.1.

Saturated Fat and Dietary Cholesterol

Many studies over the past 40 years have established that saturated fats (SFA) are positively correlated with the blood levels of total cholesterol and LDL-C. Dietary cholesterol also increases total cholesterol and LDL-C levels but to a much lesser degree than SFA. However, the association is complex since findings from RCTs seem to differ from cohort studies.

RCTs have demonstrated that diets low in SFA (<7% of energy intake) and cholesterol (<200 mg/day) bring about reductions in LDL-C levels of approximately 10%. A recent Cochrane review of RCTs found that a reduction in SFA intake is associated with a reduction in TC and LDL-C [3]. The review also reported that the SFA intake reduction has little or no effect on the risk of CHD or CVD mortality, regardless of what replaces it. There was, however, a 17% reduction in the risk of CHD events, especially when the SFA was replaced by PUFA, although the evidence was limited and judged to be of low quality. For combined cardiovascular events, the reduction was 21% and the evidence was considered to be of mod-

Table 8.1 Common recommendations for modification of dietary fat intake

Dietary fat	Recommendation[a]	Major dietary sources
Total fat	20–35% energy intake	As below
Saturated fats (SFA)	<7% energy intake	Animal products (fatty meat, processed meat, cheese, butter, cream, lard, shortening, full-fat milk, ice cream), cocoa butter, chocolate, coconut oil, palm oil, cakes, pastry products, cookies
Trans fats (TFA)	<1% energy intake	Stick margarine (hard margarine made with hydrogenated oils), cakes, pastry products, cookies, chips, many fast foods. This fat has been almost entirely removed from foods sold in the USA
Cholesterol	<200 mg/day	Liver, kidney, egg yolk, shellfish
Polyunsaturated fats (PUFA)	4–10% energy intake	Soft margarines, vegetable oils (corn, safflower, soybean, sunflower)
Monounsaturated fats (MUFA)	<20% energy intake	Olive oil, canola oil, peanut oil, avocados, olives, almonds, cashews, peanuts
n–3 PUFA	0.5–2% energy intake	Sardines, mackerel, herring, pilchards, salmon, tuna Walnuts, flaxseed oil, soybean oil, canola oil

[a] Different health agencies make different recommendations. The recommendations shown are not necessarily ideal for minimizing risk of CHD but are the most common ones currently given

erate quality. The greatest reduction in cardiovascular events was seen when SFA represents less than 10% of energy intake [3]. This evidence synthesis, based on the findings from RCTs, is therefore suggestive that a reduced intake of SFA may lower the risk of CHD and CVD but does not affect mortality.

Meta-analyses of cohort studies that have investigated the relationship between intake of SFA and risk of CHD present a similar story but with some differences. These findings suggest that the intake of SFA has only a rather weak association with risk of CHD. Comparison of the extreme quintiles indicates a risk ratio [RR] of 1.06 (95% CI: 0.95–1.17) for total CHD (non-significant) [4] and 1.10 (95% CI: 1.01–1.21) for CHD mortality (significant) [5]. These findings call into question whether the intake of SFA is indeed a major factor in the causation of CHD [6].

There are similar findings regarding dietary cholesterol and its main source, namely eggs. Cohort studies point to a lack of association between the quantity of eggs that people eat and their risk of CHD [7, 8]. Eggs are a nutritionally complex food which provide a range of nutrients. Their consumption, although correlated to an increase in TC and LDL-C, also increases HDL-C levels [9, 10]. A whole diet approach considering other dietary factors, including how eggs are prepared and which foods are consumed alongside, may have a greater impact on cardiovascular health than focusing on eggs alone [11].

Trans Fats

Trans fats (TFA) raise TC and LDL-C levels. In that respect they are similar to SFA, but whereas SFA tend to increase HDL-C, TFA lower it. The net result is that TFA cause an increase in the ratio of TC to HDL-C which, as noted earlier, is the strongest predictor of risk of CHD. This strongly suggests that TFA are likely to increase the risk of CHD.

Strong evidence from cohort studies confirms this belief: a recent meta-analysis of these studies suggested that the risk of cardiovascular disease (CVD) increased 16% for an increment of 2% energy/day of TFA intake [12]. Previous studies have shown that TFA intake is associated with a 16% increase in CHD risk when comparing the top and bottom thirds of intake [4].

These findings have led to public health initiatives directed at removing as much TFA as possible from the food supply. For example, the World Health Organization developed the "REPLACE" action package of 2018 [13] which aims to eliminate industrially produced TFA from the food supply completely by 2023.

These efforts have met with much success. TFA have been almost entirely removed from foods sold in the USA and Canada. However, there is a concern that fats and oils high in saturated fats, instead of the healthier unsaturated fats, might be used to replace TFA [14].

n-6 Polyunsaturated Fats and Monounsaturated Fats

PUFA and MUFA are the major unsaturated fats. PUFA fall into two main groups: n-6 PUFA and n-3 PUFA. n-6 PUFA are found in abundance in vegetable oils. Two especially rich sources of MUFA are olive oil and canola oil, with nuts also being a good source. Considering that different types of fat have very different effects on the blood lipid levels, it is assumed that change in blood lipids is closely associated with the change in risk of CHD.

MUFA tend to have a neutral effect on the blood levels of TC and LDL-C. Consistent with this, meta-analyses have suggested no association between intake of MUFA and risk of CHD [2] and CVD [12].

An increased intake of PUFA, by contrast, lowers TC and LDL-C levels. Not surprisingly, therefore, people with a higher intake of PUFA are at reduced risk of CHD [15], although the latest assessment of the evidence suggests that the effect of n-6 PUFA on CHD events is still unclear as the evidence is of poor quality [16].

What is especially noteworthy is that when SFA is partly replaced with PUFA, the LDL-C is lowered but without lowering the HDL-C. The overall result is a decrease in the ratio of TC to HDL-C. We can predict that these favorable changes in blood lipids will help prevent CHD. Although the overall evidence that replacing SFA with n-6 PUFA helps in the prevention of CHD is unclear, cohort studies have previously indicated that making this dietary change does indeed lead to a significantly reduced risk of CHD [15, 17, 18]. Higher levels of n-6 PUFA biomarkers in circulating and adipose tissue were also associated with a significantly lower risk of total CVD, cardiovascular mortality, and ischemic stroke, although not significantly with lower CHD risk [19].

Let us now summarize the key points. To date, the evidence supports that adding extra PUFA (i.e., n-6 PUFA) to the diet at the expense of SFA is likely to be beneficial for the prevention of CHD. In general, long-term dietary changes that bring about favorable changes in blood lipids will promote beneficial coronary health effects.

Fish and n-3 Polyunsaturated Fats

Many prospective cohort studies have demonstrated an inverse association between fish consumption and risk of CHD. These studies indicate that each 100 grams daily increase in fish consumption is associated with a lower risk of CHD (RR: 0.88; 95% CI: 0.79–0.99) [8, 20].

A systematic review found that the fish cooking method plays a role in the association with CVD risk, with fried fish consumption being associated with an increased risk of overall CVD events and myocardial infarction [21].

A widely shared belief *is* that the benefit provided by fish is mainly accounted for by n-3 PUFA from fatty fish (Table 8.1). A recent pooled analysis of cohort studies supports this indicating that the association with a lower risk of CVD is only present when the intake was from fish with high n-3 PUFA content [22]. The major n-3 PUFA found in fatty fish are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These long-chain fatty acids are believed to exert several cardio-protective actions including improving endothelial function and reducing the risk of inflammation and arrhythmias [23].

It logically follows that supplements of fish oil should be protective against CVD. This possibility has been tested in several dozen RCTs. In many of these studies, the subjects have existing CHD or are at high risk for the disease. Reductions in cardiac death have been reported in several of these studies [24]. However, findings have been conflicting regarding whether supplements of fish oil do indeed lower the risk of CVD [24, 25]. A reasonable conclusion at this

time, based on the totality of the evidence, is that fish oil achieves, at most, little benefit against CVD. So, as above, dietary advice to increase fish consumption will lead to a range of dietary changes that may improve cardiovascular health, while supplements of fish oil are only weakly effective in this regard.

Alpha-linolenic acid (ALA) is an n-3 PUFA with a slightly shorter chain length (number of carbons). It is found in some plant oils, namely flaxseed (richest source), soybean, and canola oil (poorest source). Walnuts are another source. ALA can be converted to a limited extent in humans to EPA but almost not at all to DHA [23]. The possible benefit of ALA has been much less researched than is the case with fish oil. A meta-analysis suggested that ALA may slightly reduce the risk of CVD and of fatal CHD [25].

The overall picture that emerges from this research is that fish, especially fatty fish, is protective against CHD. For this reason, fish is widely recommended as a part of a healthy diet. However, there is little hard evidence that this benefit can also be achieved by fish oil supplements. ALA may provide a small degree of protection against CVD but further investigation is required. Typical recommendations for n-3 PUFA are shown in Table 8.1.

Meat and Coronary Heart Disease

Meat falls into three distinct groups: red meat (beef, pork, and lamb), processed meat (ham, sausages, bacon, salami, etc.), and poultry (chicken and turkey). Until a few years ago, any consideration of a relationship between meat and CHD was viewed as being a reflection of the fat content of the meat. Accordingly, meat with a high content of SFA was seen as posing considerably more risk of CHD than is the case for lean meat. However, we now understand that the relationship between meat consumption and CHD is more complex.

A recent summary of cohort studies concluded that each additional 100 grams per day of red meat is associated with an increased risk of CHD of 15% while each extra 50 grams per day of processed meat is associated with an increased risk of 27% [8]. Clearly, intake of processed meat is associated with poorer cardiovascular health than is red meat, but the evidence for causality is still of low- or very-low-certainty [26]. The most likely reason why processed meat impacts health negatively is because of the considerable amounts of preservatives used in meat processing including large amounts of sodium.

Studies on poultry indicate that this type of meat has no association with cardiovascular risk. As mentioned earlier, fish as a replacement for red and processed meat is strongly protective against CHD.

An additional complicating factor with respect to meat consumption with an expanding planetary population is sustainability. Recommendations to increase fish consumption will further erode the availability of many fish species. Expanded production of red meat, especially beef, comes at the cost of increased production of greenhouse gases and rainforest degradation. These topics—sustainability—are discussed in greater detail by Berardy and Sabate in Chap. 27.

Carbohydrates and Coronary Heart Disease

Carbohydrate Intake

Just like fats, different carbohydrates sources have different effects on metabolism. As a result, CHD risk depends not just on the total amount of carbohydrate intake but also the balance between different sources and the glycemic load [27].

Since the early 1970s, there has been a marked increase in population carbohydrate intake and a decrease in fat intake [28]. This shift coincided with a range of factors, one being the dietary guidelines recommending the lowering of fat intake. Another factor was the increase in intake of ultra-processed food (UPF) [29], which accounts for a markedly high intake of sugar, refined cereals, SFA, and TFA [30, 31].

Replacing dietary SFA with carbohydrates lowers total cholesterol (TC), LDL-C, and HDL-C, resulting in little change in the ratio of TC to HDL-C [32]. However, this dietary change

also causes a rise in the blood level of triglycerides [32] and this may cause some elevation in CHD risk. Overall, the changes in blood lipids are unlikely to have any benefit on risk of CHD. Consistent with these observations, cohort studies have shown no evidence that replacing SFA with carbohydrates reduces the risk of CHD [33]. A recent Cochrane review concluded that replacing SFA with carbohydrates reduces CHD risk [3], but the analysis did not differentiate between carbohydrate sources. We will now examine in more detail how different food sources of carbohydrates can impact on CHD risk.

Sugar

Much of the refined carbohydrates found in the diet are present as sugar. Here we are referring to two distinct types of sugar. Sucrose is added to many foods. High-fructose corn syrup is added to many sugar-sweetened beverages (SSB) and other foods. SSB are a major dietary source of sugar. Sugar is also naturally present in some foods especially fruit. However, in contrast to added sugar, there is a clear inverse association between the consumption of fruit and the risk of CHD (see later).

Many studies have been conducted exploring the relationship between sugar and CHD. Experimental studies have revealed that sugar causes an increase in blood pressure and the blood levels of triglycerides, TC, and LDL-C [34]. These changes in risk factors allow us to predict that a relatively high intake of sugar will be associated with an elevated risk of CHD. Confirmation of this comes from a meta-analysis of cohort studies where intake of SSB was found to be associated with risk of CHD. A 17% greater risk of CHD was seen for each additional daily serving [8].

Whole Grains

Whole grains present an altogether different picture compared to sugar regarding risk of CHD. This is largely explained by their high fiber content and consequent impact on coronary health [35, 36], but recent studies have also indicated a role for nutrients found in whole grains beyond fiber [36].

A meta-analysis of cohort studies concluded that persons with the highest intake of whole grains have a 20% lower risk of CHD in comparison with people with the lowest intake. There was also a dose–response association effect for each 15 grams more whole grains consumed per day (RR 0.93; 95% CI: 0.89–0.98). A daily dietary fiber intake between 25 and 29 g is associated with the greatest risk reduction in a range of health outcomes, including CHD [27].

Refined Grains

A recent meta-analysis observed a trend (RR 1.11; 95%: CI 0.99–1.25) for a positive association between refined grain intake and risk of CHD when comparing the highest to the lowest categories of intake [8]. Refined cereals are different to added sugar in terms of metabolism since they also provide modest amounts of fiber, phytochemicals, and nutrients. However, both contribute to the glycemic load, playing a potential role in CHD risk. The ratio between whole grains and refined grains is therefore an important factor to be considered, besides the absolute amount of carbohydrate and total energy intake [27, 37].

Fruit, Vegetables, and Coronary Heart Disease

Fruit and vegetables are complex foods and contain a great many bioactive substances that have a positive effect on health, including folate, potassium, magnesium, dietary fiber, and hundreds of phytochemicals, while also having a negligible amount of fat. By virtue of their high content of fiber and low energy density (i.e., a low calorie content per 100 g), a generous intake of fruit and vegetables also helps counter the development of obesity. For these reasons, it is not surprising that cohort studies have shown that consumption of

fruit and vegetables has a strong protective association with risk of CHD.

A recent meta-analysis of these studies found a lower risk of CHD incidence associated with the highest versus the lowest intakes of fruits and vegetables (RR 0.88; 95% CI: 0.83–0.92), fruits alone (RR 0.88; 95% CI: 0.84–0.92), and vegetables alone (RR 0.92; 95% CI: 0.87–0.96), especially green leafy vegetables (RR 0.82; 95% CI: 0.76–0.89). There was a consistent linear dose–response association between fruits and vegetables and CHD, with a maximum daily intake of 7 fruit and 7 vegetable servings showing a risk reduction of ≈20% in CHD incidence and ≈30% for CHD mortality [38].

There is mixed evidence regarding the relationship between consumption of potatoes and health. Findings from cohort studies suggest that potatoes have no association with risk of CHD [39]. Overall, boiled and baked potatoes have fairly little effect on health in contrast to the strongly beneficial effects of most other vegetables. But potatoes may pose some health risk when eaten as French fries as they appear to increase the risk of type 2 diabetes and hypertension [39], and tend to be eaten with other CHD risk-increasing foods [40].

Salt and Cardiovascular Disease

There is a well-established link between salt and hypertension as examined in the following chapter. As hypertension is a major risk factor for CHD, a reduction in salt/sodium intake is strongly recommended. A meta-analysis of cohort studies that included 617,000 people showed that, compared with individuals with low sodium intake, those with a relatively high intake have a 19% greater incidence of CVD [41]. Moreover, there is a dose dependent association: the risk of CVD increased up to 6% for every one gram increase in dietary sodium [41]. Consistent with these observations, RCTs have shown a reduced risk of CVD when subjects with elevated blood pressure were placed on a diet with a reduced salt content [42].

When we think about dietary advice, it is not only salt added during cooking and at the table that should be taken into account. Most of the salt intake comes from processed, restaurant, and fast foods, which tend to go unnoticed by the population. Nutritional intervention for CHD prevention should include education on food labels and encouragement to reduce the intake of processed foods high in salt, in addition to control of the use of table salt.

Alcohol and Cardiovascular Disease

The relationship between alcohol and health is explored in Chap. 12. Here we briefly discuss this with a particular focus on CHD.

Based on the totality of the evidence we can conclude as follows: the lowest risk of CHD is seen at an alcohol intake of about one drink per day, but possibly less. This is also true for CVD in general. There is no dispute that, as alcohol intake climbs above 4 drinks/day, so does the risk of CVD, especially stroke and heart failure.

There has been much speculation that red wine is more potent than other forms of alcoholic beverages for the prevention of CHD. But when the epidemiological evidence is looked at as a whole, it appears that all forms of alcoholic beverages—beer, spirits, and wine, both red and white—have similar patterns of association. Based on the current inconsistent evidence, we can conclude that recommendations for alcohol should be for low to moderate intake, with a possible protective effect of red wine still to be confirmed [43].

Should We Recommend Dietary Supplements?

Many RCTs have been carried out that have investigated the possible benefit of various dietary supplements in the prevention of CHD. Most attention has focused on antioxidant supplements (beta-carotene and vitamins C and E) as well as vitamin D and CoQ (also known as CoQ10 or coenzyme Q10). The findings generated by these studies have been mostly disappointing. As a result, none of these supplements can be recommended for CHD risk reduction.

The possible value of these supplements on other aspects of health is further discussed in Chap. 31.

Whole Diet Approaches and Reduction in Risk of Coronary Heart Disease

Much of the research effort that has investigated how dietary changes can be used in the prevention or therapy of CHD has focused on single nutrients and food components. Many investigators are now of the viewpoint that a strategy that is likely to achieve much more success is to investigate the efficacy of a whole diet approach for CHD prevention and therapy [44].

Diet changes that are, in general, related to lower CHD risk include higher amounts of fruit, vegetables, legumes, whole grains, fish, vegetable oils, and nuts, as well lower intakes of processed meat, red meat, *trans* fat, saturated fat-rich foods, and added sugar. These changes are likely to benefit heart health if there is long-term adherence, but it is important to set realistic goals and consider food accessibility. These dietary changes come together in the following diets.

The Mediterranean diet is the diet pattern with the strongest evidence supporting a positive effect on cardiovascular health. The diet varies from one country to another around the Mediterranean Sea, but typical features include a high content of plant foods (i.e., fruit, vegetables, cereals, legumes, nuts, and seeds); moderate amounts of fish, poultry, milk, and other dairy products; and small amounts of red and processed meat. The diet includes olive oil as the main fat in food preparation; and low to moderate alcohol consumption (especially red wine consumed mainly at meals). Meta-analyses of cohort studies have consistently reported significant inverse associations between adherence to the Mediterranean diet and CHD risk [45].

We now have strong evidence that the Mediterranean diet pattern is much healthier than the diet patterns commonly eaten in most of the Western world including the USA. Studies have suggested that the strongest protective effect of the diet is associated with the intake of olive oil, fruits, vegetables, and legumes.

Extra virgin olive oil is preferable to regular olive oil as it appears to achieve a greater reduction in CHD risk [46]. The presumed explanation for this is that extra virgin olive oil is a rich source of phytochemicals. The health benefits of the Mediterranean diet are further discussed in Chap. 16.

Another dietary pattern that can be recommended is the Dietary Approaches to Stop Hypertension (DASH) diet. This was originally developed with the goal of lowering elevated blood pressure but studies have now shown other benefits for cardiovascular health [47]. It is described in more detail in Chap. 17.

The Importance of Obesity

Obesity is strongly associated with CHD and CVD outcomes as well as several CHD risk factors, such as hypertension, insulin resistance, dyslipidemia, and physical inactivity [48].

BMI is the most widely used measure to determine if a person is obese. However, the distribution of adiposity is also important when assessing disease risk. Excess abdominal visceral fat seems to be a risk factor, independent of BMI. Waist circumference, a measure of abdominal adiposity, appears to have a stronger association with CHD risk than BMI [48]. For the practicing physician and health-care professional, waist circumference offers a quick and useful tool to assess the degree to which a patient is carrying excess abdominal fat and its threat to cardiac health. While cut-points for BMI for overweight and obesity are widely accepted, further research is required to determine analogous cut-points for waist circumference in different sex, age, and ethnic groups. However, commonly used cut-points are waist circumferences of >90 cm (>35.4 in) for men and >80 cm (>31.5 in) for women in some countries, and >102 cm (40 in) for men and >85 cm (>35 in) for women in the United States.

Promoting the dietary changes that are intended to improve cardiovascular health may

also improve metabolic efficiency and reduce adiposity in people with obesity. Physical activity is also an important allied factor to reduce adiposity and assist with other benefits; it will now be discussed.

Physical Activity

Physical activity, by which we mean aerobic exercise, has consistently been associated with a reduction in CHD events in both primary and secondary prevention [49]. Indeed, a sedentary lifestyle is now recognized as one of the big four risk factors, alongside dyslipidemia, smoking, and hypertension (five, if we include diabetes). Much of the benefit of physical activity can be explained in terms of its favorable effects on several factors associated with CHD, namely adiposity, blood pressure, blood lipid profile (including HDL-C), insulin resistance, and glucose tolerance [50].

There is widespread agreement among medical organizations that everyone should be encouraged to engage in an exercise program. Typical recommendations are for at least 30 min of moderate intensity physical activity, such as walking at a speed that induces mild exertion, on at least 5 days per week. As the benefits are cumulative, the exercise can be done as several short activities every day or as one or two long activities at the weekend. The relationship between the quantity of exercise and the degree of risk reduction seems to be dose dependent. Carrying out 300 min of moderate intense exercise per week has been suggested to decrease CHD risk by 20% compared to 14% for individuals engaging in 150 min per week [49]. Engaging in vigorous intensity exercise, such as jogging, is likely to produce further benefits.

A major challenge in this area is to determine what behavioral strategies will motivate individuals to engage in a long-term program of physical activity.

Conclusion

We now have compelling evidence that a healthy lifestyle, especially a healthy diet, can substantially reduce the risk of CHD.

A strong predictor of risk of CHD is the ratio of the blood levels of total cholesterol to HDL-C. Dietary changes that raise this ratio increase the risk of CHD, and vice versa. The key determinant is the type of fat, not the amount. For that reason simply lowering the percentage of energy from dietary fat has little effect on the ratio and therefore on risk of CHD. *Trans* fats are the worst type of fat. Fortunately, these fats have been almost eliminated from the diet in the USA and much reduced in many other countries. It is a mistake to focus on reducing the intake of one energy source without simultaneously advising consumers what dietary sources will offer the same level of satiety and improve cardiovascular health. Replacing SFA with polyunsaturated fats (PUFA) lowers the ratio of total cholesterol to HDL-C (and therefore is likely to help prevent CHD), while replacing it with refined carbohydrates achieves little or nothing. Likewise, monounsaturated fats have a neutral effect. These contrasting effects that are seen when SFA are replaced with different macronutrients and different food groups help explain why cohort studies have commonly failed to see a direct association between intake of SFA and risk of CHD.

In recent years, the focus of CHD prevention has shifted away from individual food components and toward foods, food groups, and dietary patterns. We can state with a high degree of confidence that the risk of CHD can be greatly reduced by a diet that contains generous amounts of fruit, vegetables, whole grains, and nuts, plus at least two servings per week of fish, preferably fatty fish. The diet should also be low in salt, red meat, processed meat, and refined carbohydrates, especially sugar-sweetened beverages. This dietary pattern has much in common with that found in the traditional Mediterranean diet.

Two other critically important factors in the prevention of CHD are the avoidance of excess weight gain and engaging in regular exercise. These factors are key components of a healthy lifestyle that together with a healthy diet have the potential to substantially reduce the burden of CHD. This was convincingly demonstrated in a recent analysis of more than 110,000 participants in the Nurses' Health Study and the Health Professionals Follow-up Study [51]. They identified the participants who led a low-risk lifestyle based on BMI, physical activity, never smoking, moderate alcohol consumption, and better diet quality. Adherence to a healthy lifestyle at midlife was associated with a longer life expectancy free of major chronic diseases, including CHD.

The focus of this chapter has been CHD. We can conclude with some comments on other types of CVD. While the relative importance of different risk factors varies from one form of CVD to the next, the general recommendations made here will go far to achieving the prevention of all types of CVD. This is certainly true for stroke. Finally, the dietary guidelines to prevent CHD will not differ markedly if we consider treatment of the disease or secondary prevention.

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9 Nutritional Influences on Blood Pressure

TanYa M. Gwathmey and Jamy D. Ard

Key Points

- Hypertension is a major risk factor for heart disease and stroke, affecting ~50% of the U.S. adult population.
- Obesity can lead to hypertension, but weight loss can help to reduce blood pressure.
- High levels of dietary sodium will increase blood pressure for some individuals; reductions in sodium intake can lower blood pressure and risk of hypertension.
- High levels of alcohol consumption increase blood pressure; reductions in alcohol may help to decrease blood pressure.
- Dietary patterns play an important role in helping to achieve/maintain a healthy blood pressure.

Introduction

High blood pressure (hypertension) is one of the major risk factors for cardiovascular disease, contributing to almost 50% of strokes and coronary heart disease [1]. Moreover, chronically high blood pressure (BP) affects >1.13 billion people worldwide and causes ~9.4 million deaths every year due to complications [1]. It is associated with both renal failure and dementia and is therefore recognized as a major global health threat [1]. Hypertension affects individuals at every age, with a growing incidence of hypertension in the pediatric population (ages 12–19) occurring in one out of 25 children and pre-hypertension (elevated BP) occurring in one out of 10 children [2]. Nearly one out of two adults within the U.S. population has hypertension (108 million people), and ~82 million of those individuals do not have their hypertension under control [3]. Ninety-five percent of individuals with high BP have *essential* or *primary hypertension* (unknown cause); the principle causes of *secondary hypertension* in the remaining 5% include obstructive airway disease, hormonal abnormalities, thyroid disease, and high intake of dietary salt or alcohol. Approximately 20–30% of individuals with high BP are characterized by *resistant hypertension* and require at least three different types of medications to achieve BP control. Resistant hypertension is generally more prevalent in individuals who are older, obese, female, African American, or have an underlying illness such as diabetes or renal disease. Table 9.1 provides the classification of BP categories, as defined by the American Heart Association.

Treatment for hypertension is primarily dietary or pharmacological. The latter includes antihypertensive medications that fall in the

T. M. Gwathmey (✉) · J. D. Ard
Wake Forest School of Medicine,
Winston Salem, NC, USA
e-mail: tgwathme@wakehealth.edu;
jard@wakehealth.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_9

Table 9.1 Classification of hypertension

Blood pressure category	Systolic (mmHg)		Diastolic (mmHg)
Normal	<120	and	<80
Elevated	120–129	and	<80
High blood pressure (Hypertension Stage 1)	130–139	or	80–89
High blood pressure (Hypertension Stage 2)	>140	or	>90
Hypertensive crisis (Requires immediate care)	>180	and/or	>120

categories of thiazide diuretics, calcium channel blockers, beta blockers, and therapeutic targets of the renin-angiotensin-aldosterone system (RAAS), which is responsible for regulation of BP and fluid volume. RAAS blockade is largely represented by angiotensin converting enzyme (ACE) inhibitors and angiotensin II (Ang II) receptor antagonists (ARBs).

In addition to the primary treatment strategy with antihypertensive drugs, alternative or complimentary approaches to BP control include changes in physical activity, modifications of diet, and the use of nutraceuticals (whole foods or components of foods that provide health benefits in addition to their nutritional value), or dietary supplements. This chapter focuses on the impact of nutrition on BP control.

Blood Pressure and the Blood Glucose Relationship

Approximately 50% of patients with essential hypertension display insulin resistance [4]. In addition to its role in the regulation of BP, the RAAS also plays a key role in the pathophysiology of insulin resistance through the actions of angiotensin II (the primary bioactive peptide of the RAAS) in the dysregulation of insulin secretion, adipogenesis, and microvascular blood flow to muscle [4, 5]. Angiotensinogen is cleaved by angiotensin converting enzyme (ACE) to produce angiotensin I, and subsequently angiotensin II by angiotensin converting enzyme 2 (ACE2). Both angiotensinogen and ACE are found in adipocytes, suggesting the production of local/tissue-generated Ang II to mediate these actions [5]. Indeed, a vast number of clinical trials comparing the effects of ACE inhibitors or angiotensin receptor blocking drugs (ARBs) versus other anti-hypertensives (thiazides, β-blockers, and calcium channel blockers) have consistently demonstrated that greater improvements in insulin sensitivity are achieved by RAAS blockade [5]. Insulin resistance is a primary risk factor for the development of type 2 diabetes; it is associated with dysregulation of blood glucose levels/hyperglycemia, abnormalities in carbohydrate, fat, and protein metabolism, accumulation of visceral fat, and increased body weight.

Body Weight

There is a linear relationship between higher body mass index (BMI) and BP, with no apparent threshold. Individuals with obesity (BMI $\geq$ 30 kg/m^2) have 3.5 times greater likelihood of developing hypertension, and the population attributable risk due to obesity for hypertension is estimated to be 60–70% [6]. While BMI is generally related to BP, the distribution of excess body fat is a more specific marker of risk for elevated BP. For example, waist-to-hip ratio, a marker of central distribution of adiposity, is associated with higher BP independently of BMI [7]. Abnormal adipocyte function in high-risk fat depots may be one of the central links between obesity and the development of elevated BP. The adipocyte also plays a role in the regulation of vascular tone via the secretion of other adipokines including leptin, adiponectin, resistin, chemerin, and visfatin; these substances interact directly with vascular smooth muscle and endothelium. Adipokine levels increase as fat mass increases, resulting in a cascade of responses that include recruitment of circulating macrophages that support low-grade inflammation, increased insulin resistance, compensatory hyperinsulinemia, sodium retention, and increased intravascular volume [6].

Weight loss of 3–5% of initial weight has been associated with reductions in BP [8]: each kg of weight lost leads to a reduction in SBP of 1 mmHg

and 0.9 mmHg for DBP. BP reduction can be achieved by lifestyle behavioral therapy (LBT), anti-obesity pharmacotherapy, or bariatric surgery. LBT is a key component of most comprehensive treatment programs for obesity and produces a typical weight loss of 5–8% of initial weight which is lower than pharmacotherapy and surgery [8]. Pharmacotherapy can be a useful adjunct to LBT, but for some medications, such as phentermine, poorly controlled BP is a contraindication due to potential short-term increase in BP. Bariatric surgery provides the largest and most sustained weight loss response but is only indicated for those with a BMI $\geq$ 40 kg/m^2 or those with both a BMI $\geq$ 35 kg/m^2 plus associated complications of obesity that are not well controlled [8]. Bariatric surgery is often recommended for people with prediabetes or early diabetes who have a BMI of 30–35 kg/m^2 [9].

Dietary Components and Their Effects on Blood Pressure

The relationship between individual dietary components, such as macronutrients and minerals, and BP is important to understand but does not capture the interactions of the food matrix that affect BP. We need to understand how BP is influenced by the pattern of foods that we eat in varying combinations. The Dietary Approaches to Stop Hypertension (DASH) dietary pattern is an example of this optimal combination of foods. The DASH dietary pattern was developed based on an understanding of some of the relationships between individual nutrients and BP. The diet was designed to provide magnesium, potassium, and calcium at approximately the 75th percentile of population intake. The diet was then synthesized based on combining foods that provide higher levels of those key nutrients into a menu plan that guaranteed achievement of the nutrient targets with consumption of the appropriate foods and amounts [10].

In this section of the chapter, we will review the relationship between key nutrients and BP, but ultimately point back to how this informs a pattern of food intake that might be optimal for controlling BP.

Macronutrients

Protein

Protein intake may affect BP via several mechanisms including inhibition of angiotensin converting enzyme (ACE) by bioactive peptides, increases in key amino acids that have vasodilatory actions, and improvements in insulin sensitivity [11, 12]. In the USA, the average protein intake is approximately 15% of calories, or 75 g of protein per day with a 2000 kcal/day diet. Table 9.2 shows the protein intake prescribed in the DASH and the OmniHeart dietary patterns [13].

The source and quality of protein may also have an impact on BP. Observational data suggest that plant protein may be more beneficial for BP control but clinical trials have not demonstrated major differences between plant and animal protein with regard to BP-lowering effects [12]. One systematic review suggested that intake of soy protein which contains isoflavones can reduce the risk of developing hypertension [14]. These effects are not seen when protein is consumed as a supplement.

Fat

Total fat intake may not be a defining factor for BP control; however, fat sources and the ratio of unsaturated to saturated fat appear to be relevant. Saturated fat has generally been targeted for replacement, using unsaturated fat options, namely mono- and polyunsaturated fatty acids (MUFA and PUFA). The DASH diet is lower in fat but emphasizes MUFA and PUFA as the primary sources of fat (Table 9.2) [10]. In the OMNIHeart trial, despite a higher fat intake, the unsaturated fat arm had a similar BP effect as the DASH-based diet, suggesting that higher amounts of unsaturated fat as part of an otherwise healthy diet do not increase the BP [13].

Omega-3 fatty acids (n-3 FA), which are primarily derived from marine sources, have been associated with lower BP in observational and randomized clinical trials [15]. While fish is the primary source of n-3 FA, in particular eicosapentaenoic acid and docosahexaenoic acid, the amounts of n-3 FA associated with BP reduction have typically come in the form of supplements

Table 9.2 Comparison of three dietary patterns for blood pressure reduction

Nutrient/Food component	DASH diet	OmniHeart protein	OmniHeart unsaturated fat	Key food sources	Key notes
Protein, % kcal	18	25	15	Poultry, fish, lean meat, beans, legumes, grains, nuts, seeds	Red and processed meat limited; nearly 50% of protein from plant sources
Fat, % kcal	27	27	37	Unsaturated oils like olive, canola, safflower, nuts, seeds	Saturated fat 6% in all patterns
Monounsaturated, % kcal	13	13	21		
Polyunsaturated, % kcal	8	8	10		
Carbohydrates, % kcal	55	48	48	Fruit, vegetables, whole grains, beans, legumes	Added sugar from sweets and beverages limited
Fiber, g/1000 kcal	14.7	14.3	14.3	Fruit, vegetables, whole grains, beans, legumes, nuts, seeds	There may be bloating with increased fiber intake. Decreasing sodium may mitigate bloating
Potassium, mg/2100 kcal	4700	4700	4700	Fruits, vegetables, beans, legumes, nuts, and whole grains	
Calcium, mg/2100 kcal	1200	1200	1200	Low-fat dairy	Recommend nuts, seeds, beans, leafy greens, and fortified foods to get dietary calcium in those with significant lactose intolerance
Magnesium, mg/2100 kcal	500	500	500	Nuts, seeds, legumes, whole grains, and green leafy vegetables	

in the range of 3–4 g daily of fish oil. Plant based n-3 FA, such as alpha-linolenic acid, derived from sources like flaxseed, do not appear to be as effective for reducing BP [15].

Recently, intermittent fasting, the temporary cessation of caloric intake for periods of 12–48 h, has gained popularity as a new dietary approach to weight loss. This short-term restriction of fat as well as protein and carbohydrate intake has been associated with a decrease in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and a decrease in BP [16].

Carbohydrates

The DASH diet is rich in carbohydrate (Table 9.2), suggesting that a high carbohydrate intake can be part of a pattern that lowers BP. Like the other macronutrients, carbohydrates are not uniform in quality, structure, or effect, so further examination of the type of carbohydrates associated with lower BP is warranted. Fiber intake may be one of the best indicators of carbohydrate quality. A recent meta-analysis of 15 randomized controlled trials suggests that higher intakes of fiber (25–29 g/day), compared with lower intakes, lead to a mean difference in SBP of −1.3 mmHg (95% CI: −2.5 to −0.04) [17]. Similar estimates of effects are seen with whole grain intake. Sugars, on the other hand, represent energy-dense, low-nutrient versions of carbohydrates that appear to have an adverse effect on BP and were therefore limited in the DASH diet. The effects of sugar on BP may depend on an interaction with sodium. Evidence from the INTERMAP study showed that in individuals above the median for 24-h urinary sodium excretion, fructose intake higher than 5.6% of

energy is associated with higher BP of 2.5/1.7 mmHg [18]. Fructose may affect BP by several putative mechanisms including chronic activation of the sympathetic nervous system, endothelial dysfunction, and increased salt absorption [19].

Micronutrients

Sodium

Sodium is often the primary intervention target in clinical practice for reducing BP. The omnipresence of sodium in the food supply, especially in processed food, means that reducing sodium in industrialized countries requires an individual to significantly reduce processed food and food eaten away from home. Individuals can expect a mean reduction in SBP/DBP of 2/1 mmHg when reducing sodium from ~3300 to 2400 mg per day [20]. Further reduction in BP could be achieved (7/3 mmHg) when reducing sodium to 1500 mg per day. In general, for someone consuming a higher sodium intake, counseling to reduce sodium by 1150 mg per day (~1/2 teaspoon salt) would be expected to achieve 3–4/1–2 mmHg reduction in BP. It should be noted that reducing sodium intake while also implementing the DASH dietary pattern has been shown to be more effective than doing either intervention alone [20].

Potassium

Potassium is thought to play a protective role in blunting the hypertensive effects of higher sodium intakes. Low dietary potassium intake is associated with salt-sensitive hypertension [21]. The mineral may also have direct vascular effects and is involved in natriuresis. Dietary potassium interventions have typically failed to demonstrate an independent effect. Use of potassium supplements for lowering BP has a slightly stronger evidence base. A meta-analysis of randomized control trials using potassium supplementation suggested BP-lowering effects of 4.7/3.5 mmHg (95% CI: 2.4–7; 1.3–5.7). The effect was noted to be greater in those who had hypertension (6.8/4.6 mmHg) [22].

Calcium

Prospective cohort studies have shown that individuals with a higher dietary calcium intake have a lower BP and a lower risk of hypertension. For example, a recent meta-analysis found that the risk of developing hypertension in the general population was lower for the highest levels of calcium intake (relative risk = 0.89; 95% CI: 0.86–0.93) and for each 500 mg/day increment (relative risk = 0.93; 95% CI: 0.9–0.97) [23]. However, the evidence for the effects of calcium supplementation on BP is mixed. A 2006 Cochrane review of 13 randomized control trials found that calcium supplements significantly reduce SBP (−2.5 mmHg) but have no effect on DBP in individuals with elevated BP at baseline. The evidence was graded as weak due to poor quality trials and significant heterogeneity [24].

Magnesium

Dietary magnesium intake has also been associated with lower BP. A systematic review and meta-analysis of 10 prospective cohort studies showed an inverse association between magnesium intake and the risk of hypertension (relative risk = 0.92; 95% CI: 0.86–0.98) [25]. A 100 mg/day increment in magnesium intake was associated with a 5% lower risk of developing hypertension. However, there is no association between the serum magnesium level and the risk of hypertension. Supplementation with magnesium has been shown to produce small decrease in BP [26]. A 2016 meta-analysis of 34 trials showed a statistically significant reduction of SBP and DBP (−2.0, −1.8 mmHg). The authors of this study estimated that a 300 mg/day dose for at least one month would be sufficient to lower BP.

Other Food Components

Caffeine

Caffeine is a stimulant alkaloid that affects the central nervous system and is the most commonly consumed pharmacologically active food substance [27]. In the USA, the mean intake of caffeine from all beverages is about 165 mg per day. Intakes ranging between 100 and 400 mg have

been widely studied and consistently shown to increase both SBP and DBP acutely in the majority of instances [28]. However, observational studies of long-term daily coffee consumers have not identified an association between coffee consumption at various levels and long-term BP. In populations of people without hypertension at baseline, prospective cohort studies have not identified an increased risk of developing hypertension with increasing levels of intake of caffeine, primarily as coffee [28].

Alcohol

It has been recommended by the Joint National Commission on Blood Pressure that daily alcohol intake be limited to two drinks for men and one drink for women. It is estimated that nearly 10% of the population burden of hypertension in the USA is due to alcohol [29]. The impact of alcohol on BP is seen at high levels of intake rather than at low levels. A 2017 meta-analysis of 36 trials of alcohol reduction interventions showed that reducing alcohol for those who drank less than two drinks per day was not associated with reduced BP [30]. By contrast, reducing alcohol intake from higher amounts leads to decreases in BP in a dose-dependent fashion. For those who drank large quantities of alcohol on a regular basis (e.g., >6 drinks/day), reducing alcohol by 50% was associated with a decrease in SBP and DBP of −5.5 and −4.0 mmHg, respectively (95% CI: −6.7 to −4.3 and −4.7 to −3.3).

Grapes, Wine, and Resveratrol

Resveratrol, a member of the stilbenoids group of polyphenols, is found in the skin and seeds of red grapes, red wine, berries, pomegranate, and cherries, and exhibits a wide range of beneficial properties, including antioxidant and anti-inflammatory activities. Resveratrol and other polyphenols, such as flavonoids, exhibit cardioprotective activity and BP-lowering effects by increasing nitric oxide (NO) availability and improving insulin sensitivity [31]. A systematic review and meta-analysis of randomized, controlled, clinical trials demonstrated that long-term supplementation with resveratrol (300 mg daily) markedly reduced SBP, DBP, and mean arterial pressure (−9.4, −6.2, −7.3 mmHg, respectively) compared to those subjects receiving placebo [31], indicating that resveratrol may serve as a potent vasorelaxant.

Tea

Tea, the second highest consumed beverage in the world after water, and cocoa are both rich in flavanols, a subgroup of flavonoids, whose consumption is associated with increased NO levels and improved elasticity of blood vessels. Green tea is especially rich in epigallocatechin-3-gallate (EGCG), a catechin flavanol that upregulates eNOS (endogenous nitric oxide synthase) expression, resulting in enhanced NO production and improved endothelial function through modulation of prostaglandin E1 [32]. Moreover, EGCG acts as a potent ACE inhibitor, increases gamma-aminobutyric acid (GABA), and alters sympathetic nervous system activity, thereby modulating BP [33]. A number of systematic reviews and meta-analyses have shown improvements in BP following consumption of EGCG, including a meta-analysis of 14 randomized clinical trials (including 971 participants) where supplementation with green tea/green tea extract resulted in reductions in both systolic and diastolic BP compared to placebo in subjects who were obese or overweight [32].

Artichokes

Artichokes are rich in antioxidants and phenolic compounds (caffeoylquinic, apigenin, and luteolin). Extracts of the vegetable may help to treat hypertension through reductions in intracellular reactive oxygen species and oxidized low-density lipoproteins via increased eNOS gene expression and improved NO production in vascular endothelial cells [34, 35]. A systematic review and meta-analysis examined the effects of artichoke supplementation in 8 randomized controlled trials. Subjects received between 100 mg and 19.5 g/day of artichoke supplementation in the form of juice, powder, or leaf extract. No effects of artichoke supplementation on BP were seen in normotensive subjects compared to controls. However, SBP and DBP were significantly reduced in hypertensive patients (−3.2, −3.3 mmHg, respectively) [36].

Beetroot Juice

Beetroot juice is a natural source of NO through its metabolism from nitrate. Beetroot is rich in betacyanins, betaine, and betalain, and functions to improve NO availability in the endothelium. This promotes vasodilation and reduces levels of oxidative stress and inflammation. A meta-analysis of 18 randomized clinical trials evaluating the consumption of beetroot juice reported a significant decrease in systolic BP [37], while a systematic review of 9 crossover studies with a beetroot juice intervention for up to 28 days reported significant improvements in vascular and endothelial function and a reduction in BP [38].

Licorice

Licorice is derived from the root of the Glycyrrhiza glabra plant and produces a sweet flavor used in candies and sweetened beverages. It has been used widely in traditional Chinese, Middle Eastern, and Greek medicine to treat peptic ulcer and skin and respiratory diseases [39]. Glycyrrhiza has reported antioxidant, anti-inflammatory, and antimicrobial properties [40, 41]. However, licorice has been associated with an increase in BP; excessive consumption may mimic primary hyperaldosteronism through the inhibition of the kidney enzyme 11-ß-hydroxysteroid dehydrogenase enzyme type 2, thereby promoting water and sodium retention resulting in increased blood volume and pressure [42]. A systematic review and meta-analysis of 18 studies reported a significant increase in SBP and DBP (5.4, 3.2 mmHg, respectively; 95% CI: 3.5–7.4, 0.1–6.3) after chronic ingestion of licorice [43], such that only 50 g of licorice ingested daily is sufficient to cause a notable increase in SBP over a period of 2 weeks [44].

Dietary Supplements

A number of dietary supplements tout cardiovascular benefits, including reductions in BP. While many claimed benefits may be anecdotal, a few show clinical relevance as evidenced in clinical trials, or demonstrate significant reductions in BP compared to lifestyle modifications [45]. Supplements that show some evidence of benefit include fish oil, L-arginine, and allicin [45].

Fish oils, a rich source of omega-3 polyunsaturated fatty acids, are reported to substantially lower BP. This may occur via reductions in aldosterone levels, alterations in sodium transport, and increased vasodilatory activity through stimulation of prostaglandins E1 and G1, and eNOS/NO production [45]. RCTs have evaluated the effects of fish oil supplementation (180 mg eicosapentaenoic acid and 120 mg docosahexanoic acid, daily) for between 13 days and 2 months. Reductions in BP were observed that ranged from −6 to −12 and −5 to −8 mmHg for systolic and diastolic BP [45].

L-arginine is a non-essential amino acid which acts as a precursor of NO to promote relaxation of the endothelium, while also acting as a strong antioxidant and anti-inflammatory agent. A comprehensive meta-analysis of 11 randomized control trials, including 387 participants, reported that oral intervention with L-arginine (4–24 g daily) for up to 12 weeks lowered SBP and DBP (−5.4, −2.7 mmHg, respectively) [46].

Garlic is a rich source of allicin. This substance enhances NO synthesis to promote vasodilation and is a strong inhibitor of ACE activity. A meta-analysis and systematic review of 20 randomized control trials, including 970 subjects, showed that supplementation with garlic extract (600–900 mg daily for 8–12 weeks) resulted in lower SBP and DBP (−5.1, −2.5 mmHg, respectively) when compared to placebo [47].

Summary/Conclusion

Control of BP through pharmacotherapy remains the primary approach for individuals with hypertension; however, behavioral/lifestyle modifications, including specific dietary patterns, may play an important role in achieving BP control. The precise balance of macronutrients and micronutrients (minerals in particular) must be optimized to fit individual dietary needs and health conditions. Inclusion of nutraceuticals and dietary supplements that promote a healthy BP should be considered when developing an ideal

meal plan; however, the efficacy of dietary supplements suggests an adjuvant role as therapy for the reduction of BP in hypertension.

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Nutrition, Physical Activity, and Cancer Prevention

10

Rachel A. Murphy and Fidela Mushashi

Key Points

- Maintaining a healthy body weight helps to reduce the risk of many of the common and most fatal types of cancer.
- Regular moderate-to-vigorous physical activity and minimal sedentary behavior can help achieve a healthy body weight and reduce cancer risk.
- Consuming any amount of alcohol increases the risk of cancer.
- A diet high in whole grains, a variety of fruits and vegetables, low in red meat, and with little, if any, processed meat, can reduce the risk of cancer.
- Cancer survivors should follow recommendations with respect to nutrition and physical activity for cancer prevention when possible.
- Healthy behaviors should be encouraged throughout life - healthy behaviors start early in life but adoption of a healthy lifestyle even later in life can still reduce the risk of cancer.

Introduction

Cancer collectively refers to over 200 diseases that arise from uncontrolled cellular proliferation. Globally, there were an estimated 19.3 million new cases of cancer in 2020 [1]. The prevalence of cancer is projected to increase to 28.4 million in 2040, largely reflecting population growth and aging [1]. This large burden of cancer will place a considerable strain on health systems. Primary cancer prevention has consequently been identified as a key strategy by the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR).

Healthy lifestyles are a cornerstone of cancer prevention. Evidence on the relationship between diet and cancer began to build in 1981 when Doll and Peto estimated that ~35% of cancer deaths could be attributed to diet [2]. Subsequent reports helped to establish the importance of diet and nutritional factors in relation to cancer risk. Major reports included the US National Academy of Science "Diet, Nutrition, and Cancer" [3], the Surgeon General's Report on Nutrition and Health [4], and the US National Research Council of the National Academy of Sciences, Diet and Health: Implications for Reducing Chronic Disease Risk [5]. These reports helped to inform the 1997 landmark WCRF report: Food, Nutrition and the Prevention of Cancer: A Global Perspective [6]. This report summarized the global literature on how diet, nutrition, physical activity, and weight

R. A. Murphy (✉) · F. Mushashi
Cancer Control Research, BC Cancer, and the School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada
e-mail: rachel.murphy@ubc.ca

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_10

affect cancer risk and provided cancer prevention recommendations. The WCRF report was updated in 2007 [7] and 2018 [8]. These reports are the most comprehensive, evidence-based recommendations on how lifestyle behaviors can reduce the risk of cancer. The evidence is broadly grouped into "strong" or "limited," which reflects how strong any evidence of causality is between a given behavior and risk of cancer.

Although the WCRF recommendations and the proceeding sections of this chapter are focused on cancer prevention, the recommendations are similar to those for prevention of other chronic diseases, such as type 2 diabetes and cardiovascular disease, that share common risk factors and etiologic pathways. Cancer prevention recommendations tend to be framed toward adults as nearly 90% of cancers are diagnosed among people aged 50 and older [9]. However, the latency period of cancer generally spans several decades and may reflect exposures earlier in life. As such, adolescence and early adulthood are key times to encourage health-promoting behaviors. Studies suggest that older age is also an etiologically relevant time to reduce cancer risk via lifestyle related behaviors [10, 11]. Collectively, the evidence and strategies presented in this chapter are therefore applicable to the broader population.

Body Weight

Maintaining a healthy body weight is one of the most important things a person can do to reduce their risk of cancer [8]. Excess body weight, generally assessed using body mass index (BMI) or waist circumference, is increasingly prevalent. BMI categories established by the World Health Organization (WHO) are underweight <18.5 kg/m^2; normal 18.5–24.9; overweight 25.0–29.9; obese 30.0–39.9; and severely obese ≥40.0. Globally, 1.9 billion adults are overweight or obese [12]. In the United States, obesity disproportionately affects particular populations. African Americans (49.6%), Hispanics (44.8%), and middle-aged adults (40–59 years, 44.8%) are among those with the highest prevalence of obesity [13].

A large body of evidence shows that excess body weight contributes to many of the most common cancers, including esophageal adenocarcinoma, colon, rectal, kidney, pancreatic, gallbladder, postmenopausal breast, corpus uteri, and ovarian cancers [8]. Excess body weight is linked to cancer through a variety of mechanisms [14]. After menopause, adipose tissue is the main source of estrogen, which leads to elevated circulating estrogen. Prolonged high levels of estrogen are a known causal factor for breast cancer. Adipose tissue is also a major source of inflammation. Chronic inflammation may lead to carcinogenesis via effects on cell growth regulation, insulin resistance, and metabolic dysfunction [14].

Weight loss among individuals who are overweight or obese may help to mitigate cancer risk. Although trials are limited due to the extended follow-up time needed for long-latency diseases, such as cancer, compelling evidence can be drawn from the Women's Health Initiative (WHI) study [10]. WHI found a 30% lower risk of endometrial cancer among women who lost weight compared to women with a stable weight. Weight loss among women who were obese at the start of the trial was particularly impactful with a 56% lower risk of endometrial cancer. Conversely, women who gained 10 lbs or more had an increased risk of endometrial cancer. Similarly, a study of nearly 181,000 women found that even a modest amount of weight loss (>19 lbs), if maintained, is associated with lower risk of breast cancer [15]. Evidence from bariatric surgery also supports a relationship between weight loss and reduced risk of cancer [16]. Collectively, this evidence provides strong impetus to encourage people to make lifestyle changes in order to reduce excess body weight.

At the most basic level, energy balance occurs when energy intake equals energy output. A healthy diet and a physically active lifestyle are critical for achieving and maintaining a healthy

Table 10.1 Dietary recommendations for cancer prevention from the WCRF International

Eat a healthy diet with an appropriate caloric level that supports nutrient adequacy. A healthy dietary pattern includes a variety of vegetables, whole fruits, grains (at least half as whole grains), dairy products or alternatives, a variety of protein-rich foods, and oils, and minimal consumption of saturated and *trans* fats, sodium, and added sugar
Choose water and nutrient-dense beverages. Avoid sugary drinks and alcoholic beverages. If alcohol is consumed, then drinks should be limited to up to one drink per day for women and up to two drinks per day for men
Be mindful of eating habits; how, why, what, when, where, and how much is eaten
Be physically active and limit time spent sitting, based on the guidelines in sections "Physical Activity" and "Sedentary Behavior"

body weight. Table 10.1 provides actions for individuals to encourage a healthy body weight.

Physical Activity

The American Cancer Society publishes guidelines for Diet and Physical Activity for cancer prevention [17]. They recommend that adults engage in 150–300 min of moderate intensity or 75–150 min of vigorous intensity activity each week (or a combination). Ideally, people should exceed 300 min per week. Children and teens should engage in at least one hour of moderate or vigorous intensity activity every day.

Strong evidence has shown that being physically active decreases the risk of colon cancer, postmenopausal breast cancer, and endometrial cancer [17]. Vigorous physical activity, such as running and cycling, has also been shown to reduce the risk of pre- and postmenopausal breast cancer. Physical activity may reduce the risk of other types of cancer, such as lung and esophagus, although further studies are needed. Benefits of physical activity are hypothesized to occur via endocrine, immunologic, and metabolic processes as well as by helping to prevent excessive weight gain [17, 18].

Sedentary Behavior

Sedentary behavior refers to any waking behavior with an energy expenditure ≤1.5 metabolic equivalents (METs) [19]. This includes time spent in such activities as sitting, lying down, TV watching, video game playing, computer use, and driving a car. In contrast to physical activity, which people tend to participate in infrequently and for short-to-medium bursts of time, sedentary behavior tends to be prolonged.

In recent years, the importance of sedentary time as a risk factor for cancer has become clearer. Prolonged sedentary behavior is related to increased risk of colorectal, breast, and endometrial cancer, with the increased risk ranging from 17% for breast cancer to 30% for colorectal cancer for those with most versus least amount of time spent sedentary [17]. Accordingly, the WCRF and ACS recommend that people limit the time they spend in sedentary behavior and suggest breaking up times they are sedentary with physical activity.

The biological mechanisms linking sedentary behavior to cancer are poorly understood. Sedentary behavior may increase the risk of cancer indirectly since it affects energy balance and can contribute to adiposity and weight gain [20]. Sedentary behavior may also contribute to cancer risk directly. Studies have shown that prolonged sedentary time may cause low-grade inflammation such as increased production of reactive oxygen species and greater circulating levels of inflammatory markers including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [20]. Over time, chronic inflammation leads to DNA damage and the development of cancer.

Dietary Patterns

Traditionally, nutrition research has used a reductionist approach, focusing on individual nutrients or other compounds and their relationship with health. However, in recent years, there has been a shift toward a more holistic approach, and consideration of dietary patterns, that encompass the quantity, proportion, variety, or combination of different foods and drinks consumed, and the frequency with which they are consumed. This recognizes the complexity of the diet; nutrients and foods are not consumed in isolation. Rather, foods consist of an array of dietary components and there are interrelationships, synergies, and antagonisms between the thousands of substances that make up food.

The movement toward dietary patterns has been reflected in national dietary guidelines such as those from the United States (Dietary Guidelines for Americans, DGA 2020–2025) [21] and Canada (Canada's Food Guide) [22]. Formerly, these guidelines made recommendations that focused on consuming servings of foods within a respective food group in order to meet nutritional needs, but the modern trend is to encourage eating a healthy dietary pattern throughout life to achieve health and prevent chronic disease. Although dietary guidelines are not specific to cancer prevention, they align closely with recommendations for cancer prevention from the WCRF expert reports and the American Cancer Society.

Studies have shown that the more closely people follow dietary recommendations along with recommendations pertaining to weight, physical activity, and alcohol consumption, the lower is their cancer risk [11, 23]. However, the best dietary pattern with respect to cancer prevention remains unclear. Heterogeneity with respect to assessment of dietary intake and dietary patterns has made it challenging to compare across studies. Despite this challenge, the weight of the evidence suggests that a prudent or "healthy" dietary pattern, which generally refers to diets higher in consumption of fruits and vegetables, legumes, and poultry, is associated with a 23–29% lower risk of colorectal, lung, and breast cancer, respectively [24–26]. "Unhealthy" diets, also referred to as "Western" diets, which are typically higher in snacks, sweets, red meat, processed meat, and potatoes, are associated with increased risk of colorectal cancer [24].

Additional evidence suggests that a Mediterranean diet, which is rich in fish, olive oil, vegetables, whole grains, nuts, and legumes, lower in red meat and dairy, and with modest amounts of alcohol, is associated with lower risk of colorectal, prostate, and postmenopausal breast cancer as well as cancer overall [27]. Similarly, diets that closely mirror dietary guidelines have been associated with lower risk of cancer [28].

Fruits and Vegetables

The WCRF recommends making fruit and vegetables a major part of the diet, equivalent to 400 g/day or about 5 portions [8]. A large body of evidence, primarily from epidemiologic studies, has shown that greater consumption of fruit and non-starchy vegetables is protective against cancer [29, 30]. Consuming 5 or more servings per day may reduce the risk of certain cancers as well as mortality attributable to cancer by ~10% [31]. Consumption of fruits and vegetables also contributes to the control of energy balance and body weight. The recommendations further specify choosing a variety of fruits and vegetables and focusing on non-starchy vegetables, such as carrots, artichokes, and turnips, that contain less carbohydrate than starchy vegetables, such as potatoes, yams, and corn.

The protective action of these foods may reflect bioactive components, namely essential micronutrients, such as vitamins A, C, and E, minerals, and phytochemicals. Phytochemicals are plant components that may provide color, flavor, or protection to the plant. The composition of phytochemicals varies by fruit and vegetable and include salicylates, phytosterols, saponins, glucosinolates, polyphenols, protease inhibitors, monoterpenes, phytoestrogens, sulfides, indoles, isothiocyanates, terpenes, and lectins. Some of the most prominent examples of how phytochemicals affect carcinogenesis are phytoestrogens

(which are found in soy) and plant polyphenols, a large group of antioxidants found in foods such as apples and berries [32, 33]. Numerous studies have suggested that natural phenols could be used for the prevention of cancer. Enthusiasm for phytoestrogens arose from the historically low incidence rates of breast cancer in Japan where there is high soy intake. Although findings have subsequently been inconsistent, this may reflect timing of soy intake, which studies suggest may need to occur early in life to see any protective effect on cancer [34].

Dietary Fiber

Carbohydrates can be broadly divided into two groups. One group includes starch and simple sugars. These are highly digestible and easily absorbed in the small intestine. The second group is dietary fiber such as cellulose and pectin. These carbohydrates are resistant to digestion in the small intestine and are fermented by bacteria in the colon. Foods containing dietary fiber are an important part of a cancer preventive diet. There is strong evidence that eating whole grains that have intact grain, germ, and endosperm, such as whole wheat, buckwheat, millet, and quinoa, may reduce the risk of colorectal cancer by 10–21% based on comparing those with highest versus lowest intake [35]. Dietary fiber is similarly associated with reduced risk of colorectal cancer and also contributes to maintenance of a healthy body weight [8]. The WCRF recommends that individuals consume at least 30 g/day of dietary fiber. However, the vast majority of people in North America typically consume about half of this amount. Examples of fiber-rich foods are shown in Table 10.2.

Table 10.2 Foods high in dietary fiber

Whole grains	Cereals, oats, popcorn, crackers, chapati/roti, tortillas, bulgur, spelt, teff, barley
Vegetables	Artichoke, beans, lentils, broccoli, peas, Brussels sprouts, potatoes, yams, avocado, carrots, kale, okra, cabbage, beets
Fruits	Berries, grapes, apples, oranges, pears, bananas, dates, apricots, figs, peaches, persimmon, guava, soursop, passionfruit, durian, starfruit
Protein foods	Seeds (pumpkin, chia, sunflower), almonds, coconut, nuts (pine, pistachio), hazelnuts, chestnuts

Consuming these foods allows people to meet the WCRF International's goal of consuming at least 30 g per day of fiber

Dietary fiber has dynamic properties, including binding nutrients, generating new metabolites, and modulating nutrient absorption and metabolism. Some types of fiber, such as oat bran, pectin, and guar, are fermented into short-chain fatty acids (acetate, propionate, and butyrate) in the colon. These fatty acids have physiological roles in pathways involved in carcinogenesis [36]. Acetate reduces levels of lipopolysaccharide-stimulated cytokines TNF-alpha, IL-6, and nuclear factor (NF)-κB. Propionate similarly reduces levels of TNF-alpha and NF-κB, affects food intake by increasing satiety (via leptin), and reduces cancer cell growth and proliferation. Butyrate plays a critical role in maintaining the health of colonocytes and the colon epithelium. It is also a potent inhibitor of proinflammatory cytokines and may thus minimize chronic inflammation. There is also substantial evidence that short-chain fatty acids have effects on cell cycle, migration, and apoptosis that counteract early colonic carcinogenesis [36].

Supporting evidence on the protective role of fiber on colorectal cancer comes from preclinical animal or cell culture models. Epidemiologic studies are generally consistent although some studies have reported null associations. This may reflect, in part, variation in the gut microbiome and consumption of dietary fiber which both influence production of short-chain fatty acids and their action. Dietary fiber is one of the most influential nutritional factors with respect to the composition and metabolic activity of the gut microbiota [37]. Dietary fiber and production of short-chain fatty acids are directly related; low intake and low production of these fatty acids have been observed in people with colon cancer compared to healthy individuals [38]. The overall composition of the gut microbiota also differed between the two groups.

Meat

Meat can be classified as white, red, or processed. White meat refers to poultry. Red meat refers to beef, veal, pork, lamb, mutton, and goat. Processed meat has been preserved with salt, cured, fermented, smoked, or another type of process/preservation. There is strong evidence from preclinical and epidemiologic studies that consumption of red meat and processed meat, even in modest amounts, increases the risk of colorectal cancer [39, 40]. If a person chooses to eat red meat, consumption should be limited to less than 3 servings/week and little, if any, processed meat. The International Agency for Research on Cancer (IARC) has classified red meat as a Group 2A carcinogen, reflecting a probable relationship, while processed meat is classified as a grade Group 1 carcinogen which is known to be carcinogenic to humans.

Although the strongest and most consistent evidence points to a relationship between both red meat and processed meat with colorectal cancer, there is also evidence of increased risk for other cancers. Greater red meat consumption is associated with increased risk for pancreatic and prostate cancer [41] while greater processed meat consumption is linked with increased risk for stomach cancer [42]. It is important to note, however, that meat, including red meat, is an important source of nutrients including protein, iron, zinc, selenium, and vitamins B6 and B12. Healthy dietary patterns (see section "Dietary Patterns" above) that are associated with reduced cancer risk may include modest amounts of meat, particularly poultry.

Dairy

Dairy foods can be an important part of a healthy diet as dairy products are rich in many nutrients including calcium, vitamin D, and other bioactive constituents such as lactoferrin and short-chain fatty acids. The Continuous Update Project (CUP) from the WCRF, which refreshes cancer prevention recommendations with the latest evidence, has concluded that higher intake of dairy products, particularly milk, cheese, and dietary calcium, are associated with a decreased risk of colorectal cancer [43]. There is also some limited evidence that dairy products and foods that are high in calcium may be associated with lower risk of breast cancer. The protective functions of dairy products are believed to be due to calcium and, to a lesser extent, other components of dairy products including conjugated linoleic acid, sphingolipids, butyric acid, and fermentation products.

There is conflicting evidence regarding consumption of dairy products, particularly milk, and the risk of prostate cancer. Several prospective cohort studies have reported that a relatively high intake of milk increases the risk of prostate cancer. For example, more than 2.5 servings of dairy products per day were reported as being associated with increased risk of prostate cancer, while one glass of whole milk was associated with higher risk of fatal prostate cancer [44]. The association between dairy products and prostate cancer may reflect the fat content of milk, calcium content, or effects on hormone levels. However, findings from other studies have not found any elevated risk of prostate cancer with dairy consumption [45]. The CUP has also concluded that evidence linking dairy products to prostate cancer is limited [43]. Given that dairy products are important sources of nutrients that are low in the diet of many people (e.g., calcium and vitamin D) and the role of dairy in the prevention of other cancers and the prevention of chronic disease, it may be advisable to encourage people to include dairy foods in their diet.

Dietary Supplements

Whenever possible, people should aim to meet their nutrient needs through food, not dietary supplements. The exception may be vitamin D as a large section of the population of North American live at latitudes where UVB radiation is insufficient for vitamin D synthesis all-year round and dietary consumption is inadequate to meet this deficit [21].

Despite much public interest in dietary supplements for the prevention of cancer, and among cancer survivors, the balance of evidence suggests dietary supplements may, at best, offer no benefit, and for some micronutrients may actually increase the risk of cancer. For example, dietary selenium and vitamin D have U-shape relationships between dose and cancer risk [46, 47]. This is a cause for concern as the quantity of micronutrients in dietary supplements often exceeds levels obtained in the diet. Another important factor that argues against the value of supplements is that some components of whole foods that also carry benefits such as fiber and phytochemicals are seldom provided by dietary supplements.

Fruits and vegetables are rich in carotenoids that are thought to contribute to the reduced risk of cancer associated with a relatively high intake of those foods. This provided a rationale for testing the value of beta-carotene supplements in cancer prevention. Other evidence suggested that vitamin E supplements might also prevent cancer. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study assigned male smokers aged 50–69 to supplementation with either alpha-tocopherol (vitamin E, 50 mg/day), beta-carotene (20 mg/day), both supplements, or placebo. No reduction in lung cancer risk was observed for men who were assigned to alpha-tocopherol alone or together with beta-carotene [48]. Conversely, men who were assigned to beta-carotene alone had an 18% higher risk of lung cancer. The Beta-Carotene and Retinol Efficacy Trial (CARET) randomized participants who had a history of smoking or exposure to asbestos to beta-carotene + retinyl palmitate supplementation or placebo. Compared to placebo, participants who were assigned to the active intervention had a 28% increased risk of lung cancer, 17% increased risk of death, and an increased risk of death from cardiovascular disease [49]. There is also suggestive evidence from observational studies that beta-carotene supplementation may increase the risk of stomach cancer although findings for other cancer types are unclear.

When it began in 2001, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) was the second large chemoprevention trial for prostate cancer, with a goal of randomizing 32,400 men to one of four groups: selenium, vitamin E, selenium + vitamin E, or placebo. There were statistically non-significant increase in risk of prostate cancer in the vitamin E group ($p = 0.06$) and risk of type 2 diabetes in the selenium group. As such the data and safety monitoring committee recommended discontinuation of the supplements [50]. It is possible that the high dose of vitamin E (400 IU/day), which is well beyond what an individual would obtain in the diet, had adverse effects on cytochrome p450 enzymes that are key in the formation of cancer.

The picture that clearly emerges from the above chemoprevention trials is that the supplements tested failed to prevent cancer and may have increased the risk of the disease. More research is needed to understand the mechanisms that explain why these supplements have adverse effects.

Folic acid is another micronutrient that may increase the risk of cancer when given as a supplement. The findings from various epidemiological and experimental studies led to speculation that a low dietary intake of folate may increase risk of cancer while supplements of folic acid may reduce the risk [51]. However, evidence from several cohort and randomized trials indicates that the reality is much more complex. Indeed, supplemental folic acid may increase the risk of cancer at several sites, including the breast, lung, and prostate [52].

Alcohol

An estimated 741,300 or 4.1% of all new cancer cases diagnosed globally in 2020 were attributed to alcohol consumption [53]. The largest risk was observed among those with heavy drinking (six or more drinks per day) but consumption of any amount of alcohol, or any type of alcoholic beverage—beer, wine, or spirits—increases the risk of cancer. The risk is particularly evident for some cancers including mouth, pharynx and larynx, esophagus, liver, colorectal, and pre- and postmenopausal breast cancer [8]. For example, each standard sized glass of wine is associated

with a 6% increased risk of breast cancer [53]. Two or more drinks per day are associated with a 15% increased risk of colorectal cancer, and consumption of three or more drinks per day is associated with a 6% increased risk of stomach and liver cancer [8]. To reduce the risk of cancer, it is therefore best to avoid alcohol [8].

Ethanol has been classified by the IARC as a Group 1 carcinogen; an agent that is known to be carcinogenic to humans [54]. Consumption of beer, wine, and spirits can all increase the risk of cancer since they all contain ethanol in addition to other carcinogenic compounds such as acetaldehyde, aflatoxins, and ethyl carbamate. The mechanisms through which alcohol consumption leads to cancer development include genotoxic effects of acetaldehyde, effects on cytochrome p450 enzymes, increased oxidative stress, altered folate and estrogen metabolism, and reduced DNA repair [24]. It has also been suggested that alcohol consumption may contribute to increased cancer risk, in part, through effects on body weight since alcoholic drinks tend to be energy dense and can led to energy imbalance.

Conclusions

Adopting a healthy lifestyle can reduce the risk of cancer by ~30 to 40% and of cancer mortality by ~42% [55]. A healthy lifestyle, which includes a diet rich in fruits and vegetables, whole grains, beans and other legumes, limited consumption of red and processed meat, alcohol, processed foods, and sugar-sweetened beverages, regular physical activity, and maintenance of a healthy body weight, should therefore be promoted as a key strategy for cancer prevention. The benefits of a healthy lifestyle extend well beyond cancer and include improving overall health and reducing the risk of other chronic diseases such as diabetes and cardiovascular disease.

There are, it must be stressed, gaps in the evidence on the relationship between diet and cancer. In particular, there are problems with self-reported assessment of diet, particularly over the long term, and a limited number of dietary biomarkers. Also, there is inadequate evidence to support causality, which reflects the predominance of epidemiologic studies. These are some of the key areas that need to be addressed in order to move forward [56].

A number of challenges are clearly present with respect to the implementation of cancer prevention recommendations. For example, some of the recommendations from the WCRF are not quantified (e.g., “limit” sedentary behavior) and as a result interpretations may vary. Guidelines often provide a one-size-fits-all approach which does not reflect individual differences with respect to risk of cancer due to genetics, age, sex, or family history. There is also little consideration as to how to adapt dietary guidance for populations where traditional foods fall outside of common recommendations (e.g., starchy foods such as cassava and yam). Personalized approaches to encourage a healthy diet, physical activity, and a healthy body weight may be more likely to resonate with individuals, although the effort needed to achieve this is considerable. Messaging from national agencies (e.g., the Canadian Cancer Society) that emphasize “starting small,” and the benefit of even small changes, such as avoiding alcohol, may also help encourage people to take action. With respect to public health programs and policies, it may be advantageous to prioritize action on diet-related risk factors, such as obesity and alcohol consumption, that current evidence has the largest impact on cancer risk [56].

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Nutrition and Eating Disorders

11

Maija B. Bruzas and Kelly C. Allison

Key Points

- For anorexia nervosa (AN), inpatient treatment featuring a multi-disciplinary team and family-based therapy (e.g., Maudsley family therapy) or outpatient family-based therapy are the first-line treatments.
- No pharmacological agents are indicated to assist in the treatment of the core symptoms of AN.
- For bulimia nervosa, cognitive behavior therapy (CBT) and CBT with adjunct pharmacotherapy are the best supported treatment approaches.
- Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, the monoamine oxidase inhibitor (MAOI) phenelzine, and the anticonvulsant topiramate are supported psychopharmacological treatments.
- The SSRI fluoxetine is the only FDA-approved medication for bulimia nervosa.
- For binge eating disorder, CBT is well supported.
- Behavioral weight loss (BWL) is indicated to produce weight loss in the patients with overweight or obesity. A combination approach can be used as well. The stimulant lisdexamfetamine, SSRI antidepressants, and the anticonvulsants topiramate and zonisamide are supported psychopharmacological agents for this disorder.
- The stimulant lisdexamfetamine is the only FDA-approved medication for binge eating disorder.
- CBT for avoidant/restrictive food intake disorder is currently being investigated, and preliminary results are promising.
- There is some evidence that the tetracyclic antidepressant mirtazapine may help with weight gain.
- Diaphragmatic breathing is indicated for rumination disorder.
- Night eating syndrome can be effectively treated with CBT, psychoeducation, progressive muscle relaxation, and the SSRIs sertraline and escitalopram.

Introduction

Eating disorders represent extremes in nutrition. These extremes of under- and overnutrition can exist within the same person, as in the anorexia nervosa-binge eating/purging type. Alternatively, the extremes can be found in anorexia nervosa-restricting type and binge eating disorder. Current diagnostic criteria for eating and feeding disorders are outlined in the Diagnostic and Statistical Manual—Fifth Edition [1] from the American Psychiatric Association and include

M. B. Bruzas
Health Psychology Associates PC, Greeley, CO, USA

K. C. Allison (✉)
Center for Weight and Eating Disorders, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
e-mail: kca@pennmedicine.upenn.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_11

anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED) , avoidant/restrictive food intake disorder (ARFID), rumination disorder (RD), and otherwise specified feeding or eating disorder (OSFED). Night eating syndrome (NES) and purging disorder (PD) are two forms of disordered eating that are growing in recognition and are included in the OSFED category. This chapter describes diagnostic criteria for these eating disorders, their prevalence, behavioral and psychopharmacological treatments, and prevention efforts.

Eating Disorder Diagnostic Criteria

Anorexia Nervosa

Anorexia nervosa (AN) frequently begins in adolescence or young adulthood and occurs primarily in females [1, 2]. AN features a significant restriction of energy intake relative to physical requirements, leading to a significantly low body weight for one's age, height, sex, developmental trajectory, and physical health status. For adults, a body mass index (BMI) of <17.0 kg/m^2 is considered by the World Health Organization to indicate "significantly low body weight." For children and adolescents, a BMI percentile below the fifth percentile on the Center for Disease Control and Prevention's BMI-for-age-and-sex percentile charts is typically used to classify "significantly low body weight."

Another key feature of AN is an intense fear of gaining weight or of having overweight and persistent engagement in behaviors that cause weight loss or interfere with weight gain [1]. This intense fear is rarely alleviated with weight loss. Another core feature of AN is excessive influence of weight or shape on self-evaluation. There is a disturbance in how one experiences one's weight or shape, and typically there is a persistent lack of recognition of the negative consequences of one's low body weight. Many individuals with AN may not recognize or admit their fears of weight gain and are not likely to present for treatment for AN, but may be brought to treatment by loved ones or present with complaints of somatic and psychological symptoms related to their malnutrition or comorbid mental health conditions.

There are two subtypes of AN [1]. The restricting subtype of AN involves sole use of caloric restriction and excessive exercise as a means of weight control. The binge eating/purging subtype of AN includes binge eating and/or inappropriate compensatory measures, such as vomiting or misuse of laxatives, diuretics, or enemas. Those with AN binge eating/purging subtype have extremely low body weight, which differentiates them from those with BN. Others may notice that individuals with AN appear low in weight, seem fatigued, have trouble tolerating the cold and have lanugo on their upper body, have spells of dizziness or fainting, report gastrointestinal complaints, and have irregular or absent menstrual periods [3].

All physical systems are negatively impacted by the malnutrition and weight loss in AN [4, 5]. Physical effects of restrictive eating include cardiovascular abnormalities (e.g., bradycardia, hypotension), hypoglycemia, osteoporosis, slowed gastric motility, hypothermia, dental problems, amenorrhea, infertility, and an increased risk of miscarriage and having a child with low birth weight [1, 4, 5]. In the binge eating/purging subtype, purging causes additional physical damage (see the section on BN).

Mortality rates are higher for AN than many other psychiatric disorders [5]. Twenty to 30 percent of deaths in those with AN are due to suicide, and approximately half of deaths are due to medical complications [4, 5].

Bulimia Nervosa

Bulimia nervosa (BN) frequently begins in adolescence or young adulthood [1]. The core features of BN are binge eating and subsequent use of inappropriate compensatory behaviors to prevent weight gain or to lose weight. A binge episode is defined as an episode in which a person eats an unambiguously large amount of food within a two-hour period and experiences loss of control when eating. What is considered "unambiguously large" is based upon what most people would eat in a two-hour period under sim-

ilar circumstances. Inappropriate compensatory behaviors include vomiting, restrictive eating, excessive exercise, or misuse of laxatives, diuretics, or enemas. Vomiting is the most common method of purging in those with BN. For those with BN, caloric intake during a binge eating episode prior to purging is an average of 2722 calories [6]. As with AN, there is an over-valuation of weight and shape in self-evaluation [1]. The binge episodes and inappropriate compensatory behaviors must occur at least once per week for at least 3 months. Screening for BN is difficult because individuals typically have normal weight or overweight status.

Common signs of regular vomiting include "Russell's sign" (thickening of the skin on the knuckles due to self-induced vomiting), swollen cheeks, and dental erosion [4]. Vomiting can cause electrolyte imbalance, cardiac arrhythmias, gastroesophageal reflux disease, tears and ruptures of the esophagus, gastric ruptures, and metabolic alkalosis [1, 4].

Overuse of laxatives can cause severe electrolyte disturbances, especially low levels of potassium in the blood, which can contribute to muscle weakness or paralysis, notable renal impairment, and cardiac arrhythmias [7]. It can also cause inflammation, ulceration, and neuropathy of the colon and steatorrhea. Other consequences include dehydration, hypotension, tachycardia, dizziness, and metabolic alkalosis [1, 7].

Binge Eating Disorder

Binge eating disorder (BED) frequently begins in adolescence or young adulthood, but sometimes begins in adulthood [1]. The hallmark of BED is recurrent binge episodes. A binge episode is defined as an episode in which a person eats an unambiguously large amount of food within a two-hour period and experiences loss of control when eating. What is considered "unambiguously large" is based upon what most people would eat in a two-hour period under similar circumstances. Additionally, at least three of the five following signs must be present during binge episodes: (a) eating more rapidly than normal; (b) eating until feeling uncomfortably full; (c) eating when not physically hungry; (d) eating alone due to embarrassment; and (e) feeling disgusted, depressed, or markedly guilty afterward. Diagnosis requires that the episodes occur, on average, at least once per week for 3 months. BED is positively associated with overweight and obesity and prospectively increases the risk of developing obesity [8].

Avoidant/Restrictive Food Intake Disorder

Avoidant/restrictive food intake disorder (ARFID) frequently begins in infancy or early childhood [1]. ARFID is characterized by lack of interest in eating or food, aversion to the sensory characteristics of certain foods, and/or avoidance of eating broadly or eating certain foods due to fears of aversive consequences (e.g., choking, vomiting). ARFID leads to weight loss or difficulty with weight gain, nutritional deficiencies, dependence on enteral feeding or oral nutritional supplements, and/or considerable interference with psychosocial functioning. Most individuals with ARFID are not preoccupied with being thin, as is the case with AN. The medical consequences of ARFID include the side effects of malnutrition, which are also seen in AN, such as fatigue, dizziness, amenorrhea, bradycardia, orthostatic hypotension and tachycardia, cold intolerance and hypothermia, pallor, and lanugo [9]. These consequences are often noticeable and concerning to caregivers.

Rumination Disorder

The onset of rumination disorder (RD) is typically in infancy, childhood, or adolescence, but can also occur in adulthood [1, 10]. RD features recurrent involuntary regurgitation of ingested food several times per week for at least 1 month. This regurgitation typically occurs during or briefly after eating and is followed by re-swallowing, rechewing, or spitting out of the regurgitated food [1, 10]. RD can lead to dental damage, malnutrition, electrolyte disturbances, and weight loss. Individuals

with RD may avoid certain social eating situations, due to a desire to avoid regurgitating during a meal or in a public restroom or having others find out about their regurgitation [10]. Habitual abdominal wall contractions are considered to be the primary cause of RD. One behavioral theory of RD is that physical responses to certain foods, symptoms of physical illness (e.g., gastrointestinal disorders), recurrent purging due to an eating disorder (bulimia nervosa with purging or purging disorder) or physical illness, and/or negative emotions lead to abdominal wall contractions, which lead to pressure or discomfort in the abdomen and/or esophagus, which cause premonitory urges to regurgitate food. If food is regurgitated, this leads to relief of the premonitory urges and physical relief, which is negatively reinforcing. Thus, over time, the contractions become more frequent. Learned cognitive associations between regurgitation and certain foods, activities, or visceral sensations can make regurgitation more likely. Additionally, regurgitation can lead to reduction of negative emotional states, which can also be reinforcing. Some individuals with RD have comorbid eating disorder symptoms (e.g., voluntary vomiting, excessive exercise, restrictive eating, caloric restriction, preoccupation with eating, shape, and/or weight) while others do not. Thus, for some individuals with RD, regurgitation may lead to desired and reinforcing expulsion of high-calorie foods, weight loss, etc.

Other Specified Feeding or Eating Disorders

There are types of disordered eating that cause psychological and physical distress that do not fit the diagnostic criteria for the aforementioned disorders. These are captured in the OSFED category [1].

Night Eating Syndrome

Night eating syndrome (NES) typically appears in young adulthood or adulthood [11]. NES involves consuming at least 25% of one's daily calories after the evening meal and/or experiencing at least two nocturnal eating episodes (rising from sleep to eat) per week, for at least 3 months [12]. For a diagnosis of NES, three of the five following features must be present: (a) a lack of desire to eat in the morning and/or breakfast is omitted on four or more mornings per week; (b) a strong urge to eat between dinner and bedtime and/or during the night; (c) sleep onset and/or sleep maintenance insomnia occur four or more nights per week; (d) the belief that one must eat in order to get to sleep; and (e) mood is frequently depressed and/or mood worsens in the evening. Individuals with NES must have awareness and recall of the evening and nocturnal eating episodes; if they do not, then clinicians should assess for sleep-related eating disorder, which is a parasomnia marked by impaired consciousness and often includes the consumption of unusual food or nonedible objects in addition to normal food. The nocturnal ingestions in NES are typically the size of a snack or small meal and do not need to be objectively large, as is the case of objective binge eating episodes in BED and BN. People who live with an individual with NES may notice the individual waking up at night and may observe signs that the individual ate food between bedtime and the morning.

There are mixed findings regarding the association between NES and BMI, with approximately half of studies showing a positive correlation and the other half showing a non-significant association [13]. Whether NES produces weight gain may be dependent on the frequency of evening eating and nocturnal ingestions and the quantity and type of foods and beverages ingested during these episodes. Individuals with NES demonstrate worse control of diabetes and higher diabetes complication rates than individuals without NES [11]. Nocturnal ingestions also predict worse oral health.

Purging Disorder

The onset of purging disorder (PD) is typically in young adulthood [14]. PD features weekly purging behaviors (e.g., vomiting, laxative use, or diuretic misuse) for a course of 3 months with the intention to influence one's weight and shape

[1, 14]. Individuals with PD do not engage in binge eating and do not have significantly low body weight [1]. Some individuals with purging disorder experience subjective binge episodes, in which they eat a portion of food that is not unambiguously large and feel a sense of loss of control. Overvaluation of shape and weight is frequently experienced by individuals with PD and they often have high levels of dietary restraint and endorse specific dietary rules, such as "I cannot eat fried foods, because they will cause weight gain. If I do eat any fried food, then I have to purge."

In those with PD, caloric intake during an eating episode featuring loss of control before purging is 535 calories on average, which is significantly lower than the average 2722 calories consumed before purging in those with BN [6]. The signs and consequences of purging in PD are described in the section on BN.

Atypical Anorexia Nervosa

In atypical AN, an individual has lost a significant amount of weight and all of the criteria for AN are met, except the person has not reached a significantly low body weight [1]. This disorder can occur in individuals with overweight or obesity who have lost a significant amount of weight rapidly with behavioral weight loss efforts, bariatric surgery, and/or weight loss medication and have developed extremely restrictive eating practices and/or excessive exercise routines.

Bulimia Nervosa (of Low Frequency or Limited Duration)

In subclinical BN, all diagnostic criteria for BN are met except that the frequency of the binge episodes and compensatory behaviors is, on average, less than once per week and/or for less than 3 months [1]. An example would be an individual who purges three or fewer times per month and has three or fewer objective binge episodes per month. This person might have more frequent subjective binge eating episodes, which involve a sense of loss of control when eating a quantity of food that is not unambiguously large (e.g., five small cookies).

Binge Eating Disorder (of Low Frequency or Limited Duration)

In subclinical BED, all diagnostic criteria for BED are met except that the binge episodes occur, on average, less than once per week and/or for less than 3 months [1]. An example would be an individual who has a combination of subjective and objective binge eating episodes or only occasional objective binge eating episodes, with three or fewer objective binge eating episodes per month.

Unspecified Feeding or Eating Disorder

This diagnosis may be used when any individual has subthreshold symptoms for an eating disorder and shows significant distress or psychosocial impairment and not enough information has been collected to make a full diagnosis (e.g., in an emergency situation) or further diagnostic clarification is needed [1].

Prevalence of Eating Disorders

The cross-gender lifetime prevalence of the DSM-5 eating disorders reported in U.S. adults is 0.80% for AN, 0.28% for BN, and 0.85% for BED [2]. Gender-specific lifetime prevalence values for AN are 1.42% of women and 0.12% of men; for BN is 0.46% of women and 0.08% of men; and for BED is 1.25% of women and 0.42% of men [2]. In North America, 5–12% of patients presenting for eating disorder treatment at outpatient clinics meet criteria for ARFID [9]. The prevalence of NES ranges from 1 to 2% in community samples and increases in samples seeking treatment for obesity [11]. Lifetime prevalence of PD across age groups is 6.2% [15]. The prevalence range of RD in com-

munity samples is 0.8–10.6%, which suggests that the prevalence of RD is not yet certain and more research is needed [10]. It is also important to consider the prevalence of subclinical eating disorder symptoms. Project Eating and Activity in Teens and Young Adults was a longitudinal study that measured seven disordered eating behaviors across time [16]. These behaviors included: (1) high importance placed on weight and shape, (2) extreme unhealthy weight control behaviors, (3) frequent dieting, (4) episodic overeating, (5) distress about overeating [in those who overeat], (6) experience of loss of control during overeating [in those who overeat], and (7) overeating with loss of control more than once per month [in those with overeating featuring loss of control]. Baseline assessment occurred between ages 11 and 17 years and follow-up occurred between 27 and 33 years of age. Nearly 51% of the girls and 34% of the boys in this sample reported at least one of these disordered eating behaviors at baseline. A larger percentage of girls (29.2%) reported two or more of these behaviors than boys (12.4%). In all participants, BMI was relatively higher at all timepoints for those with more eating disorder symptoms, with increasing number of eating disorder symptoms corresponding to higher BMI values. Distress about overeating and overeating featuring loss of control emerged as two significant predictors of higher BMI. These results suggest that subclinical eating disorder symptoms are common in 11–17-year-old girls and boys and can lead to significant increases in BMI in the long term.

Behavioral Treatment for Eating Disorders

Table 11.1 provides an overview of effective behavioral and pharmacological treatments. Health insurance coverage for behavioral treatments is variable across all of the eating disorder diagnoses, and many providers may be out of network for coverage, so individuals must check with their insurance providers to determine coverage.

Psychotherapy and Nutrition Therapy for Anorexia Nervosa

Anorexia Nervosa Inpatient Treatment

Indicators for inpatient treatment for AN include a precipitous drop in body weight, a BMI <15 kg/m^2, significant nutritional deficiencies and medical consequences of the disorder (e.g., bradycardia, biochemical disturbances), a longer duration of illness, a history of multiple relapses, failure to respond to outpatient treatment, and/or having severe comorbid mental health conditions or suicidality [5]. Increased mortality is seen in patients with BMIs <17.5 kg/m^2, so inpatient treatment should be considered in individuals with a BMI below this level who also have other indicators suggesting inpatient treatment.

Inpatient treatment involves nutritional restoration (refeeding) including therapeutic meals, typically involving health professionals and/or family members, where patients are tasked with eating nutritionally balanced meals and snacks at regular intervals each day [3]. Initial caloric intake depends on age. For adults, an initial intake of 1600 kcal/day is recommended. This is increased by 300 kcal per day every 2–3 days, reaching up to 3500–4000 kcal per day for optimal refeeding. The goal is for patients to gain approximately 1–2 lb. (0.45–0.91 kg) per week. More conservative feeding regimens are associated with suboptimal outcomes, e.g., are less likely to produce sustained recovery from AN. Care must be taken to avoid refeeding syndrome, which can occur when a malnourished individual (<70% below average body weight) eats too many calories early in refeeding and develops hypophosphatemia and other laboratory abnormalities [17]. This can lead to delirium, cardiac and respiratory failure, profound muscle weakness, and in the worst cases, death.

Oral refeeding of regular meals with standard nutritional recommendations is the preferred approach, but if that is not tolerated, liquid meal supplements may be used, followed by nasogastric (NG) feeding in the context of food refusal [17]. Psychological treatment during inpatient treatment typically involves group and individual psychotherapy, with treatment involving family

Table 11.1 Effective behavioral and pharmacological treatments for eating disorders

Disorder	Age of onset	Prevalence	Psychological treatments	Psychopharmacological treatments
Anorexia nervosa	Adolescence or young adulthood	Lifetime: 1.42% female; 0.12% male	Adolescents: family-based treatment, Maudsley family therapy, inpatient multi-disciplinary treatment, adolescent focused therapy, family systems therapy. Moderate support for CBT-enhanced Adults: the Maudsley model of anorexia nervosa treatment for adults, specialist supportive clinical management, focal psychodynamic psychotherapy	No medications have been proven effective for AN
Bulimia nervosa	Adolescence or young adulthood	Lifetime: 0.46% female; 0.08% male	CBT is most strongly supported. Other psychotherapy approaches have some support Strong support for SSRIs	Tricyclic antidepressants: desipramine, amitriptyline, imipramine Others: anticonvulsant topiramate, MAOI-phenelzine Contraindicated: unicyclic antidepressant bupropion-immediate-release
Binge eating disorder	Adolescence or young adulthood, but sometimes adulthood	Lifetime: 1.25% female; 0.42% male	CBT is strongly supported BWL is supported for patients with overweight or obesity and a desire to lose weight without severe eating disorder behaviors and cognitions	Strong support for SSRIs Stimulant: lisdexamfetamine dimesylate Anticonvulsants: topiramate, zonisamide Others: unicyclic antidepressant bupropion, mood stabilizer lamotrigine
Night eating syndrome	Young adulthood or adulthood	1–2% cross-gender, community samples	CBT is supported Progressive muscle relaxation Psychoeducation- on night eating syndrome, healthy eating, and sleep	Moderate support for SSRIs Case reports with topiramate
Avoidant/ Restrictive Food Intake Disorder	Infancy or early childhood	5–12%, cross-gender, in patients presenting to outpatient clinics	Preliminary support for CBT	Unknown effects of SSRIs The tetracyclic antidepressant mirtazapine may help with weight gain

CBT cognitive behavioral therapy, *SSRI* selective serotonin reuptake inhibitor, *MAOI* monoamine oxidase inhibitor, *BWL* behavioral weight loss

members for adolescents. Once a patient is well-nourished, has made progress toward or reached the target weight, and is medically stable, the patient can be transitioned to partial hospitalization or day treatment programs. Then, they can transition to outpatient treatment.

Anorexia Nervosa Outpatient Treatment in Adolescents

For adolescents, family-based therapy (e.g., the Maudsley Model) is the favored treatment approach, with the best outcomes [18]. In the Maudsley Model of family-based therapy, care-

givers are initially tasked with taking control of their child's eating behavior and weight restoration through structured and appropriate feeding behaviors. Later in treatment, parents transition the majority of control of eating behavior and weight back to the child, once the child shows evidence of acceptance of the new feeding rules within the home (the child is eating more and has been gaining weight, etc.). These therapies also focus on fostering positive relationships within the family. There is moderate evidence to support the use of family system therapy, adolescent focused therapy, and cognitive behavioral therapy-enhanced (CBT-E) for adolescents.

Anorexia Nervosa Outpatient Treatment in Adults

Treatment options for adults with AN that have moderate support include CBT-Enhanced (CBT-E), the Maudsley model of AN treatment for adults (MANTRA), specialist supportive clinical management (SSCM), and focal psychodynamic psychotherapy [18]. CBT-E is based on the transdiagnostic theory that there are core eating disorder psychopathology factors that underlie and maintain multiple eating disorders, such as overevaluation of body shape, low self-esteem, and dietary restraint [19]. It involves determining what stimuli, behaviors, and thoughts are maintaining the eating problem and making goals to manage them [18]. MANTRA is a cognitive-interpersonal treatment that involves helping the patient build an identity separate from the disorder. SSCM is a supportive therapy involving psychoeducation, setting weight, eating behavior, and nutrition goals and monitoring progress. Focal psychodynamic psychotherapy focuses on creating a positive therapeutic alliance, exploring ego-syntonic beliefs that lead into the disorder and pro-anorexic behaviors, and examining the interaction between interpersonal relationships and the eating disorder behaviors. None of these psychotherapies is superior to the others for treatment of AN in adults.

Prognosis for Anorexia Nervosa

One study involved an inpatient sample of 1145 patients with AN, with a mean age of inpatient admission of 24.9 years [20]. The mean follow-up time was 9.8 years. Full remission was found in 29.6% of the sample, and partial remission was seen in 6.4%. BMI significantly increased in the sample, from a mean of 14.7 to 18.8 kg/m^2. The main predictors of poor outcome were lower BMI at inpatient admission and higher age at admission. In a small subsample (N = 112) that completed 20-year follow-up, 39.3% achieved full remission and 3.6% achieved partial remission. Another study involved longitudinal follow-up of 228 patients with AN or BN [21]. At 9-year follow-up, 31.4% of patients with AN had recovered and at 22-year follow-up, 62.8% had recovered. Early recovery was associated with a higher likelihood of long-term recovery in anorexia nervosa, with an odd's ratio of 10.5.

Bulimia Nervosa

Individual CBT is the first-line treatment for BN, producing the best results in terms of achieving full remission, reducing binge eating and compensatory behavior, and reducing eating disorder cognitions [22]. CBT for BN involves self-monitoring of eating disorder symptoms and their antecedents (e.g., thoughts, feelings, behaviors, exposure to certain foods or situations) and consequences (e.g., positive and negative thoughts, feelings, and behaviors) to determine what factors trigger or maintain eating disorder symptoms, psychoeducation, and goal setting to improve management of common triggers, intervene during episodes, and mitigate consequences, cognitive restructuring, emotion coping training, and planned behavioral exposures (e.g., to trigger foods) [23]. Other forms of psychotherapy (e.g., interpersonal psychotherapy, behavioral therapy) and combined treatment (multiple forms of psychotherapy or psychotherapy coupled with pharmacotherapy) are second-line treatment approaches, followed by self-help as a third-line treatment. Pharmacotherapy alone is not adequate as a treatment approach.

Prognosis for Bulimia Nervosa

One study involved longitudinal follow-up of 176 patients with AN or BN [21]. At both the 9-year and 22-year follow-up assessments, 68.2% of patients with BN had recovered. Mean age at 22-year follow-up was 45 years. The median time to recovery was 3.8 years.

In another study of 173 women diagnosed with BN, 11.5 years later 46.8% were in full remission, 23.1% were in partial remission, 11% still met full criteria for BN, 0.6% met criteria for AN, and 18.5% met criteria for an unspecified eating disorder [24]. Longer duration between BN onset and presentation for treatment of BN was a significant predictor of poorer outcome. Lifetime history of substance use problems and diagnosis of a substance use problem at baseline predicted more recent binging and purging episodes in participants at follow-up.

Binge Eating Disorder

CBT, behavioral weight loss (BWL), or a combination of the two are the first-line treatments for BED [25, 26]. Pharmacotherapy is an efficacious adjunct treatment, which can help improve eating behaviors and weight, but cannot produce significant changes in eating disordered cognitions. In terms of reduction and elimination of binge eating and eating disorder cognitions, CBT typically outperforms BWLT. However, in terms of weight loss, BWL outperforms CBT. CBT produces larger reductions in binge episodes as compared to other psychotherapies (interpersonal, humanistic, and psychodynamic therapies) and self-help treatment [25]. Internet-based CBT guided self-help programs are generally slower-acting and less effective than in-person CBT sessions for individuals with subclinical and clinical binge eating disorder, although little research exists comparing telehealth and in-person delivery modalities for CBT [27].

Treatment choice is largely dependent on the patient's goals for treatment, weight status, level of eating disorder psychopathology, and psychiatric comorbidities. When a patient with BED presents with a desire to lose weight, has overweight or obesity, and has mild eating disordered behaviors and cognitions, behavioral weight loss (BWL) would likely be the treatment of choice. In this case, a clinician should also tell the patient that he/she can discuss pharmacotherapy options with his/her doctor if this is of interest. When a patient with BED presents with severe disordered eating behaviors and cognitions, regardless of their weight status or desire to lose weight, CBT would be the treatment of choice and transition to BWL could occur once eating disorder psychopathology significantly improved. Combined treatment might be optimal if a patient has overweight or obesity, desires to lose weight, and has moderate eating disordered behaviors and cognitions.

Prognosis in Binge Eating Disorder

One study followed a sample of 62 inpatients with BED, with a follow-up at 12.6 years [28]. Mean age at follow-up was 41.8 years. At follow-up, 36% of the patients with BED still met criteria for the disorder. Patients with BED reduced their mean BMI from 34 at admission to 32 at 12.6 year follow-up. Psychiatric comorbidity and higher BMI at baseline predicted worse general severity of BED at follow-up. Impulsivity predicted worse bingeing episode outcome at follow-up.

Avoidant/Restrictive Food Intake Disorder

CBT for ARFID, typically 20–30 sessions, is the primary treatment in children 10 years of age and older [9]. Preliminary data show improvements in weight, nutritional deficiencies, and dietary variety. For patients with ARFID who have underweight, increasing dietary volume and correcting nutritional deficiencies are the first goals, followed by increasing dietary variety. For individuals with normal weight, maintaining or increasing dietary volume and increasing dietary variety can be targeted simultaneously. A primary aspect of treatment is behavioral exposure to avoided foods, both inside and outside of psychotherapy sessions.

Rumination Disorder

The first-line evidence-based treatment for RD is diaphragmatic breathing [10]. The diaphragmatic breathing leads to abdominal wall relaxation and is believed to operate as a competing response to the abdominal wall contractions seen in RD. A health professional can teach diaphragmatic breathing to the patient with RD and develop a post-meal diaphragmatic breathing schedule with the patient. If the patient is also triggered by exercise, stress, or other stimuli, the health professional can also structure breathing practice around these activities. Case studies have suggested that using various cognitive-behavioral strategies can also be helpful with RD (e.g., cognitive restructuring, behavioral exposure to frequently regurgitated foods or other triggering stimuli, emotion coping strategies to manage premonitory urges). If a patient with RD is significantly underweight, inpatient treatment with enteral feeding may be necessary for medical stabilization. If a patient with RD has eating disorder symptoms not encompassed in the RD diagnosis (e.g., overexercise, restrictive eating for weight loss), he/she should also receive evidence-based treatment for that eating disorder.

Purging Disorder

No randomized-controlled trials have examined treatment for PD [6]. However, a case series reported that in 57 women who received 16 sessions of CBT, 17.5% achieved full remission and 24.6% achieved partial remission [29].

Night Eating Syndrome

One uncontrolled clinical trial indicated that a 10-session course of CBT for NES was able to significantly reduce evening hyperphagia and frequency of nocturnal ingestions [12]. One randomized-controlled trial comparing three groups across a 21-day intervention demonstrated that engagement in psychoeducation groups and a psychoeducation plus progressive muscle relaxation group (PMR) resulted in significant reductions in evening hyperphagia and nocturnal ingestions, and the group that practiced PMR showed a significantly greater reduction in evening hyperphagia as compared to those who only received psychoeducation [30].

Pharmacological Treatment for Eating Disorders

Psychotropic medications serve various purposes in the treatment of eating disorders, and Table 11.1 provides an overview of effective behavioral and pharmacological treatments. They can be used to augment treatment in patients that have not responded strongly to psychotherapy, for patients who do not have access to psychotherapy for eating disorders, for patients who have comorbid mental health disorders, and/or for patients who have a preference for medication treatment rather than psychotherapy, with the exception of patients with AN [31].

There are no FDA-approved medications for the treatment of AN [32]. There is no evidence that psychotropic medications can effectively treat the core symptoms of AN although psychotropic medications can be added to treat comorbid mental health conditions [5, 18]. Sometimes a second-generation antipsychotic, such as olanzapine, is used in addition to psychotherapy to induce weight gain in patients with AN, but many patients with AN are not willing to take a medication known to cause weight gain [31]. No clinical trials have investigated the use of psychotropic medications to treat ARFID or purging disorder [6, 9]. However, a small uncontrolled study has indicated that the tetracyclic antidepressant mirtazapine may be helpful in promoting weight gain in patients with ARFID [31].

Selective serotonin reuptake inhibitors (SSRIs) are helpful in the treatment of bulimia nervosa (BN), binge eating disorder (BED), and night eating syndrome (NES). Fluoxetine, sertra-

line, citalopram, and escitalopram are effective in reducing symptoms of BN and BED [31, 33]. The SSRI fluoxetine is the only FDA-approved medication for bulimia nervosa. Sertraline and escitalopram can effectively reduce night eating symptoms, with sertraline helping with weight loss among those with overweight or obesity [12]. The serotonin-norepinephrine reuptake inhibitor duloxetine improves symptoms of BED [31]. The unicyclic antidepressant bupropion improves symptoms of BED, but immediate-release bupropion is contraindicated in patients with BN due to medical consequences of purging and the lowered seizure threshold that this medication produces. Various tricyclic antidepressants (desipramine, amitriptyline, imipramine) and the monoamine oxidase inhibitor phenelzine are other effective treatments for BN.

The stimulant lisdexamfetamine dimesylate is the only FDA-approved medication for BED and has been approved for use for moderate to severe BED in adults since 2015 and is able to significantly reduce binge eating episodes and reduce body weight [25, 32, 33].

The mood stabilizer lamotrigine successfully reduces symptoms of BED [31]. The anticonvulsant topiramate has shown promise for reducing binge eating and weight in those with BED and binge eating and purging in those with BN [33]. Zonisamide is another anticonvulsant that is helpful with binge eating and weight in patients with BED. However, the use of anticonvulsants is limited by their undesirable side effect profile. Preliminary evidence shows reductions in binge episodes with the glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide [34]. These new GLP-1 receptor agonist agents (e.g., semaglutide, tirzepatide) are promising for BED, but more research is needed.

Finally, for RD, one placebo-controlled trial suggested that baclofen (an antispasmodic agent) reduced regurgitation frequency more than a placebo agent [10]. Thus, for patients who do not respond to diaphragmatic breathing and indicated cognitive-behavioral techniques, baclofen use could be considered.

Effects of COVID-19 on Eating Disorders

Few studies have been completed examining the effect of the COVID-19 outbreak on eating disorders. One sample of 42 patients with BED had been involved in a treatment trial for BED 3 years earlier and were interviewed before and after COVID-19 lockdown [35]. Participants showed a significant increase in binge eating episodes for the month during lockdown as compared to before the COVID-19 outbreak. Binge eating episodes were at a similar level during lockdown as compared to the end of the BED treatment trial but eating disorder pathology was higher during lockdown than at the end of the BED treatment trial. This increase in binge episodes and eating disorder psychopathology may be explained by spending more time at home near to the kitchen, loss of one's typical routine/structure, life stressors (unemployment, financial stress, stress related to caretaking, etc.), purchasing large quantities of pre-packaged, processed foods due to changes in grocery shopping behaviors, or other factors.

Various researchers have hypothesized about the possible negative effects of COVID-19 on eating disorders [36, 37]. COVID-19 interrupted face-to-face care of individuals with eating disorders, as many programs temporarily shut down, switched to telehealth platforms, or modified programs temporarily. The care of patients with eating disorders changed fundamentally during COVID-19 lockdown and some patients may have received less quality care for the months during lockdown. Some patients may have avoided entering care during lockdown due to fears of infection in hospital settings. COVID-19 has led to significant stress about many matters, including fear of infection or fear of loved ones getting infected, new work stressors (e.g., switching to providing education or care as a professional using digital platforms, fewer staff working in certain departments due to layoffs), fear of losing one's job, unemployment, financial insecurity, taking care of children while working, etc. These stressors have also been coupled

with social isolation, due to recommended social distancing practices and government mandates related to social gatherings. Stress and social isolation could trigger more eating disorder cognitions and behaviors. During quarantine, gyms and other health practices were closed. This may have interfered with positive health routines for those with eating disorders. Greater exposure to social media during COVID-19 may have increased exposure to images of thin or muscular individuals, which may be triggering for those with eating disorders. Another consideration is that COVID-19 has led to financial instability for many and food insecurity. Food insecurity has been shown to be positively associated with binge eating, bulimia nervosa, and obesity. Stress related to food insecurity may trigger binge eating, and this binge eating may result in higher levels of guilt, due to limited financial resources. For those with restrictive eating, reduced stock of certain foods at grocery stores may lead to greater restrictive eating practices. In time, research studies will be able to determine which consequences of the pandemic were most significant in those with eating disorders.

Prevention

Universal prevention efforts for eating disorders target a broad sample with varied level of risk for eating disorders, typically adolescents [38]. These efforts are often implemented in the form of programs based in middle and high school. Selected prevention efforts for eating disorders target individuals at increased risk for eating disorders, usually late adolescents and young adults. Indicated prevention efforts for eating disorders target individuals with subthreshold eating disorders. These programs are commonly implemented with college students. Additionally, competitive athletes, particularly in appearance- and weight-based sports, are at increased risk for developing eating disorders and would likely benefit from increased monitoring of possible symptoms and prevention efforts [39–41].

A research group conducted a systematic review of nine eating disorder prevention programs with at least a 6-month follow-up that have shown to be effective at reducing eating disorder pathology or preventing the onset of eating disorder pathology [38]. Description and results for the nine programs are below.

The Weigh to Eat is a 10-week program that was developed by Neumark-Sztainer and tested in 1995 in high school students [38]. The program is based on social-cognitive theory and focuses on healthy eating, exercise, media literacy (understanding the effects of media on body-image and self-esteem), and assertiveness related to health behaviors. The intervention group reported lower rates of eating disorder pathology (unhealthy dieting and binge eating) at 2-year follow-up compared to controls.

Stewart et al.'s 6-week cognitive-behavioral, school-based program was studied in middle and high school girls in 2001 [38]. The results revealed that girls in the intervention group reported greater reductions in dietary restraint and eating disorder pathology at 6-month follow-up as compared to the control group.

Planet Health was developed by Austin et al. and tested in 2005 [38]. It is a 32-session school-based program that focuses on health behavior changes (nutritious dietary choices, exercise, sedentary behaviors) and is based on social-cognitive theory. Students in schools that had higher exposure to the Planet Health program had lower odds of reporting disordered weight control behaviors (e.g., vomiting, laxative use, and diet pill use) after 3 years.

Student Bodies, developed by Taylor et al. and tested in 2006, is an 8-week online cognitive-behavioral program for college women with high weight and shape control concerns [38]. Individuals who received this intervention showed significant reductions in body dissatisfaction, drive for thinness, and eating disorder pathology at 1-year follow-up.

The Body Project is a brief 3-session cognitive dissonance intervention developed and tested by Stice et al. in 2006 for adolescents with high body dissatisfaction [38]. The Body Project has participants engage in verbal, written, or behavioral exercises that convey opposition to the current thin cultural beauty ideal. The Body Project

participants had greater reductions in thin-ideal internalization, body dissatisfaction, dieting, and eating disorder pathology at 1-year follow-up compared to a control group and alternate intervention group. Furthermore, the Body Project participants had a greater reduction in their risk of eating disorder pathology onset at 3-year follow-up, compared to controls. This program has also been adapted for college students.

The Healthy Weight program is a 3-session behavioral weight loss program designed by Stice et al. and tested in 2006, which is designed to promote nutrition and physical activity in adolescents as was designed as a comparison intervention for the Body Project [38]. The Healthy Weight program for adolescents showed reduced risk of eating disorder pathology onset at 3-year follow-up compared to controls. The Healthy Weight-2 program for college students showed lower body dissatisfaction and eating pathology at 2-year follow-up and reduced risk of eating disorder pathology onset at 2-year follow-up compared to controls.

New Moves is a 16-week program developed by Neumark-Sztainer et al. that was tested in 2010 [38]. It is a program designed for high school girls with overweight or who are at risk of overweight. This program is based on social-cognitive theory and is designed to prevent and reduce eating disorder psychopathology and weight difficulties. Girls who received this intervention showed significant improvements in body satisfaction and reductions in eating disorder pathology (e.g., skipping meals, fasting) at 9-month follow-up compared to controls.

An untitled 12-week program developed by Yager and O'Dea that was tested in 2010 was developed for college students majoring in health or physical education, who are a high-risk group [38]. This program featured psychoeducation on healthy weight control, nutrition, several cognitive dissonance components, and other topics. The dissonance components produced a reduction in excessive exercise through 6-month follow-up in the intervention group as compared to the control group.

Eating, aesthetic feminine models, and the media was developed by González et al. and tested in 2011 [38]. This 4-session program was developed for middle schoolers and is based on social cognitive theory. The program focuses on media literacy, by critically examining the accuracy of media images and their portrayal of beauty. One version of the program also provides psychoeducation on nutrition. Students who received the program as compared to control participants had lower eating disorder pathology and reported that their body satisfaction was less influenced by sociocultural ideals of beauty at 30-month follow-up.

Most of these nine prevention programs were able to reduce eating disorder pathology such as dieting, body dissatisfaction, and thin-ideal internalization [38]. The Body Project and Healthy Weight program had the additional benefit of reducing the risk of onset of eating disorder pathology compared to control groups over 2–3 year follow-ups. Eleven randomized-controlled trials have investigated programs to address eating psychopathology in athletes, primarily in high schools and universities [41]. Eight of the 11 programs demonstrated significant reductions in eating psychopathology for those in the intervention groups, as compared to control groups, from pre- to post-intervention, showing moderate to large effect sizes. A few of these studies have shown reductions in eating disorder cognitions and behaviors over follow-ups of 6 weeks to 3 years.

Conclusions

Eating disorders range from severe caloric restriction to severe overeating. Extreme dissatisfaction with weight and shape is present across most of the diagnoses. For anorexia nervosa (AN), weight restoration is the first goal, followed by psychological improvements. In adolescents, the most effective approaches are inpatient treatment involving the family and a multi-disciplinary team or family-based outpatient treatment, primarily dependent on the patient's weight and medical status. For adults with AN, there are a number of inpatient and outpatient psychotherapy varieties to choose from. For bulimia nervosa (BN), CBT is the preferred approach and SSRIs,

tricyclic antidepressants, and topiramate can be a helpful addition to treatment. For binge eating disorder (BED), CBT and/or BWL are the mainstays of treatment, with lisdexamfetamine, topiramate, and SSRIs as helpful additions to treatment. Night eating syndrome (NES) can be effectively treated with CBT, sertraline, escitalopram, psychoeducation, and progressive muscle relaxation. Currently CBT for ARFID is under investigation, with preliminary findings showing positive effects, and diaphragmatic breathing remains the most promising therapy for RD. Nine known eating disorder prevention programs have been shown to reduce eating disorder pathology. Specifically, the Body Project and Healthy Weight program reduced the risk of onset of eating disorder pathology compared to control groups over 2–3 year follow-ups.

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Part III

Nutritional Importance of the Parts of the Diet

Alcohol Consumption and Health

12

Ted Wilson and Norman J. Temple

Key Points

- The lowest risk of coronary heart disease (CHD) is seen at an alcohol intake of under 100 grams per week (one drink per day), but possibly less. This is also true for cardiovascular disease in general.
- As alcohol intake increases, so does the risk of cardiovascular disease, especially stroke and heart failure.
- A similar J-shaped relationship has also been reported for several other disorders.
- Risk for various health disorders increases sharply in heavier drinkers (more than four drinks per day).
- Abuse of alcohol, especially binge drinking, is associated with accidents, violence, and suicide.
- Alcohol results in other negative health effects, most notably fetal alcohol syndrome and an increased risk of cancer.
- Life expectancy is longest when alcohol intake is between zero and one drink per day. As alcohol intake increases, life expectancy falls.
- The benefits of alcohol are seen in those aged over 50 or 60 years, but not in those aged under 40 years.
- The commonly used guidelines that set limits on alcohol consumption of one to two drinks per day may be a little too high.
- Alcohol is best consumed in small regular amounts rather than binge drinking.

Introduction

The widespread consumption of alcoholic beverages and their potentially harmful health impacts makes a discussion of this topic vitally important. The acute effects of alcohol (ethanol) consumption on behavior, motor function, and health risks are plainly observed in an emergency room on a Saturday night. The long-term effects of moderate consumption—years or decades rather than hours—are much less clinically obvious. There is much suggestive evidence that a moderate intake of alcohol is associated with enhanced health and well-being, especially with respect to cardiovascular disease and overall mortality, but alcohol consumption is also associated with increased rates of several types of cancer. Beer remains the largest single source of alcohol intake in the USA, although wine consumption has steadily increased to about 30% of intake, especially in women and those aged over 60 years [1]. The biological effects of a drink are mostly related

T. Wilson
Department of Biology, Winona State University, Winona, MN, USA

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_12

to its alcohol content, alcohol metabolites, and the other substances found in alcoholic beverages (i.e., sugars and phenolic compounds). This chapter briefly reviews the health effects of alcohol consumption.

The majority of Americans consume alcoholic drinks, at least occasionally: a national survey carried out in 2019 reported that among American adults 59% of men and 51% of women stated that they consumed at least one drink in the previous month [2]. An important aspect of alcohol consumption is binge drinking. This is commonly defined as consuming four drinks for women or five drinks for men in about 2 h. The above national survey reported that 30% of adult men and 22% of adult women had engaged in binge drinking in the previous month [3].

A Look at Alcoholic Beverages

Appreciating the quantity of alcohol consumed is important for assessing the potential impact of alcohol on health. In the USA, a drink is defined as containing 14 g or 0.6 fluid ounces of alcohol. The volume of different beverages that contains one drink is shown in Fig. 12.1 [3]. Beer typically has an alcohol content of about 5%. But this can vary from 3 to 9%; this means that a 12 oz (355 mL) bottle or can provide between 0.6 and 1.8 drink equivalents (8.4–25.2 g alcohol). Wine has an alcohol content of about 12% while spirits are about 40%. Containers of alcoholic beverage in the USA are required to state the percent alcohol content. When one considers the wide range of bottle sizes, glass sizes, and percent alcohol content, it is little wonder that consumers are often confused; this can play an important role in overconsumption.

Most alcoholic beverages have additional calories because of their content of carbohydrates. Typically, a glass of wine or a can of beer contains about 100–140 kcal. However, this can be quite variable; a sweet wine, for example, may have 240 kcal per glass while some brands of "light beer" are low in sugar and therefore have few nonalcoholic calories. A can of light beer may therefore have as little as 110 kcal.

Alcohol is not technically a nutrient but is a source of calories (7 kcal/g). One drink therefore delivers about 98 kcal of energy from alcohol. Alcohol is primarily metabolized in the liver. Alcohol dehydrogenase converts ethanol into acetaldehyde which is then converted by acetaldehyde dehydrogenase into acetate. The acetate

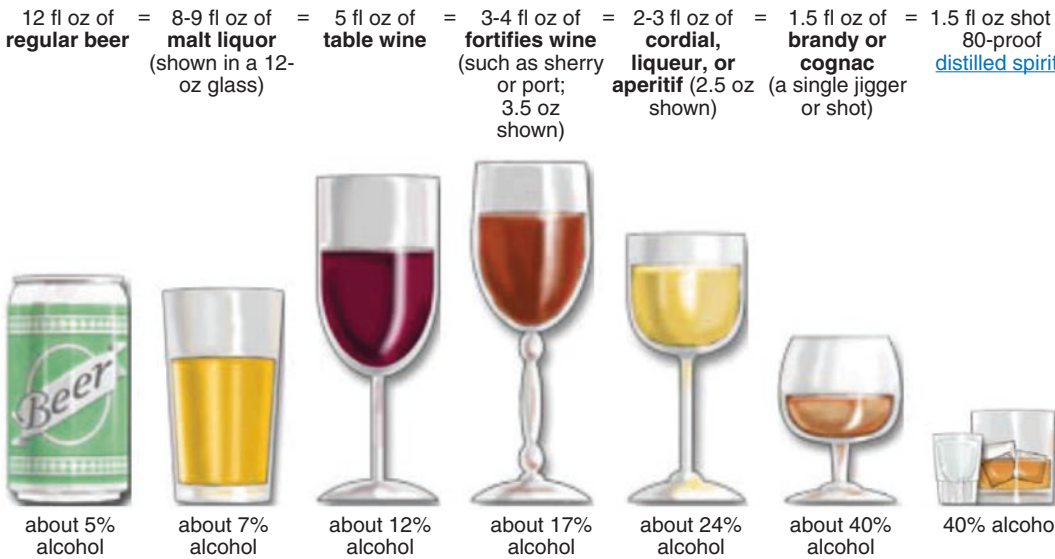

Fig. 12.1 Equivalent beverages volumes that provide the US definition of one "drink" containing 14 g of alcohol [3]

can then be converted to fatty acids or oxidized to carbon dioxide in the mitochondria.

Possible Beneficial Health Effects Associated with Alcohol Consumption

Alcohol and Coronary Heart Disease

A substantial body of epidemiological evidence has accumulated over the past several decades regarding the relationship between alcohol intake and health. A major analysis of this evidence was published in 2018 [4]. The focus of that study was on cardiovascular disease and total mortality. The authors combined the findings from 83 prospective cohort studies that included, in total, 787,000 subjects. These numbers dwarf previous studies. For that reason, the following discussion relies heavily on the findings reported in that study.

Many cohort studies have reported a clear negative association between moderate alcohol consumption and risk of coronary heart disease (CHD). These findings suggest that moderate consumption—one or two drinks per day—reduces risk. Millions of people have been more than happy to accept these findings as they seem to justify drinking moderate amounts of alcohol. Alcohol may therefore be a welcome exception to the rule: all the best things in life are illegal, immoral, or fattening.

This epidemiological story has generated heated debate in the medical literature because of possible sources of error. This reflects the pitfalls that often arise when interpreting the findings of epidemiological studies. There has been an active debate on this question for many years with little sign of settlement. We must therefore be hesitant before coming to a firm conclusion that a moderate intake of alcohol does indeed offer a significant degree of protection against CHD.

Taking all this evidence together, what can we reasonably conclude? The lowest risk of CHD is seen at an alcohol intake of about one drink per day, but possibly less. This also appears to be the case for cardiovascular disease in general. There is no dispute that as alcohol intake climbs, so does the risk of cardiovascular disease, especially stroke and heart failure.

Research studies indicate that alcohol brings about an increase in the blood level of HDL-cholesterol [5, 6]. This is likely to be an important mechanism by which alcohol achieves a protective action against the risk of CHD. Other significant factors that help explain why alcohol may lower the risk of CHD are the blood level of HbA_{1c} and fibrinogen [5].

Alcohol and Diverse Health Problems

There are several other disorders besides cardiovascular disease where a J-shaped relationship between alcohol consumption and risk has been observed [7, 8]. This means that people who consume alcohol in moderation have a lower risk of those disorders than that seen in non-drinkers, while risk increases sharply in heavier drinkers (more than 4 drinks per day). This serendipitous discovery has been made for the cognitive decline that occurs with aging. It is well known, of course, that heavy drinking has a damaging effect on brain function. But research has revealed that moderate drinkers actually have an enhanced cognitive ability or a slower rate of decline with aging [9]. This effect is generally more pronounced in women. These benefits may even extend to the risk of dementia, mostly Alzheimer's disease. Similar findings have been reported for type 2 diabetes.

That excessive alcohol intake leads to poor erectile function is well known. As Shakespeare put it: "It provokes the desire, but takes away from the performance" (Macbeth, Act 2, Scene 3). Although erectile dysfunction was originally thought to be purely psychogenic in nature, 80-90% is likely due to biological factors that may share a similar profile to the effect of nitroglycerin in those experiencing angina. Research findings have pointed to a modest beneficial effect of moderate alcohol consumption [10]. In the case of erectile dysfunction, therefore, a J-shaped curve appears to be true in more ways than one.

Reports have appeared which suggest that alcohol in moderation may also be protective against the following conditions: gallstones, hearing loss, chronic obstructive pulmonary disease (COPD), and benign prostatic hyperplasia. Alcohol is also associated with a higher bone mineral density which implies protection against osteoporosis. However, alcohol poses an obvious risk to elderly drinkers as they may be more likely to suffer injuries if they have a fall.

These findings suggest that a moderate intake of alcohol provides some protection against the health problems mentioned above. But we must be cautious before jumping to bold conclusions that the observations reflect a cause-and-effect relationship. This is because of possible sources of error in the epidemiological evidence. The same problem was mentioned earlier with respect to the relationship between alcohol intake and risk of CHD.

Harmful Effects of Alcohol

Alcohol consumption has myriad effects on the body, many of which are damaging to health. For example, one potentially harmful effect of alcohol is that it may alter the efficacy, metabolism, and effect of medications.

Accidents, Violence, and Suicide

It is well established that abuse of alcohol, especially binge drinking, is associated with accidents, violence, and suicide. Alcohol use is a predictive factor for domestic and child abuse, It is a factor in about one-third of all traffic-related deaths in the United States. The most dramatic evidence of the dangers of binge drinking comes from Russia. Between 1984 and 1994, there was serious economic decline and great political turmoil in that country. At the same time, there was a dramatic jump in mortality rates reflected by a decline in life expectancy of 4 years in men and 2 years in women. A major factor was apparently widespread alcohol abuse, particularly binge drinking, which led to large increases in deaths from accidents, homicide, and suicide, as well as heart disease and stroke [11, 12].

Chronic Alcohol Abuse

For many people, years of alcohol abuse eventually lead to chronic nutritional and health problems. Alcoholic beverages have a very low content of nutrients, apart from some sugars and minerals, and, in some cases, limited amounts of amino acids. Hard liquors, in particular, have negligible quantities of anything apart from alcohol. Heavy drinkers are at high risk of malnutrition, especially for folate and thiamin (Wernicke–Korsakoff syndrome). The end result following years of heavy drinking is fatty liver, alcoholic hepatitis, and, eventually, cirrhosis. The consumption of hard liquor is more strongly associated with alcoholism, cirrhosis, and accidental death than is the case with beer or wine.

Alcohol and Pregnancy

Alcohol use during pregnancy can induce fetal alcohol syndrome (FAS). This irreversible condition encompasses a variety of symptoms that include prenatal and postnatal growth retardation, mental retardation, and the hallmark clinical sign of abnormal facial features. A subclinical form of FAS is known as fetal alcohol effects (FAE). Children with FAE may be short in stature or have only minor facial abnormalities, or develop learning disabilities, behavioral problems, or motor impairments.

Four drinks per day poses a real threat of FAS, although one or two drinks per day may still retard growth; the epidemiological data are weaker and somewhat inconsistent at these lower levels of consumption. Women who have an occasional drink during pregnancy should not fear harming their fetus. However, the lower limit of alcohol intake associated with increased risk of FAS remains unknown. For this reason, it is generally accepted that any woman who is or might be pregnant should abstain from alcohol.

Alcohol and Cancer

Breast cancer risk increases for women at levels as low as 5–15 g/day of alcohol [13, 14]. An alcohol intake at the high end of moderation (2 drinks per day in women, 4 in men) is associated with relative risks (RRs) for different types of cancer as follows: 1.8 for mouth and pharynx, 2.4 for esophagus, and 3.0 for liver [15]. For all types of cancer combined, a significant risk is seen at an alcohol intake of 4 drinks per day, with a RR of 1.22 [16]. Colorectal cancer manifests a rather different pattern: there is a J-shaped relationship with this type of cancer [17]. The RR is 0.92 for an intake of up to 2 drinks per day, suggesting a minor degree of protection. But when intake exceeds 3 drinks per day, the RR climbs to 1.25. Much like other diseases, heavy consumption of alcohol is associated with a substantially increased risk of several types of cancer.

The relationship between alcohol and cancer, including the possible mechanisms by which alcohol increases the risk of cancer, is further discussed in Chap. 10 by Murphy and Mushashi.

Alcohol and Body Weight

The effects of alcohol consumption on body weight are unclear. Alcohol, of course, is a source of calories (7 kcal/g) and, as mentioned earlier, most types of wine and beer also contain carbohydrates that add additional calories. A half-liter of wine contains about 350 kcal while 3 cans of beer provide about 250–450 kcal, clearly enough to tip the energy balance well into positive territory. These numbers help explain the popularity of low-calorie "light beers." It is predictable, therefore, that alcohol consumption should be associated with excess weight gain, but is this actually the case in the real world?

Several long-term cohort studies have been carried out to examine the relationship between alcohol intake and body weight. In the Health Professionals Follow-up study, a cohort study of 16,600 men aged 40–75, change in alcohol intake was not associated with change in waist circumference over 9 years of follow-up [18]. In the Women's Health Study, a cohort study of 19,200 women who had a normal BMI at baseline, alcohol intake displayed a clear negative association with risk of becoming overweight or obese over the following 13 years [19]. In sharp contrast, other cohort studies have reported a positive association between alcohol consumption and weight gain [20]. At present, therefore, it is far from clear whether alcohol intake poses a risk for weight gain [21, 22].

Effect of Alcohol on Total Mortality

Alcoholic beverages have many different effects on health. The dose–response relationship seems to vary from one disorder to the next. This begs the question: What is the impact of different levels of alcohol intake on total mortality? Here, age is an important variable. For younger people (below age 40), alcohol can cause much harm while doing very little to improve health. That is because the leading cause of death in Americans under age 40 is accidents, with homicide and suicide also being major causes, especially in men. They are all linked to excessive consumption of alcohol. The sole positive attribute of alcohol for people in this age group is providing enjoyment.

It is only among people older than about 50 or 60 where alcohol consumption in moderation may cause a reduction in total mortality. At that age, the possible health benefits, especially the prevention of heart disease, dominate the picture. As a result, it is among this age group that we see a J-shaped relationship between alcohol intake and risk of mortality. The critical importance of age in determining the relationship between alcohol intake and total mortality is illustrated by a report from the Nurses' Health Study. A moderate intake of alcohol has a protective relationship with total mortality in women aged over 50 years (RR is 0.80–0.88) but is associated with a doubling of the risk of death in those aged 34–39 years [23]. Similar findings were reported from England and Wales: a net favorable mortality outcome was seen only in men over age 55 and women over 65 years [24]. But, as with

CHD, there is debate as to whether this protection is real or spurious [25].

The best evidence for the effect of alcohol on life expectancy comes from the study that was described earlier that pooled the findings from 83 prospective cohort studies and included 787,000 subjects. This study concluded that for persons aged between 40 and 50 life expectancy was longest when alcohol intake was under 100 g/week (between zero and one drink per day) [4]. As alcohol intake went up, life expectancy fell as follows:

- by 6 months at an intake of 100–200 g/week (between one and two drinks per day),
- by 1.8 years at 200–350 g/week (between two and 3.5 drinks per day),
- and by almost 5 years at over 350 g/week (3.5 drinks per day).

These highly credible findings led the authors to conclude that current guidelines set limits on alcohol consumption that are too high.

Drinking Pattern

Many studies have investigated the relationship between the pattern of drinking and health outcomes. The findings demonstrate that alcohol is most protective when consumed in small regular amounts rather than binge or episodic drinking. This has been demonstrated for total mortality, cardiovascular disease, hypertension, and type 2 diabetes. These findings are hardly surprising: many dietary components cause no harm in small, frequent doses but are toxic when a large dose is taken.

Phytochemicals in Alcoholic Beverages

While we can confidently state that a diet rich in foods that contain an abundance of phytochemicals, such as fruits and vegetables, is likely to be healthy and should be recommended, there is still a great deal to be learned about the disease-preventing action of specific substances. Many alcoholic beverages, especially red wine and dark beers, contain a variety of phytochemicals with biological activities that may interact with the health effects of alcohol. These phytochemicals come from the raw plant foods from which the particular beverage is fermented. Knowledge regarding the thousands of phytochemicals in alcoholic drinks is still quite limited. Most of these phytochemicals are phenolics. The topic of phytochemicals is discussed in detail in Chap. 14.

Red wine contains phenolic compounds such as resveratrol, tannins, and catechins. These substances have been associated with antioxidant protection, vasodilation, inhibition of platelet aggregation, and improved plasma cholesterol profile. Beer, particularly darker ones, tends to have a higher phenolic content and greater antioxidant capacity relative to light beers. However, spirits, because of the distillation process, usually have a very low content of phytochemicals.

It has long been speculated that red wine may be especially beneficial for the prevention of CHD. This is based on the so-called French Paradox. It was noticed many years ago that French people have a surprisingly low rate of CHD in comparison with some northern European countries, such as the United Kingdom [26]. This could not be easily explained by the "usual suspects" as France has high rates of both smoking and consumption of foods rich in saturated fat. It was reasoned that the explanation for the French paradox could be found in the popularity of red wine in that country and the phenolic compounds that give red wine its color.

But when we carefully examine the evidence as a whole, red wine does not appear to live up to the hype [27]. Cohort studies indicate that all types of alcoholic beverages—wine, beer, and spirits—have a similar association with risk of CHD. It is true that some cohort studies have reported a lower risk of CHD in wine drinkers than in consumers of other types of alcoholic beverages. Possible explanations for this are as follows: drinking pattern (i.e., wine is often consumed in moderation with dinner) and that wine drinkers tend to have a higher socioeconomic status (which is associated with a lower risk of

CHD). What is a reasonable conclusion from this rather inconsistent evidence? It appears that red wine provides little or no protection against CHD beyond that provided by other alcoholic beverages.

Conclusions

Clearly, alcohol can do much harm. But it can also provide potential health benefits. Based on the evidence reviewed here, the healthiest level of drinking is a maximum of one drink per day. The more common limit of one to two drinks per day may be a little too high.

It is important to bear in mind that the beneficial effects of alcohol mainly occur in those folk aged over 50–60 years and the most harmful societal effects of alcohol occur in those under 40. The large majority of the harmful effects of alcohol can be avoided by sensible drinking, by drinking in moderation, and by the avoidance of alcohol when driving.

Despite the potential health benefits of light or moderate drinking, it is not appropriate to advise non-drinkers to commence drinking. A major reason for this is that around 5–10% of alcohol users become problem drinkers. However, if a person is already a light drinker and has no sign of an alcohol-related problem, there is little reason to advise them to stop. For the person who can drink sensibly and can avoid alcohol's negative side, alcohol can be of considerable benefit. Like so much else in life, it's a matter of balance. While alcohol should perhaps not be prescribed [28], neither should it be proscribed.

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13 Nonalcoholic Beverages: Clinical Recommendations, Concerns, and Opportunities

Ted Wilson and Anne Roesler

Key Points

- The hydration requirements of the body are met by water and many other beverages that also provide nutrients and potential caloric intake.
- Potable water remains the best source of hydration.
- Consumption of tea and coffee is associated with health benefits and relatively few health risks.
- Cow's milk is a nutrient-rich beverage, while plant-based milk alternatives have a variable nutrient content; they are becoming ever more popular.
- Juices can provide a way to increase fruit and vegetable consumption, although juice should not be used as a complete substitute for whole fruit and vegetables.
- Sugar-sweetened beverages are associated with potential excess caloric intake and increased health risks so intake should be limited; non-nutritive sweeteners may or may not be preferable from a health perspective.
- Energy drinks provide caffeine although clinical studies demonstrating deleterious human health are difficult to find.

Introduction

Water intake plays a major role in determining overall nutritional health and is the most commonly consumed nutrient on the planet. In addition to tap water, sources of water include tea, coffee, milk, fruit and vegetable juices, soft drinks and other sugar-sweetened beverages (SSB), energy drinks, sports drinks, and weight management drinks. Alcohol is present in many beverages and clearly affects human health. It was discussed in detail in the prior chapter by Wilson and Temple. Determining the nutritional consequences of beverages and even tap water is complicated by their content of fluoride, sugars, fats, minerals, vitamins, caffeine, and many other substances. These substances can alter the taste and nutritional consequences of beverages. For persons over age 20, beverages account for 54% of total added sugar intake by both sexes, representing 24% and 23% of total caloric intake of men and women, respectively, and are consequentially important in terms of weight management and total nutrition [1]. This chapter reviews the many ways that nonalcoholic beverages impact human health. Much more detailed information is presented in another book in this series [2].

T. Wilson (✉) · A. Roesler
Department of Biology, Winona State University, Winona, MN, USA
e-mail: twilson@winona.edu; ao9201aq@go.minnstate.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_13

Water

Water represents approximately 60% of a healthy person's total body weight, and 45% in obese individuals. This helps explain why obese persons are more vulnerable to dehydration than are those of a healthy weight. Daily water intake must be sufficient to account for losses that are part of our normal physiological functions, such as perspiration, ventilation, urination, and bowel movements. For adults who are not exercising, the adequate water intake from all food and beverage sources is approximately 2.7 and 3.7 L/day for women and men, respectively [3]. Water needs during exercise increase by about 1 mL for each kcal of energy utilized. When we ingest water from a tap or other source, there are invariably contents, besides H_2O, that can also affect our health as outlined by the WHO [4].

While water is the most common substance on Earth, human access to drinkable and safe water remains a major concern. Serious problems caused by unsafe drinking water still emerge even in the USA. One well-known example occurred in Flint, Michigan, which has struggled for years with lead contamination in its tap water [5]. In 2017, the WHO estimated that two billion people were drinking water contaminated by human feces [6]. In contrast, the fluoridation of tap water helps prevent dental caries in much of the developed in the world and remains one of the top ten greatest healthcare achievements in the USA [7].

Socioeconomics describes how water is consumed and by whom. In Western societies, bottled water products, such as Fiji®, Voss®, Smart Water®, and VitaminWater®, are popular. These products often contain various substances such as supplemental vitamins, minerals, herbs, and taste essences. Some of these products actually contain a significant quantity of sugar and calorics, or non-nutritive sweeteners (NNS). While these products claim to be superior to tap water, there is seldom credible evidence that they are of truly superior nutritional value. To make matters worse, they can cost upwards of 5 dollars/gallon making them infinitely more costly than tap water and more likely to be consumed by persons with greater affluence.

The widespread consumption of bottled water also creates a significant environmental and carbon footprint. Vast numbers of plastic bottles are used for this purpose, most of which are not reusable and end up in landfills. Environmental problems are made much worse when the bottled water is imported from distant places, such as Greenland, Norway, or Fiji. For a cleaner (and possibly safer) tap water, a far cheaper and more environmentally friendly approach is to simply filter tap water (e.g., using a Brita®) into a reusable bottle.

Tea

Tea is the most popular beverage in the world after water. Leaves from the tea plant *Camellia sinensis* are the source of the traditional tea types, namely green, black, and oolong. These teas derive their color, taste, and chemical characteristics from the way their leaves are processed using non-fermented, fermented, and semi-fermented methods. There are also a plethora of "herbal tea" products which contain no tea leaves at all. These can be found at any supermarket. While popular the discussion of these products is outside the scope of this review.

The catechins represent a group of polyphenolic compounds present in green tea and, to a lesser degree, black and oolong teas. They may be responsible for various health benefits. Epigallocatechin-3-gallate (EGCG) is a catechin that makes up more than 40% of the total polyphenolic mixture and appears to be the polyphenol responsible for much of the beneficial effects of green tea [8]. Green tea catechins have been suggested to improve weight management and factors related to the metabolic syndrome, especially in overweight and obese persons [9, 10]. Although some evidence suggests that green tea improves glycemic control [11], findings are not consistent [12]. Regular consumption of green and black tea may also reduce the risk of cardiovascular disease and decrease overall mortality [13]. Another possi-

ble benefit of green tea is the prevention of influenza and COVID-19 [14, 15].

Maximal plasma concentrations for EGCG are achieved 1.3–2.4 h after consumption. It is classified by the FDA as "generally recognized as safe" (GRAS) and is a popular food additive and nutraceutical supplement. Tea also contains caffeine, though considerably less than in coffee, as well as theophylline, a substance similar to caffeine in both its chemistry and pharmacological effects.

Validating and determining the health impact of tea are difficult because people consume different kinds of tea, in different amounts, at different times in their life cycle, and because they have gut microbiomes that create different metabolomes. As a general guideline, consumption of up to 3 or 4 cups/day should be sufficient to provide health benefits and not be associated with any negative effects.

Coffee

Low-to-moderate coffee consumption (≤3 cups/day) is unlikely to cause harm and probably provides the consumer with health benefits as reviewed in greater detail by DiMaso et al. [16]. Caffeine is responsible for most of the stimulant effects of coffee consumption. Epidemiological studies show little or no association between coffee intake and most common neoplasms; indeed, there may be an inverse relationship with risk of colorectal cancer [17]. Coffee consumption has also been associated with neutral or moderately beneficial effects on blood pressure, cardiovascular disease risk, and overall mortality, as well as asthma control and protection against neurodegenerative diseases [18, 19]. In addition, recent evidence suggests that coffee consumption may lower the risk of type 2 diabetes [20] and slow cognitive decline [21]. These effects may or may not be partly attributable to caffeine; most studies have shown that decaffeinated coffee has less or no beneficial health effects.

The caffeine content of coffee is quite variable as are its stimulant effects. For example, Starbucks Blonde Roast, Dunkin' Donuts Coffee, and Starbucks Pike Place decaffeinated coffees contain 270, 162, and 19 mg caffeine per 12 oz cup, respectively [22], and these values are even more variable when we consider the method used for brewing. The type of coffee (American, French press, percolated, or espresso), the amount of coffee (1 oz espresso or 16 oz large mug), the duration of brewing, the type of coffee bean, and the conditions under which it was cultivated at the many different equatorial locations around the globe may all affect the phenolic and caffeine content of the coffee we actually drink. Collectively, these factors make it difficult to study the health effects of coffee.

When estimating coffee consumption, it is important to consider the size of the container, the habit of refilling the cup, the variability of coffee drinking between different days (weekdays/weekends), and seasonal differences in intake. A general guideline for coffee is at most 2–3 cups/day. However, there is scant evidence that higher amounts, say 5 cups/day, pose any significant risk to health.

Milk

Dairy milk consumption has long been recommended for meeting the requirements for calcium and vitamin B12 intake. Milk is an excellent medium for vitamin D fortification with an 8 oz serving containing about 100 IU of the vitamin. Vitamin D absorption is likely to be more efficient from milk that contains fat. Milk is also an excellent source of potassium, magnesium, and protein. The popularity of various recommendations for milk has had its ups and downs and ups over the last 20 years.

A recent review concluded that increasing low-fat dairy consumption, including low-fat milk, is associated with a lower risk of type 2 diabetes [23]. Consumption of dairy foods does not appear to alter the risk of diabetes after a myocardial infarct [24]. The findings from three cohort studies reported that dairy foods are not associated with risk of mortality, cardiovascular mortality, or cancer mortality [25]. However, these outcomes were each associated with intake of

full-fat (whole) milk. The effect of milk on the lipoprotein profile may be related to the fat content. However, in one clinical trial of persons with the metabolic syndrome, intake of dairy fat did not appear to affect blood lipids or blood pressure [26].

Low-fat milk has been suggested as being preferable to whole milk for weight control since the 1970s by virtue of its lower energy content, but recent evidence shows that this may be a misguided belief. Contrary to what had been widely assumed, a recent meta-analysis suggests that a diet with a higher content of milk fat (i.e., whole milk) is associated with lower childhood obesity [27]. Moreover, consumption of low-fat milk may not lower the risk of obesity in children. More research needs to be completed in order to definitively understand how dairy milk influences weight maintenance.

The above findings are suggestive that low-fat dairy foods, including low-fat milk, may be preferable to full-fat dairy for the prevention of type 2 diabetes, total mortality, and cardiovascular mortality, but the reverse is seen for childhood obesity.

Non-dairy milk is often preferred by those who do not consume dairy milk products for a variety of reasons that include lactose intolerance, dietary preferences (vegetarian), taste, or environmental sustainability. Plant-based milks were estimated to constitute upwards of 13% of the total US milk market in 2020 [28]. These milks are derived from almonds, palm, oats, rice, and other plants and are now widely accepted among consumers. Soy milk is the most popular. Almond milk contains the most calcium. Soy and cow's milk provide more than twice as much protein as the other milks [29]. While the nutritional content of cow's milk products is relatively consistent, the nutritional content of plant-based milks is more variable. Making any one recommendation that applies to all kinds of plant-based milk is more difficult because of the differing degree of nutritional content and supplementation [30].

Fruit and Vegetable Juices

Fruits and vegetables are an excellent source of many vitamins and minerals, as well as phenolic compounds. The benefits of eating fruit and vegetables for blood pressure reduction were demonstrated by the PRIME study of 2021 [31]. Consumption of 100% fruit juice does appear to be inversely associated risk with the risk of stroke (up to 200 mL/day) or total CV events (up to 170 mL/day) [32]. A high intake of these foods, including fruit juice, is associated with a lower blood pressure [32]. Although it is well known that fruit and vegetable intake is good for health, little research has been done to compare whole fruit and vegetable intake versus subtypes such as fruit and vegetable juices.

Only one in ten American adults meets the USDA recommended guideline for fruit and vegetable consumption [33]. For reasons of ease and convenience, converting a serving of whole fruit or vegetables to a serving of juice can be a useful way to increase consumption although this results in losing most of the fiber.

Fruit Juices

Juices are a popular way to increase fruit consumption because of their widespread accessibility, ease of storage, modest cost, and taste hedonics. The US food guide, MyPlate, recommends using 100% fruit juice as equivalent to a fruit serving [34]. The energy content of apple juice and orange juice (OJ) (110 kcal/240 mL serving) is about 6% higher than that of cola drinks. The energy content of white grape juice is even higher, around 150 kcal/240 mL. Despite this high energy content, the nutritional benefits of 100% fruit juice are far superior than SSB. Consumption of a 100% juice can provide a good source of several vitamins and minerals although it is still not a complete substitute for whole fruit [35].

Health Benefits of Citrus Juice

Orange juice (OJ) is the most commonly consumed citrus juice in the USA. It is also the most nutrient dense of the popular fruit juices. A 240 mL serving provides 124 mg of vitamin C (137% of Daily Value). It is also a good source of potassium (450 mg or 13% of DV), folate (60 μg or 15% of DV), and thiamin (0.15 mg or 10% of DV). Grapefruit juice is another citrus juice consumed by a great many people. It contains a similar amount of vitamin C to OJ, but has a lower concentration of potassium, and of several B-vitamins (folate, thiamin, and niacin). It also has a different profile of phenolic acids which may be responsible for an alteration of the metabolism of some cardiac medications, making it less appropriate for older persons or those likely to be prescribed medications for heart disease.

Epidemiological data, clinical investigations, and animal studies provide strong evidence that citrus juice consumption is beneficial with respect to coronary heart disease (CHD), cancer, and overall mortality [36]. Potassium functions to maintain intracellular fluid balance and, as such, a high intake is associated with lower blood pressure and a reduced risk of stroke. Consumption of OJ may help lower the LDL/HDL ratio and may also decrease LDL oxidation thereby reducing the risk of CHD. However, because the vitamin C in OJ readily oxidizes following exposure to air, especially when warm, it should be consumed within a week of opening, and stored in a sealed container in a cool place [37].

Vegetable Juices

Tomato juice has been popular for decades and may have health benefits due to the relatively high concentration of trans-lycopene, a phytochemical carotenoid that can be a precursor for vitamin A synthesis. Tomato juice and the lycopene it provides have been suggested to lower prostate specific antigen levels in men at risk of prostate cancer [38] and show promise in some but not all studies of cardiovascular disease risk factors [39]. However, the ability of circulating lycopene to reduce low-grade inflammation remains to be confirmed [40].

Although tomato juice appears to have health benefits, it is important to note that many brands contain much added salt (as high as 560–660 mg sodium/cup). Some brands, such as V8, do have a low-sodium option that is prominently stated on the label. These juices can have a relatively low energy content (50 kcal/cup as compared to 110 kcal/cup in OJ and apple juice). It is also important to recognize that many vegetable drinks include pear, white grape, or other juices as a source of sweeteners. Sugar calories from juice become mostly glucose in the body, regardless of whether they come from high-fructose corn syrup (HFCS), pear, apple, or sugar cane juice.

In recent years, green juices and smoothies have become popular. These are made from mixtures of vegetables, such as celery, kale, spinach, cucumber, and parsley. The health claims in the popular media for these juices include reductions in inflammation, cardiovascular disease risk, promoting healthy digestion, and increase in the metabolic rate. However, in a randomized trial, green juice failed to bring about significant changes in metabolic function [41].

Recommendations for Consumption of Fruit and Vegetable Juices

It is well known that calories in a beverage have far less ability to satiate the appetite relative to solid foods [42]. For that reason it is easier for caloric overconsumption to occur when juices are consumed rather than whole fruits and vegetables. It is also important to take into consideration the additives, such as sugar or salt, when consuming fruit and vegetable juices. Juices generally contain far less fiber than whole fruits and vegetables. There is no generally agreed recommendation regarding the consumption of fruit and vegetable juices. However, as with all things, moderation is best. Intake should probably not exceed one to two 240 mL servings/day; persons seeking to lose weight should be especially cautious.

Sports Beverages

A variety of beverages are consumed by athletes and for a variety of reasons. The topic of sports nutrition is discussed in greater detail by Gonzalez and colleagues (Chap. 29). Dehydration occurs during exercise with the loss of body water representing as little as 2% of body weight. This small decline can lead to diminished cognitive and physical performance [43, 44]. If it is an especially hot day and a person exercises for a prolonged time period, then dehydration is likely. Athletes are also prone to loss of electrolytes through sweat. Sports beverages can and do improve hydration status and replace lost electrolytes during long-term periods of exercise. They also provide a key component called "taste" which may encourage athletes to drink more of the beverage, thereby leading to greater improvements in their hydration and electrolyte status. Exercising people should be reminded that for the purpose of weight management sports beverages can negate most of the caloric benefits of the exercise. These drinks are not needed for a 15-min ride on an exercise bike in the gym.

Sugar-Sweetened Beverages (Soft Drinks)

SSB consumption has long been known to be associated with an increased risk of dental caries, weight gain, and a decrease in overall health. Encouragingly, it was reported that from 2003 to 2014, daily per capita consumption of SSBs declined from 225 to 133 kcal for children and from 190 to 138 kcals ($P < 0.001$) for adults [45]. Others reported similar findings [46]. As such, consumption habits may be evolving because of public health education, marketing, or simply because of consumer trends. In contrast, the NHANES data suggest that junk food intake, excluding beverages, was relatively stable in the years 2000–2018 for children and decreased for adults [47]. SSBs appear to be major contributors to the increased obesity observed in children and adults [48]. The following findings underscore the hazards of consuming SSBs. Obesity is inversely correlated with dietary nutrient density, and SSB intake is positively correlated with a reduction in HEI dietary quality scores [49].

In adults, consumption of SSBs is positively and tightly correlated with risk for developing metabolic syndrome as well as type 2 diabetes [50]. After 24 years of follow-up, women who consumed two or more servings of SSBs per day had a 35% higher risk of developing CHD compared with those who consumed less than one serving/month [51]. In adults, the consumption of SSBs is also correlated with a higher risk of mortality [52].

High-fructose corn syrup (HFCS) is a common sweetener used in the beverage industry. HFCS consists of glucose and fructose in a close to, but not quite, 1:1 ratio. It is used at a high concentration during the beverage manufacturing process which makes handling easier than using dry sugar. It is integral to many, but not all, SSBs and is often demonized in the media, websites, and blogs. After absorption in the intestine, the fructose is rapidly metabolized to glucose by the liver. HFCS does not appear to contribute negative health effects beyond those associated with excess consumption of sucrose (table sugar) or glucose (dextrose) [53].

Non-nutritive sweeteners (NNS), also referred to as artificial or low-calorie sweeteners, can have artificial or plant-based origins. Examples include stevia, aspartame, sucralose, and saccharine. While their inclusion permits a reduction in the caloric content of a beverage, this may not actually lead to reductions in overall caloric intake or improved weight management. The explanation for this is poorly understood. A recent consensus panel suggested that NNS are safe and can be beneficial for weight management when they are used to replace sugar in products consumed in the controlled diet studies *where no energy substitution occurs* [54]. These tightly controlled studies are not reflective of the human dietary condition where one can choose to make caloric substitutions freely and this reality clouds determining the real-world effects of NNS. As such, diet soda consumption is not likely to promote weight loss or improve weight management relative to SSB. Indeed, some meta-analyses actually suggest that diet soda (made with NNS) may lead to

increased risk of obesity, T2DM, hypertension, and all-cause mortality [55]. Furthermore, the ability of the public in ad lib conditions to be able to identify non-caloric sweeteners is poor, so the typical consumer usually does not know whether or not they consume SSB or sodas containing NNS, let alone know whether to avoid caloric substitution after their consumption in replacement of a traditional SSB [56].

In a perfect world, water would be the main source of beverage consumption and we would have minimal consumption of SSBs. Furthermore, public health promotion of water consumption would be supported by billion-dollar nutritional promotion campaigns. It is perhaps sensible to suggest limiting SSBs, even those with NNS, to no more than 1 or 2 cups/day. However, limiting intake of SSBs and of beverages that contain NNS to zero is clearly preferable. Furthermore, as mentioned previously with respect to the VitaminWater product, even a beverage that is marketed as "water" can contain sugar and calories, so checking nutrition labels is always warranted as is the educational ability to understand the Nutrition Facts information on the label.

Weight Loss and Meal-Replacement Beverages

For several reasons, meal-replacement beverages may have a place in the regular nutrition of many persons. A variety of meal-replacement beverages (e.g., Slim-Fast®, Met-Rx®, Premier Protein®) provide consumers with a convenient way to consume a relatively balanced nutritional intake that supplies about 200 kcal along with a typically large protein intake, as well as minerals and vitamins. Liquid meal replacements are readily available, do not require refrigeration, and are often quite palatable. However, to improve palatability some beverages contain generous amounts of fat or sugar, so nutritional content should always be checked before consumption.

While liquid meal replacements may be useful for some persons in their weight loss journey, the best nutritional advice for most people is to consume a balanced diet that emphasizes a variety of nutritious, minimally processed foods.

Health Effects of Energy Drinks

Energy drinks (ED) are popular in the United States and around the globe among consumers seeking their perceived benefits of mental and physical stimulation. They are marketed to all demographics. In 2021, 33.8% of people aged 18–29 in the USA stated that they consume energy drinks regularly [57]. In general, ED contain caffeine and sugar as well as a mixture of amino acids, electrolytes (minerals), vitamins, herbs (e.g., ginseng and gingko), and taurine. While caffeine is a primary ingredient in most ED brands, its content is quite variable, ranging from 50 to 500 mg per container. ED are designed to provide a palatable taste.

Surprisingly, in a study of 70 college-aged subjects who consumed a 240 mL serving of Red Bull or placebo, the author (TW) did not observe any statistically significant changes in heart rate, ECG QRT segments/intervals, or blood pressure during the 2 h following consumption [58]. However, overconsumption of ED in young adults and adolescents has been found to lead to anxiety disorders, nausea, shortness of breath, and, in some cases, death [59]. Furthermore, when caffeinated ED are consumed by young people, they sometimes present with mild insulin insensitivity during the following oral glucose tolerance test, especially in those who rapidly metabolize caffeine [60]. Even more caution is warranted when consuming ED with alcohol because caffeine intake can lead to increased alcohol intake [61].

Future Trends

Potable tap water is and will be the most popular beverage on the planet for years to come. The health influences, good and bad, of the currently available beverages and the over 20,000 new beverage products that entered the world market in 2020 remain to be determined [62]. Relative to

the large number of products and health claims made as part of beverage marketing and public health efforts, there are few controlled trials to help support or guide the consumer and clinician. Beverage formulations are ever evolving as manufacturers attempt to meet the changing taste demands of the consumer and meet the regulatory requirements of government. Consumer market preferences and dietary habits are a balance of taste preferences, price, and trends in popularity. Relative to the conclusions of an expert nutrition consensus committee published in the *Journal of American Medical Association* and the *American Journal of Clinical Nutrition*, actual consumer beverage habits are probably more likely to have been established based on comments by an influencer on TikTok. Such is the impact of social media.

In summary, a substantial portion of the caloric content of our diet comes from the consumption of nonalcoholic beverages, which significantly influence our overall health. Water enters our bodies in a variety of forms, and the substances dissolved in the water are important to consider with respect to their health impact. The vitamins, minerals, sugars, alcohol, phytochemicals, and other substances that may be present in beverages require ongoing study and the translation of research findings into dietary recommendations for the general public.

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Health Benefits of Dietary Phytochemicals in Whole Foods

14

Rui Hai Liu

Key Points

- Regular consumption of fruit, vegetables, and whole grains, as well as other plant-based foods is strongly associated with reduced risk of developing chronic diseases such as cardiovascular disease (CVD), cancer, type 2 diabetes, cataracts, and age-related functional decline.
- Phytochemicals are defined as bioactive nonnutrient plant compounds in fruit, vegetables, grains, and other plant foods, which have been linked to reduced risk of major chronic diseases.
- Phytochemicals are classified into phenolics, carotenoids, alkaloids, nitrogen-containing compounds, and organosulfur compounds.
- Oxidative stress can cause oxidative damage to large biomolecules such as DNA, proteins, and lipids, resulting in an increased risk for cancer and CVD.
- Phytochemical antioxidants may prevent or slow down the oxidative stress induced by free radicals.
- The additive and synergistic effects of phytochemicals in fruit, vegetables, whole grains, and other plant-based foods are responsible for their potent antioxidant and anticancer activities.
- The benefit of a diet rich in fruit, vegetables, whole grains, and other plant-based foods is attributed to the complex mixture or interactions of phytochemicals and nutrients present in these foods.
- Dietary modification by increasing the consumption of a wide variety of fruit, vegetables, whole grains, and other plant-based foods daily is a practical strategy for consumers to optimize their health benefits and reduce the risk of developing chronic diseases.
- Phytochemical benefits are best acquired through the consumption of whole foods, not from dietary supplements.

Introduction

Cardiovascular disease (CVD) and cancer are the top two leading causes of death in the United States and many industrialized countries [1]. Epidemiological studies consistently show that regular consumption of fruit, vegetables, and whole grains, as well as other plant-based foods is strongly associated with reduced risk of developing chronic diseases such as CVD, cancer, type 2 diabetes, cataracts, and age-related functional decline [2, 3]. It is estimated that 30–35% of all cancer deaths in the United States are due to diet [3–5]. This suggests that change

R. H. Liu (✉)
Department of Food Science, Cornell University, Ithaca, NY, USA
e-mail: RL23@cornell.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_14

in dietary behavior, such as increasing consumption of fruit, vegetables, whole grains, nuts, and other plant-based foods, is a practical strategy to significantly reduce the incidence of chronic diseases [2]. In addition, primary prevention of chronic diseases through dietary changes may be as effective, and less costly, than the secondary treatments of chronic diseases commonly utilized.

The value of adding citrus fruit, carotene-rich fruit and vegetables, and cruciferous vegetables to the diet for reducing the risk of cancer was specifically highlighted in 1982 by the National Academy of Sciences [6]. In 1987, they recommended consuming five or more servings of fruit and vegetables daily for reducing the risk of both cancer and heart disease [7]. From this, the Five-a-Day program was developed as a tool to increase public awareness of the health benefits of fruit and vegetable consumption and promote adequate intakes of known vitamins. The 2020 Dietary Guidelines for Americans [8] recommends that for most people fruits and vegetables should comprise half of their plate and they should eat at least nine servings (4.5 cups) of these foods a day based on a 2000 kcal diet. This consists of four servings (2 cups) of fruits and five servings (2.5 cups) of vegetables, with emphasis on whole fruits and a wide variety of fruits and vegetables [8]. Plant-based foods, such as fruit, vegetables, whole grains, and other plant-based foods, which contain significant amounts of bioactive phytochemicals, may provide desirable health benefits beyond basic nutrition to reduce the risk of chronic diseases [2, 9, 10]. While references to the importance of increased dietary fruit, vegetables, whole grains, and nuts as part of reducing chronic disease are legion, implementation has not followed. This chapter will discuss the mechanisms by which phytochemicals appear to prevent the development of chronic diseases.

Phytochemicals

The "phyto" of the word phytochemicals is derived from the Greek word "phyto" which means plant. Phytochemicals are therefore plant chemicals. They are defined as bioactive nonnutrient plant compounds in fruit, vegetables, whole grains, and other plant foods, which have been linked to reducing the risk of major chronic diseases [2, 10]. It is estimated that more than 5000 individual phytochemicals have been identified in fruits, vegetables, and whole grains, but a large percentage are still unknown and need to be identified before we can fully understand the health benefits of these substances in whole foods [10]. Phytochemicals may provide this protective effect by regulating a variety of mechanisms including limiting oxidative stress induced by free radicals which are involved in the etiology of a wide range of chronic diseases [11, 12]. Phytochemicals differ widely in their composition and ratios in fruits, vegetables, whole grains, and nuts. Their mechanisms are often complimentary to one another and probably work in synergy to each other, a topic also discussed by Jacobs and Temple in Chap. 23 of this book. It is therefore suggested that in order to receive the greatest health benefits, people should consume a wide variety of plant-based foods with different nutrients and phytochemicals daily [9, 10].

Phytochemicals are mainly derived from plant-based foods and can be classified into broad categories as phenolics, alkaloids, nitrogen-containing compounds, organosulfur compounds, phytosterols, and carotenoids (Fig. 14.1; [10]). Of these phytochemical groups, the phenolics and the carotenoids are the best understood.

Phenolics

Phenolics are compounds having one or more aromatic rings with one or more hydroxyl groups. They are generally categorized as subgroups of phenolic acids, flavonoids, stilbenes, lignans, coumarins, and tannins (Fig. 14.1; [10]). In plants, phenolics provide essential functions in the plant promoting growth and defense against pathogens, parasites, and predators, as well as the contribution to plant color. Plant phenolics also provide health benefits associated with reduced risk of chronic diseases, including cancer, CVD, type 2 diabetes, cataracts, and age-related functional decline. Among the 11 common fruits consumed in the United States,

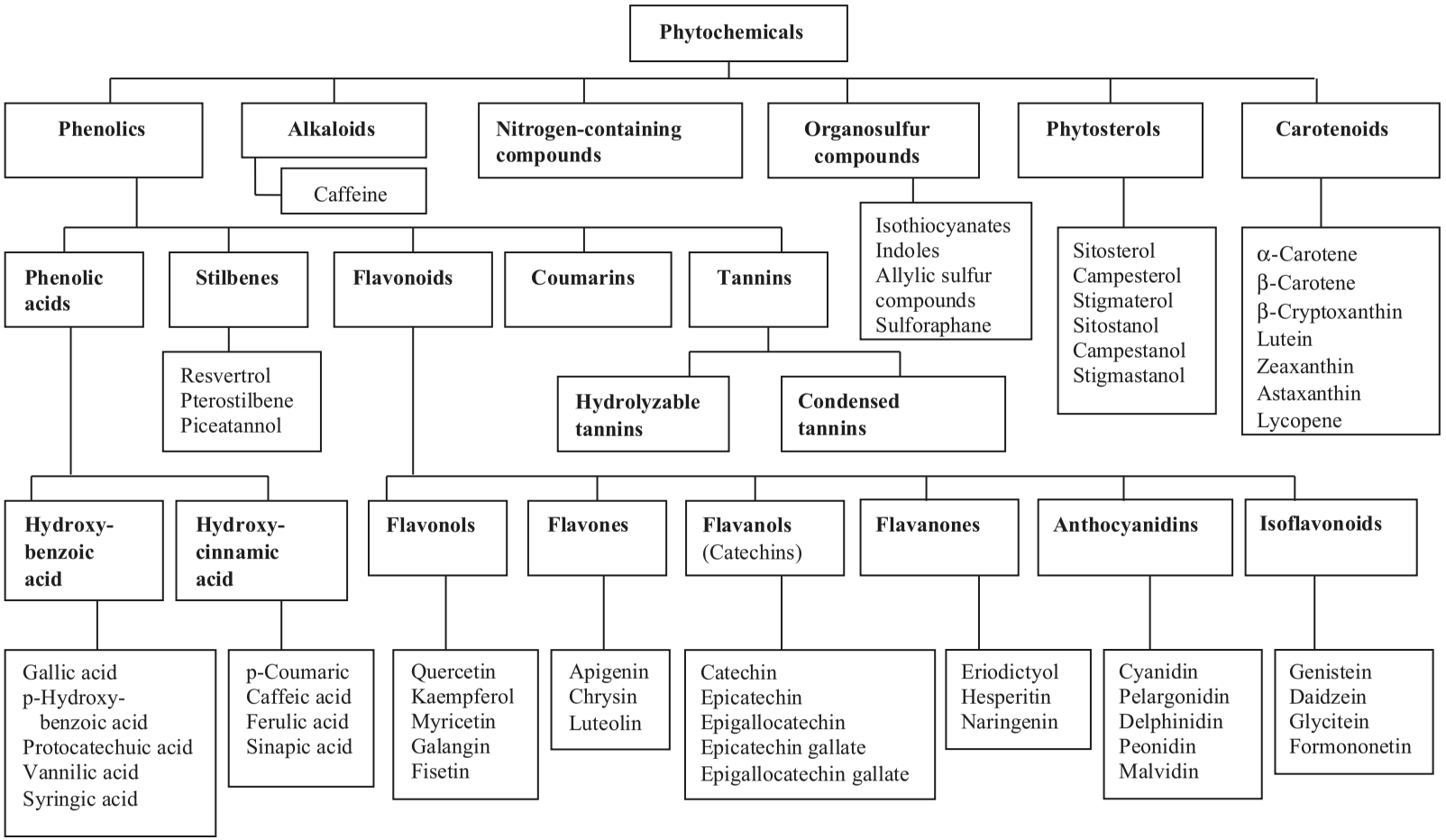


Fig. 14.1 Classification of dietary phytochemicals

cranberry has the highest total phenolic content, followed by apple, red grape, strawberry, pineapple, banana, peach, lemon, orange, pear, and grapefruit [13]. Among the ten common vegetables consumed in the United States, broccoli possesses the highest total phenolic content, followed by spinach, yellow onion, red pepper, carrot, cabbage, potato, lettuce, celery, and cucumber [14].

Flavonoids

Flavonoids account for approximately two-thirds of dietary phenolics. They are a group of phenolic compounds with potent antioxidant activities that have been identified in fruit, vegetables, whole grains, and other plant foods, and have been linked to reduced risk of major chronic diseases [2, 10]. So far, more than 4000 distinct flavonoids have been identified. Flavonoids have a generic structure consisting of two aromatic rings (A and B rings) connected by three carbons that are in an oxygenated heterocycle ring, or C ring (Fig. 14.2). Differences in the generic structure of the heterocycle C ring categorize them as subgroups of flavonols, flavones, flavanols (catechins), flavanones, anthocyanidins, and isoflavonoids (Fig. 14.3). Common dietary flavonoids in the diet include flavonols (quercetin, kaempferol, and myricetin), flavones (luteolin and apigenin), flavanols (catechin, epicatechin, epigallocatechin [EGC], epicatechin gallate [ECG], and epigallocatechin gallate [EGCG]), flavanones (naringenin), anthocyanidins (cyanidin and malvidin), and isoflavonoids (genistein and daidzein) (Fig. 14.4). Flavonoids are most frequently found in nature as conjugates in glycosylated or esterified forms, but can occur as aglycones, especially as a result of the effects of food processing, or digestion in the gut with significant with additional modification by the microbiome of the gut. Many different glycosides can be found in nature because more than 80 different

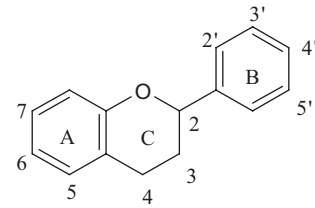


Fig. 14.2 The generic structure of flavonoids

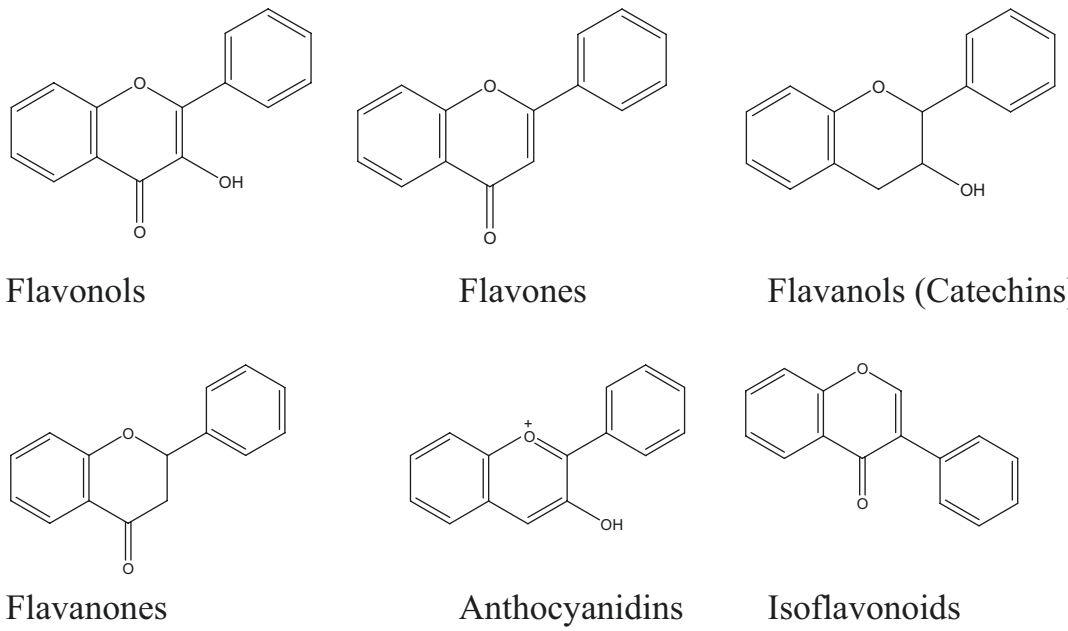


Fig. 14.3 Structures of main classes of dietary flavonoids

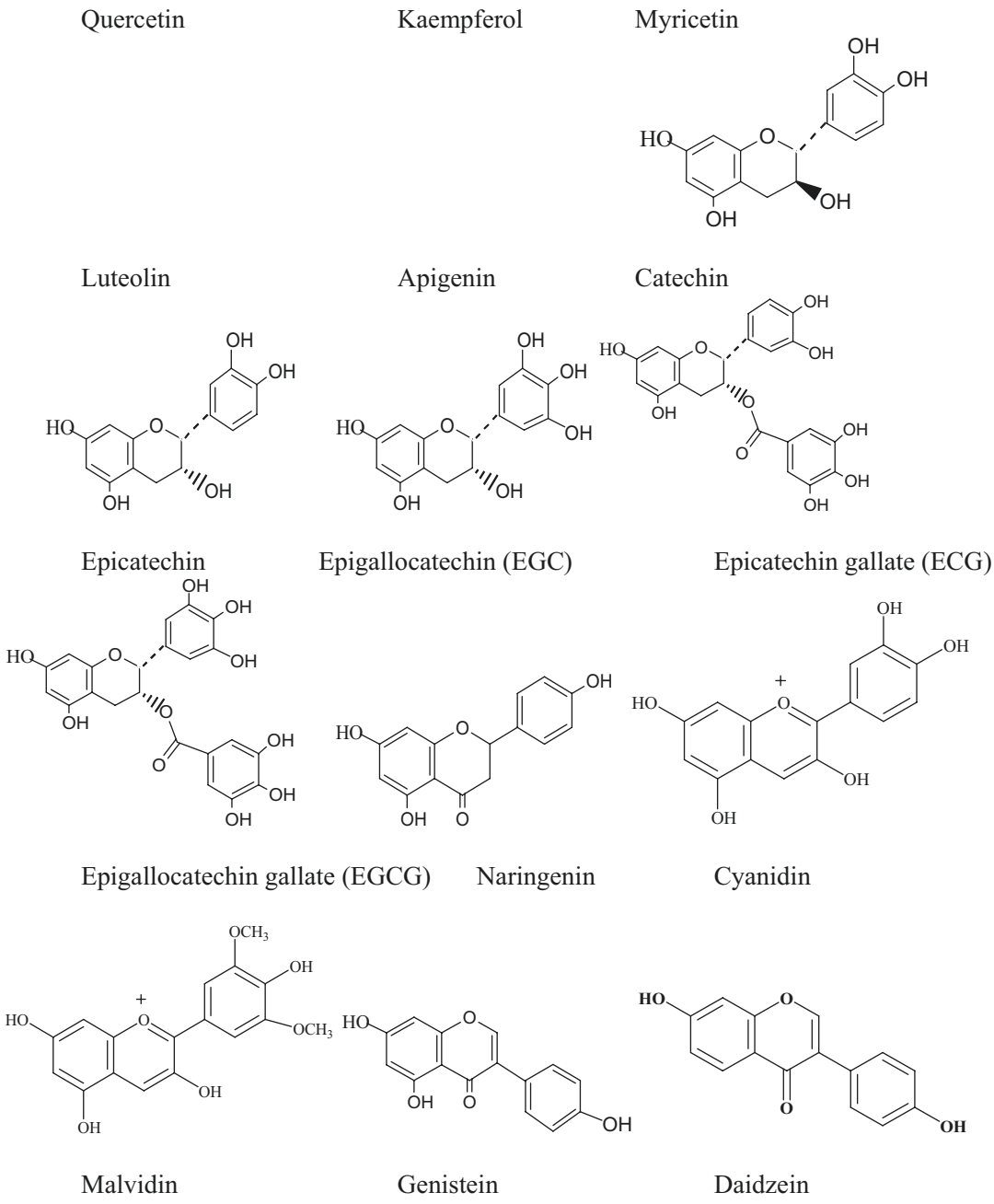
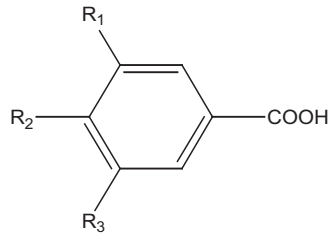


Fig. 14.4 Chemical structures of common dietary flavonoids

sugars have been discovered attached to flavonoids [15]. Anthocyanidins provide the blue and red colors associated with some fruit, vegetables, and whole grains.

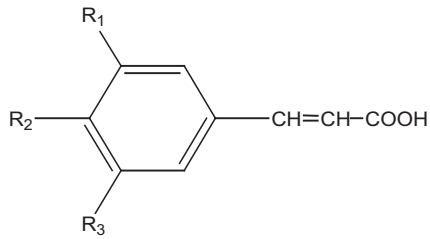
Human dietary intake of all flavonoids is estimated at a few hundred milligrams to 650 mg per day [16, 17]. The total average dietary intake of flavonols (quercetin, myricetin, kaempferol) and flavones (luteolin, apigenin) was estimated as 23 mg/day, of which quercetin contributed about 70%, kaempferol 17%, myricetin 6%, luteolin 4%, and apigenin 3% [18].

a Benzoic acid derivatives



Benzoic acid derivatives	Substitutions		
	R_1	R_2	R_3
Benzoic acid	H	H	H
p-Hydroxybenzoic acid	H	OH	H
Protocatechuic acid	H	OH	OH
Vannilic acid	CH_3O	OH	H
Syringic acid	CH_3O	OH	CH_3O
Gallic acid	OH	OH	OH

b Cinnamic acid derivatives



Cinnamic acid derivatives	Substitutions		
	R_1	R_2	R_3
Cinnamic acid	H	H	H
p-Coumaric acid	H	OH	H
Caffeic acid	OH	OH	H
Ferulic acid	CH_3O	OH	H
Sinapic acid	CH_3O	OH	CH_3O

Fig. 14.5 Structures of common phenolic acids: (**a**) benzoic acid and derivatives; (**b**) cinnamic acid and derivatives

Phenolic Acids

Phenolic acids are one of the major sources of dietary phenolics in plants. They can be divided into two major groups: hydroxybenzoic acids and hydroxycinnamic acids (Fig. 14.5; [10]). Hydroxybenzoic acid derivatives include p-hydroxybenzoic, protocatechuic, vanillic, syringic, and gallic acids. They are commonly present in the bound form in foods and are typically components of a large complex structures like lignins and hydrolyzable tannins [10]. They can also be found in the form of sugar derivatives and organic acids in foods made from plants.

Hydroxycinnamic acid derivatives include p-coumaric, caffeic, ferulic, and sinapic acids (Fig. 14.5). They are mainly present in the

bound form, linked to cell wall structural components such as cellulose, lignins, and proteins through ester bonds [10]. Ferulic acids are primarily present in the seeds and leaves of plants, mainly covalently conjugated to mono- and disaccharides, plant cell wall polysaccharides, glycoproteins, polyamines, lignins, and insoluble carbohydrate biopolymers. Wheat bran is an excellent source of ferulic acids, which are esterified to hemicellulose and lignins of the cell walls. Free, soluble-conjugated, and bound ferulic acids in whole grains are present in the ratio of 0.1:1:100 [19]. Food processing, such as thermal processing, pasteurization, fermentation, and freezing, contributes to the release of the bound phenolic acids [20].

Caffeic, ferulic, p-coumaric, protocatechuic, and vanillic acids are present in almost all plants. Chlorogenic acids and curcumin are two major derivatives of hydroxycinnamic acids present in plants. Chlorogenic acids are the ester of caffeic acid and are the substrate for enzymatic oxidation leading to browning, particularly in apples and potatoes. Curcumin is made of two ferulic acids connected by a methylene in a diketone structure and is the major yellow pigment of spice turmeric and mustard.

Carotenoids

Carotenoids are nature's most common pigments with responsibility for yellow, orange, and red colors and have also received considerable attention because of both their provitamin and antioxidant functions. They are classified into hydrocarbons (carotenes) and their oxygenated derivatives (xanthophylls). More than 600 different carotenoid compounds have been identified in nature. They are widely present in plants, microorganisms, and animals. Carotenoids have a 40-carbon frame of isoprene units (Fig. 14.6; [10]). Their most distinctive characteristic is the long series of conjugated double bonds forming the central part of the molecule. This gives them their shape, chemical reactivity, and light-absorbing properties. The structure may be cyclized at one or both ends, possess various hydrogenation levels, or have oxygen-containing functional groups. Lycopene and β-carotene are examples of acyclized and cyclized carotenoid compounds, respectively. Carotenoid compounds most commonly occur in the all-trans form in nature. β-Carotene, α-carotene, and β-cryptoxanthin have provitamin A activity and can be converted to vitamin A (retinol) after being metabolized in the body. Zeaxanthin and lutein are the major carotenoids in the macular region (yellow spot) of the retina of eyes in humans. A diet rich in zeaxanthin and lutein has been correlated with reduced risk of developing cataract and macular degeneration [21].

Orange and yellow fruits and vegetables, including carrots, sweet potatoes, pumpkin, winter squash, papaya, mango, cantaloupe, and nuts, are rich sources of the carotenoid β-carotene. Dark green leafy vegetables, including spinach, turnip greens, kale, and collards, are rich sources of lutein and zeaxanthin. Tomatoes, watermelons, apricots, pink grapefruits, and pink guavas are the most common sources of lycopene. It has been estimated that 85% of American lycopene intake comes from processed tomato products such as ketchup, tomato soup, and tomato paste. Carotenoid pigments play important roles in photosynthesis and photoprotection in plants. The photoprotection role of carotenoids derives from their ability to quench and inactivate reactive oxygen species, such as singlet oxygen, formed from exposure to light and air. This photoprotection role is also related to its antioxidant activity in human health. Carotenoids can react with free radicals and become free radicals themselves. Their reactivity depends on the length of the chain of conjugated double bonds and the properties of the end groups. Carotenoid radicals are stabilized by delocalization of unpaired electron over the conjugated polyene chain of the molecules. This also allows addition reactions to occur at many sites on the radical [22]. Carotenoids are especially powerful quenching singlet oxygen generated from lipid oxidation or radiation. Astaxanthin, zeaxanthin, and lutein are excellent lipid-soluble antioxidants that scavenge

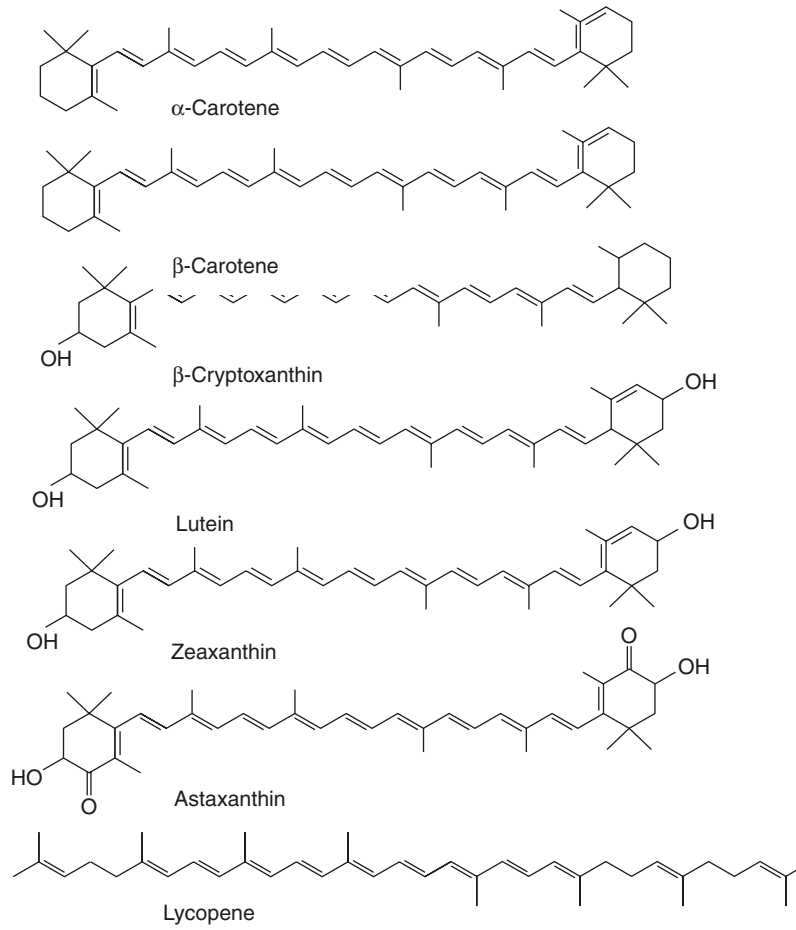


Fig. 14.6 Chemical structures of common dietary carotenoids

free radicals, especially in a lipid-soluble environment. Carotenoids at sufficient concentrations can prevent lipid oxidation and related oxidative stress.

Health Benefits of Phytochemicals

Studies have highlighted the critical role of nutrition in regulating oxidative stress [2, 10–12]. Cells in humans and other organisms are constantly exposed to a variety of oxidizing agents, some of which are necessary for life. These agents may be present in air, food, and water, or they may be produced endogenously by metabolic activities within cells. The key factor is to maintain a balance between oxidants and antioxidants in order to maintain optimal physiological conditions in the body. Overproduction of oxidants can cause an imbalance, leading to oxidative stress, especially in chronic bacterial, viral, and parasitic infections and stress [12]. Oxidative stress can cause oxidative damage to large biomolecules such as DNA, proteins, and lipids, resulting in an increased risk of cancer, CVD, and other chronic diseases [11, 12, 22]. To prevent or slow down the oxidative stress caused by free radicals, sufficient amounts of antioxidants need to be consumed. Fruit, vegetables, whole grains, and other plant-based foods contain a wide variety of antioxidant compounds (phytochemicals), such as phenolics and carotenoids, and may help protect cellular systems from oxidative damage and also lower the risk of developing chronic diseases [9, 13, 14, 19, 23–25].

Role of Phytochemicals in the Prevention of Cancer

Evidence consistently suggests that regular intake of fruit and vegetables can reduce the risk of developing cancer [26]. A prospective study involving 9959 men and women in Finland showed an inverse association between the consumption of flavonoids and incidence of cancer at all sites combined [27]. After a 24-year follow-up, the risk of lung cancer was reduced by 50% in the highest quartile of flavonol intake. Consumption of quercetin from onions and apples was found to be inversely associated with lung cancer risk [28]. The effect of onions was particularly strong against squamous cell carcinoma.

Boyle et al. [29] reported that increased plasma levels of quercetin following a meal of onions was accompanied by increased resistance to strand breakage by lymphocyte DNA and decreased levels of some oxidative metabolites in the urine.

Carcinogenesis is a multi-step process including initiation, promotion, and progression, and oxidative damage is linked to the formation of tumors through several mechanisms involved in carcinogenesis [12, 22]. Oxidative stress induced by free radicals causes DNA damage, which, when left unrepaired, can lead to base mutation, single and double strand breaks, DNA cross-linking, and chromosomal breakage and rearrangement in the initiation stage [22]. This potentially cancer-inducing oxidative damage might be prevented or limited by dietary phytochemicals found in fruit and vegetables. Studies to date have showed that phytochemicals in common fruit, vegetables, whole grains, and other plant-based foods can have complementary and overlapping mechanisms of action (Fig. 14.7 and Table 14.1), including scavenging free radicals, regulation of gene expression in cell proliferation and apoptosis, modulation of detoxification enzymes, stimulation of the immune system, regulation of hormone metabolism, and antibacterial and antiviral effects [2, 9, 22, 30, 31].

Role of Phytochemicals in the Prevention of Cardiovascular Disease

CVD is a top leading cause of death in the world. Several epidemiological studies have examined the role of phytochemicals in the prevention of

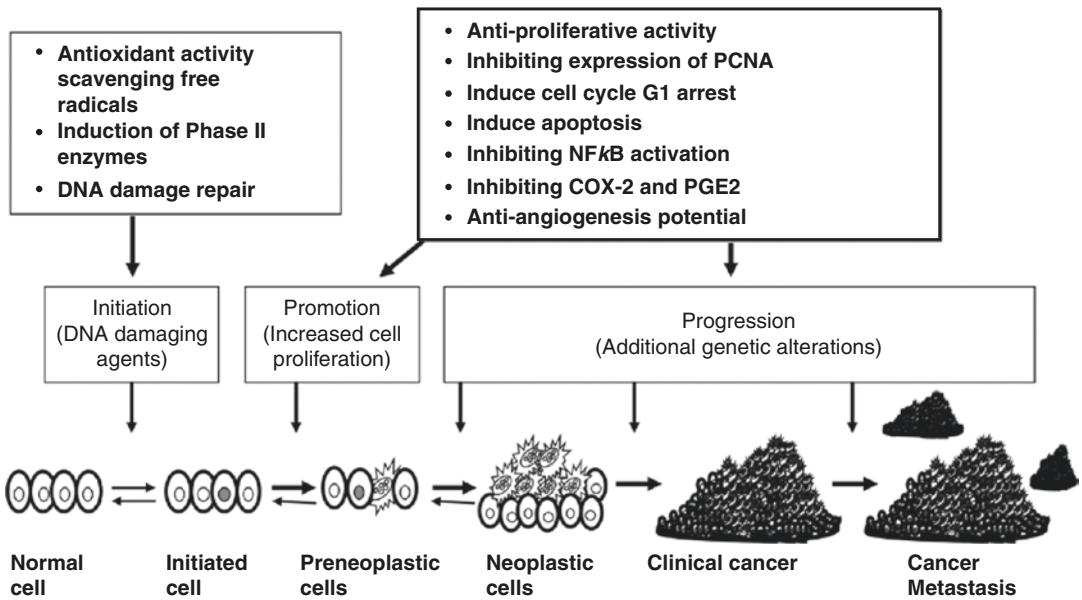


Fig. 14.7 Mechanisms by which dietary phytochemicals may prevent cancer

Table 14.1 Proposed mechanisms by which dietary phytochemicals may prevent cancer

- Antioxidant activity
  - Scavenge free radicals and reduce oxidative stress
  - Inhibit nitrosation and nitration
  - Prevent DNA binding
- Inhibition of cell proliferation
- Induction of cell differentiation
- Inhibition of oncogene expression and induction of tumor suppress gene expression
- Induction of cell cycle arrest and apoptosis
- Inhibition of signal transduction pathways
- Enzyme Induction and enhancing detoxification
  - Phase II enzyme
  - Glutathione peroxidase (GPX)
  - Catalase
  - Superoxide dismutase (SOD)
- Enzyme Inhibition
  - Cyclooxygenase-2 (COX-2)
  - Inducible nitric oxide synthase (iNOS)
  - Xanthine oxide
  - Phase I enzyme (block activation of carcinogens)
- Enhancement of immune functions and surveillance
- Anti-angiogenesis
- Inhibition of cell adhesion and invasion
- Regulation of steroid hormone metabolism
- Regulation of estrogen metabolism
- Antibacterial and antiviral effects

CVD. Dietary flavonoid intake was significantly inversely associated with mortality from coronary heart disease (CHD), and had an inverse relationship with incidence of myocardial infarction (MI) [32]. Flavonoid intake was also inversely correlated with CHD mortality [33]. Intake of apples and onions, both high in quercetin, was inversely associated with total and CHD mortality [34]. In a Japanese study, the total intake of flavonoids (quercetin, myricetin, kaempferol, luteolin, and fisetin) was inversely associated with the plasma total cholesterol and low-density lipoprotein (LDL) cholesterol concentrations [35]. As a single phytochemical, quercetin intake was inversely correlated with total cholesterol and LDL plasma levels. These studies are consistent with the findings of cohort studies which have provided strong evidence that total intake of both fruit and vegetables are each correlated with decreased risk for CHD [36]. Much other evidence demonstrates a protective association between intake of fruit and vegetables and risk of CVD [26, 37, 38].

Mechanisms have been proposed that may explain how the phytochemicals in fruit and vegetables prevent atherosclerosis. In the LDL oxidation hypothesis, oxidized LDL cholesterol has been suggested as the atherogenic factor that contributes to CVD [39, 40]. When circulating LDLs are present at high levels, they infiltrate the artery wall and increase intimal LDL, which can then be oxidized by free radicals. This oxidized LDL in the intima is more atherogenic than native LDL and serves as a chemotactic factor in the recruitment of circulating monocytes and macrophages. Oxidized LDL is typically taken up by macrophage scavenger receptors, thus inducing the formation of inflammatory cytokines and promoting cell proliferation, cholesterol ester accumulation, and foam cell formation. Gruel-like, lipid-laden foam cell accumulation in the blood vessel, forming a fatty streak, then causes further endothelial injury and leads to atherosclerotic disease.

Based on the premise that oxidized LDL plays a key role in the initiation and progression of atherosclerosis, it follows that an important therapeutic approach is giving dietary phytochemicals capable of preventing LDL oxidation. The proposed mechanism is as follows. Phytochemicals that are incorporated into LDL are themselves oxidized when the LDL is exposed to prooxidative conditions; this occurs before any extensive oxidation of the sterol or polyunsaturated fatty acids can occur [41]. Phytochemicals might therefore retard the progression of atherosclerotic lesions.

Phytochemicals also have been shown to have roles in the reduction of platelet aggregation, modulation of cholesterol synthesis and absorption, and reduction of blood pressure. C-reactive protein (CRP), a marker of systemic inflammation, has been reported to be a stronger predictor of CVD than is LDL cholesterol [42], suggesting that inflammation is a critical factor in CVD. Inflammation not only promotes initiation and progression of atherosclerosis but also causes acute thrombotic complications of atherosclerosis [43]. An Italian study investigated the association between high-sensitivity CRP (hs-CRP) and the total antioxidant capacity (TAC) of the diet. Even within groups controlled for dietary factors,

TAC was found to be significantly higher among those with a low level of plasma hs-CRP when compared to subjects with high levels [44]. This indicates that the total antioxidant capacity of a diet is independently and inversely associated with hs-CRP, and that this could be one of the mechanisms behind the protective effect of fruit and vegetables against CVD. Phytochemicals from fruit and vegetables can lower CRP dramatically. Both fruits and vegetables were inversely correlated with plasma CRP concentrations [45]. Therefore, the anti-inflammatory activity of phytochemicals may play a crucial role in the prevention of CVD.

Health Benefits of Phytochemicals in Whole Foods: Food Synergy

The hypothesis that dietary antioxidants lower the risk of chronic disease has been developed from epidemiological studies. These have consistently shown that intake of whole foods, such as fruit, vegetables, whole grains, and other plant-based foods, is strongly correlated with reduced risk of developing chronic diseases, including cancer, CVD, type 2 diabetes cataracts, age-related macular degeneration, and central neurodegenerative diseases [2, 10]. Based on these observations, it appeared to make good sense to isolate the specific bioactive compounds responsible and create a "magic bullet" to prevent those chronic diseases. It is now widely believed that the actions of dietary supplements alone do not duplicate the observed health benefits of diets rich in fruit and vegetables. This is because, taken alone, the individual antioxidants studied in clinical trials do not appear to have consistent preventive effects [46–48]. The isolated pure compound either loses its bioactivity or may not behave the same way as the compound in whole foods [49–59]. Of particular importance, single substances may lack the protective bioactivity that occurs with the complex mixture of phytochemicals found in whole foods. Evidence supporting these views is discussed in several other chapters.

Different fruits, vegetables, and whole grains have different phytochemical profiles [13, 14, 19, 23, 24, 60, 61]. Therefore, consumers should obtain their phytochemicals from a wide variety of these foods for optimal health benefits.

The additive and synergistic effects of phytochemicals in fruit and vegetables have been proposed to be responsible for their potent antioxidant and anticancer activities [2, 9, 10]. The benefit of a diet rich in fruit, vegetables, and whole grains is attributed to the complex mixture of phytochemicals present in these and other whole foods [13, 14, 23, 24, 57, 61–65]. This partially explains why no single antioxidant can replace the combination of natural phytochemicals in these foods in achieving the observed health benefits. There are thousands of phytochemicals present in whole foods. These compounds differ in molecular size, polarity, and solubility, which may affect the bioavailability, distribution, and metabolism of each phytochemical in different macromolecules, subcellular organelles, cells, organs, and tissues. This balanced natural combination of phytochemicals present in fruit, vegetables, and whole grains cannot simply be mimicked by dietary supplements.

Research progress in antioxidant and bioactive compounds has boosted the dietary supplement and nutraceutical industries. The use of dietary supplements is growing, especially among baby-boomers. However, many of these dietary supplements have been developed based on the research results derived from biochemical and chemical analyses and studies, in vitro cell culture studies, and in vivo animal experiments, without human intervention studies. The health benefits of natural phytochemicals at the low levels present in fruit, vegetables, and whole grains does not mean that these compounds are more effective or safe when they are consumed at a higher dose in a pure dietary supplement form. Generally speaking, higher doses increase the risk of toxicity. The basic principle of toxicology is that any compound can be toxic if the dose is high enough; dietary supplements are no exception. It is therefore unwise to take mega-doses of purified phytochemicals as dietary supplements

to improve nutritional status or maintain health before the appearance of strong supporting evidence. Therefore, the efficacy and long-term safety of many dietary supplements needs further investigation.

Summary

Dietary modification by increasing the consumption of a wide variety of fruits, vegetables, whole grains, and other whole foods is a practical strategy for consumers to optimize their health and reduce the risk of various chronic diseases. Phytochemical extracts from these foods have strong antioxidant and antiproliferative activities, and the major part of total antioxidant activity is from the combination of phytochemicals in whole foods. The additive and synergistic effects of phytochemicals in these foods are responsible for their potent antioxidant and anticancer activities. The benefit of a diet rich in these foods is attributed to the complex mixture of phytochemicals present. This explains why no single antioxidant can replace the combination of natural phytochemicals in fruit, vegetables, and whole grains and achieve their health benefits. Therefore, the evidence suggests that antioxidants are best acquired through whole food consumption, not from dietary supplements. The use of dietary supplements, functional foods, and nutraceuticals is increasing as industry is responding to consumers' demands. However, there is a need for more information about the health benefits and possible risks of dietary supplements so as to ensure their efficacy and safety. Further research on the health benefits of phytochemicals in whole foods is warranted.

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Functional Foods: Implications for Consumers and Clinicians

15

Karen M. Gibson, Eliza S. Dahly, and Ted Wilson

Key Points

- Functional foods are popular because of their presumptive ability to provide health benefits beyond the basic nutritional requirements of vitamins and minerals.
- Phytochemicals in plants are presumed to be largely responsible for many of the health benefits attributed to functional foods.
- Functional foods may provide antioxidant functions and antiviral activities.
- Functional foods appear to provide benefits for many conditions including, but not limited to, cardiovascular disease and type 2 diabetes.
- Consumers often make unhealthy dietary choices that include functional foods as a substitute for clinical treatments.
- Understanding about functional foods is important in the clinical setting because they may prevent disease and patients ask questions about their use.

K. M. Gibson
Department of Family and Consumer Sciences, Carson-Newman University, Jefferson City, TN, USA
e-mail: kgibson@cn.edu

E. S. Dahly · T. Wilson (✉)
Department of Biology, Winona State University, Winona, MN, USA
e-mail: Eliza.Dahly@go.winona.edu; twilson@winona.edu

What Is a Functional Food?

The days are long gone when appearance, taste, texture, and smell were the only variables consumers thought about when choosing what to eat. While those factors still play a role in consumer food choices, many people are taking a more proactive approach. Most consumers now accept that diet has a major influence on our health and can be hugely important for both the prevention and promotion of disease. The increasing acceptance of these facts has seen a rise in the consumer market for foods that improve our health and wellness, and that may serve as a complement to modern medicine.

Presently, there is no universally accepted definition of functional foods, but the Institute of Food Technologists defines these foods as "foods or food components that may provide benefits beyond basic nutrition" [1]. The key feature of functional foods is that they provide potentially bioactive non-nutrient compounds that are distinct from nutrients. We can illustrate this with the following examples. Tofu is rich in isoflavones, which are associated with a reduction in cardiovascular disease. Since we can survive without eating tofu and its bioactive isoflavones, tofu can be called functional food. Similarly, cranberry juice is often consumed to prevent urinary tract infections. Its major active ingredients are believed to be proanthocyanidins which are non-nutrients. However, a failure to ingest proan-

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_15

thocyanidins in cranberry juice does not result in a urinary tract infection.

Functional foods are in the top 10 food consumer food-trends of 2021 for the management and treatment of disease conditions [2]. The popularity of functional foods is reflected by an observed increase in worldwide revenue for functional foods from about 300 billion US dollars in 2017 to a projected amount of over 440 billion dollars in 2022 [3]. A survey of American consumers in 2018 demonstrated the generational differences in willingness to pay a premium for food that offers benefits beyond basic nutrition. In this regard, 50% of younger Millennials were willing to pay a premium for these foods, compared to only 25% of retirees and seniors [4]. This may reflect differences in dietary history, nutrition education, or socioeconomic status. Whether clinicians agree or disagree about whether functional foods do indeed improve health, the undeniable fact is that they are growing ever more popular with the consumer. For this reason, clinicians and nutritionists should be familiar with them.

Bioactive Compounds in Functional Foods and Their Chemistry

The non-nutrient bioactive compounds supplied by foods of plant origin are commonly known as phytochemicals. They are mainly obtained from whole (minimally processed) foods. Well over 10,000 individual phytochemicals have been identified in foods and classified according to their chemical structure. Their chemistry is described more thoroughly by Rui Hai in Chap. 14. Plants use these phytochemicals for a variety of purposes including protection from UV light, insects, and viruses.

Some of the many proposed biological roles of phytochemicals include antioxidant, anti-estrogenic, anti-inflammatory, immunomodulatory, and anticarcinogenic activities and the promotion of changes in the gut microbiome [5]. The biological roles of phytochemicals are difficult to establish because of their metabolism, and therefore their resultant biological activities in the body can be affected by the gut microbiota which is unique to each individual and undergoes major changes within an individual over the course of time [6].

Phytochemicals exhibit a low potency as bioactive compounds when compared to drugs. However, when frequently consumed in the amounts present in a diet dominated by whole foods, they can have significant long-term physiological effects [7]. Bioactive phytochemicals appear to work together with the many other components of food, including nutrients and fiber, to reduce human diseases. This concept is known as food synergy and is reviewed in Chap. 23 by Jacobs and Temple.

The term "nutraceutical" complicates the discussion of functional foods; the term indicates specific substances extracted from foods and which are endowed with medicinal properties. Consumption of nutraceuticals is intended to bring distinct medical and health benefits when consumed regularly. This differs from functional foods which refer to actual foods and encompasses both nutrients and phytochemicals. It can be challenging for clinicians to categorize bioactive compounds in terms of what is a functional food, a nutraceutical, and a pharmaceutical/FDA-approved drug with respect to human health.

Examples of Disease Conditions Affected by Functional Foods

Epidemiological and experimental studies have shown that consumption of particular functional foods is associated with reduced risk of several chronic diseases. A short summary of the relationship between some of these functional foods and chronic disease is presented below.

Cardiovascular Disease

More than 130 million US adults are predicted to have cardiovascular disease (CVD) by 2035, and the cost of this is projected to grow to at least $1.1 trillion per year [8]. CVD is also the leading

cause of death globally. An estimated 17.9 million people died from CVD in 2019, representing 32% of all global deaths [9]. For persons whose blood cholesterol is elevated but not high enough to require pharmacological treatment, functional foods may help lower total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides [10]. Consumption of several functional foods has been recommended by many international guidelines including the National Cholesterol Education Program and the European guidelines for the management of dyslipidemias [11]. In addition, a large amount of epidemiological and clinical data support the tolerability and safety of many functional foods with demonstrated lipid-lowering action.

Oatmeal and breakfast cereals such as Cheerios represent the epitome of the original classic functional food that is rich in dietary fiber and protects against heart disease. Many studies and meta-analyses have characterized the small but clinically significant reductions in LDL cholesterol that come from consuming dietary fiber from sources like Cheerios or oatmeal [12]. In contrast, insoluble fiber from wheat bran is more associated with protection from colon cancer [13]. However, many consumers doubtless confuse the two kinds of fiber and mistakenly consume wheat bran for the purpose of lowering LDL-C.

Functional foods may also protect against CVD by improving vascular function. Watermelon and beetroot juice are two functional foods that have been suggested for improved vascular function, most notably those with the potential to increase nitric oxide (NO) formation and the vasodilation NO creates. Watermelon is rich in citrulline which is readily converted to arginine for the production of NO; for that reason, watermelon has been suggested to improve vascular function [14, 15]. Beetroot juice is a rich source of nitrates that could be readily converted to NO in a nitric oxide-independent fashion, as such beetroot juice is often described as a functional food for improving vascular function [16].

Type 2 Diabetes

Functional foods could serve as an adjuvant therapy for type 2 diabetes (T2DM) in support of conventional lifestyle changes and hypoglycemic medications. Some functional foods appear to improve glycemic control and may help prevent complications associated with T2DM.

High-fiber foods are known to slow down the rate of gastric emptying and provide a greater sense of satiation after a meal; this may potentially lead to a reduction in caloric intake. Sweet potatoes represent a potential functional food for diabetics. While whole-food studies are lacking, a sweet potato extract that was given to diabetics for 12 weeks was shown to improve insulin sensitivity, fasting insulin, HbA1c, and total cholesterol [17]. It is also possible that the fiber content of sweet potatoes may beneficially modify the gut microbiome in this regard [18]. However, definitive whole-food studies in humans are expensive, difficult to perform in a free-living environment, and sadly have not been reported with regard to sweet potato.

There is a fine line between the functional foods that add significant weight to the diet, such as sweet potatoes, and functional foods that are used primarily to enhance flavor. Several herbs and spices that enhance flavor can be considered functional foods as they may improve glucose metabolism in persons with diabetes. Examples include cinnamon [19], garlic [20], ginger [21], green tea [22], fenugreek [23], and turmeric [24]. Supporting evidence comes from meta-analyses or extensive reviews. There is also evidence that supports other functional foods, but the interpretation of the results is difficult and seldom confirmed by robust follow-up studies.

Antioxidants

Plant-derived antioxidants are commonly used as an ingredient in foods to retard oxidation and prevent spoilage, especially for meat [25].

Antioxidant phenolic compounds in functional foods may be promising for the prevention of chronic diseases. There was much speculation in the 1980s that antioxidants may be protective against cancer. Antioxidants have also been suggested to be beneficial for reducing LDL oxidation, improving vasodilation, and helping to prevent CVD.

These possibilities have been tested in several RCTs in which subjects have been given antioxidant vitamins, notably beta-carotene or vitamins C or E. The goal of these RCTs was to determine the effectiveness of these vitamins for either primary or secondary prevention [26]. The dose has typically been several times higher than the RDA. The findings generated very little evidence that these vitamins prevent disease. More importantly, meta-analyses of RCTs indicate that supplementing with these vitamins does nothing to reduce all-cause mortality [27]. It is also particularly noteworthy that some RCTs reported a paradoxically increased risk of lung cancer in persons given beta-carotene [28]. So where vitamin enrichment studies have not succeeded, perhaps functional foods might provide food synergistic effects that provide clinically measurable benefits.

Reports have appeared indicating that some antioxidants have anti-inflammatory properties. As a result, these substances may help protect the human body from infection and reinfection, especially in the lungs [29]. This is a function that could be especially important with respect to the cytokine storm of oxidation associated with COVID-19 infection.

These findings indicate that antioxidants taken in the form of vitamin pills or other supplements do not have the same protective effects as antioxidants from dietary intake, perhaps in a fashion related to the food synergy concept (Chap. 23). So, while antioxidant claims on food packaging may appear to fall under the functional food umbrella, solid clinical evidence is mostly lacking. The "antioxidant" in association with food is well known to consumers and this is documented by the number of times the word "antioxidant" is present on food packaging.

Antiviral Functions

Dietary approaches could play a valuable role in preventing viral infections, an association made ever more important because of the COVID-19 pandemic. Functional foods may provide a safe and cost-effective strategy to enhance the immune system and help provide protection from viral infections. In the 2020 Food and Health Survey of those seeking foods or following diets for their health benefits, 40% wanted to consume functional foods that benefit the immune function [30]. In addition, 18% of Americans cited the COVID-19 pandemic as a reason why they were looking for foods to strengthen their immune system. Americans have also used the COVID-19 pandemic as an additional reason to adopt a healthier lifestyle that includes exercise in addition to functional foods [31].

There are many functional foods that may limit viral replication. It has long been suggested that garlic provides protection against viral infections; more recently this postulated protection has been extended to COVID-19 [32]. Foods rich in vitamin D may reduce the risk of contracting respiratory infections, such as COVID-19 [33], by lowering viral replication rates through cathelicidins and defensins. This may also help prevent lung damage that can lead to pneumonia [34]. Coffee contains caffeic acid (which is not chemically related to caffeine) a substance that may suppress viral replication [35]. Dietary intake of protein-rich foods, such as red meat, chicken, and seafood, contain anserine and carnosine which have been suggested to enhance the immune functions of monocytes and macrophages [36]. Although nutrition may not be a definitive measure to prevent COVID-19, it could be of value as a means to reduce the risk or severity through enhanced immunity.

Where Do Consumers Learn About Functional Foods?

Where do consumers obtain information about functional foods and how can this information lead to confusion? Many professional websites

provide nutrition information, but their utility for the general public to learn about functional foods is limited for many reasons [37].

Much of what consumers learn about functional foods is biased and comes from marketing which may lead consumers to use functional foods as a substitute for eating a generally healthy diet. Larger companies are very savvy about how to market food products by highlighting the presence of functional food ingredients that are familiar to the consumer [38]. In this regard, they use bright colors and large words on the front of their packaging to catch the attention of customers about functional foods. The label on packages of Honey Nut Cheerios includes a large red heart to persuade consumers that it will help lower cholesterol and reduce the risk of heart disease. The bright colors on Nature's Garden packaging attract and assure consumers that their Omega-3 Deluxe Mix may reduce the risk of heart disease. Walk into a grocery store and the word "antioxidant" appears frequently on food packaging to deliver a message to consumers that it is a "functional food" , even though these antioxidants may not promote measurable health benefits. Those who suffer from a condition, such as cardiovascular disease, are likely to be more inclined to buy foods that have label claims stating that the food will help prevent that condition [39].

Social media apps and online platforms have a tremendous influence on behavior and dietary decisions at all ages. Through tracking the use of consumer Google Search history and Google Map use, consumer-targeted marketing can occur as sponsored content (advertising) for functional food products. This can be done via a consumer's social media at the moment that he or she enters a grocery store as an alert or filtered content promoting biased information that promotes the sale of functional food products.

Most consumers are not able to correctly interpret the findings of research studies, including clinical trials. But they are likely to be influenced by others who they perceive as authoritative or celebrities. Consider the confusion seeded by the popular Columbia University surgeon Dr. Oz, who delivers a vast number of claims on TV, in books, and in online media regarding functional foods. Most consumers are not aware that he has been repeatedly asked to resign his position at Columbia because he generally does not base his recommendations on solid evidence [40].

The major problem with celebrity endorsements and social media is that there is minimal regulation and even less accountability for these paid endorsements. As a result, the average patient in a clinic will often have learned only enough to be confused. In this regard, a recent study of university students in Spain highlights the misperceptions that are associated with functional food and the attempts to use them to achieve healthy eating habits [41]. Knowledge about functional foods stems largely from the food package label, advertising through online, and social media, as well as from misrepresentation of facts by persons falsely perceived as nutrition authorities. What is true in Spain is also likely to be true in other countries including the USA. These valuable findings help explain the confusion often seen in the area of evidence-based nutrition education that is commonly seen among the general public.

Conclusion

It is difficult to find a single definition of what a functional food is, although most consumers likely regard these foods as being important for health. Understanding the health benefits of functional foods is further complicated by the heterogeneous nature of the bioactive compounds found in these functional foods and how they interact with each other. Adding to the complexity there are thousands of substances in the diet, and these can have an enormous number of possible interactions with the human genome.

A healthy diet is a cost-effective way to improve human health. Functional foods should be viewed as a potentially helpful addition to the diet in order to boost the body's resistance to disease as well as being clinically useful for many diseases. But functional foods should probably not be employed as an alternative to traditional medical treatments and FDA-approved pharma-

cological medications. The consumer needs to be reminded that there is no single "best" functional food for optimal health and the clinical caregiver needs to be fluent in how functional foods may have a place at the table for the consumer seeking to improve their health. We confidently predict that there will be many exciting developments in this field in the coming years.

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Part IV

Nutrition, Healthy Diets, and Public Health

The Mediterranean Diet

16

Greta Caprara

Key Points

- The Mediterranean diet (MD) is a nutritional model inspired by the traditional diets consumed, after the Second World War, within the countries surrounding the Mediterranean basin.
- This diet mainly emphasizes the consumption of plant-based foods (unrefined cereals, vegetables, fruit, legumes, nuts, and seeds), incorporates some animal-based foods (fish, dairy products, eggs, and poultry), promotes the use of olive oil as a major source of fat, includes moderate consumption of wine, and rarely includes red and processed meat, sweets, and highly processed foods.
- Scientifically, the original diet was described and characterized by Ancel Keys, in the Seven Countries Study, whose results were published in 1970.
- Since then, many other epidemiological studies have reported the significant nutritional and health benefits of the MD. This dietary pattern has been associated with many beneficial effects on health, mainly demonstrating a protective role against the development of several noncommunicable diseases (NCDs) including cardiovascular pathologies, cancer, type 2 diabetes, and neurological diseases. The MD also promotes healthy aging and thus reduces overall mortality.
- Moreover, the diet generates a lower environmental impact, compared to current Western diets, and can be highly recommended for the well-being of the planet.
- Even though it is not always possible to adapt the MD to populations living outside the Mediterranean basin, mounting evidence shows that adherence to this or similar nutritional plans is associated with several health benefits in countries beyond this geographical area.
- Indeed, it is worth trying to actively encourage adherence to the major healthy principles of this traditional dietary pattern in order to offer health benefits and improve the quality of life for many populations worldwide.

Introduction

The Mediterranean diet (MD) represents a nutritional eating plan, which arose from the food cultures of antique civilizations surrounding the Mediterranean Basin, such as Greece, Italy, Morocco, and Spain. Notably, there is not one single MD but rather a number of variants, with many common elements, adapted to the individual foods and the cultures of countries of the Mediterranean region. The definition

G. Caprara (✉)
Department of Experimental Oncology, IEO, European Institute of Oncology, IRCCS, Milan, Italy
e-mail: greta.caprara@ieo.it

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_16

"Mediterranean diet" came from the work of the American physiologist Ancel Keys who first identified the link between the traditional diets of some Mediterranean populations and their low frequency of cardiovascular disease (CVD). Subsequently, the benefits of the MD were confirmed by several studies, not only in primary and secondary prevention trials of CVD but also in counteracting overweight and the risk of developing several major noncommunicable diseases (NCDs), including cancer, type 2 diabetes, metabolic syndrome, and neurological pathologies.

In this chapter, we will first review the origins and main nutritional characteristics of the traditional MD. Then we will examine its effects on health, mainly concentrating on its protective role against the development of several NCDs. In addition, we will briefly describe why the MD is not only healthy but also generates a low environmental impact and thus represents one of the most sustainable nutritional patterns for our environment. Finally, we will discuss the possibility of employing a Mediterranean-like eating pattern in countries beyond the Mediterranean basin in order to improve the quality of life for as many people as possible.

Origins and Definition

The "Mediterranean diet" is a term used to define the nutritional model inspired by the traditional dietary habits of the antique civilizations, which developed around the Mediterranean Sea (Greece, Italy, Morocco, Spain, etc.). Even though the eating habits prevailing in these geographical areas differ by some food choices and cooking practices, specific to each country, culture, climate, and religion, they all share a common set of basic features and nutritional key components [1]. Moreover, the Mediterranean diet (from the Greek "δίαιτα," "díaita," way of life) encompasses more than just a defined diet: it also represents a set of knowledge, cultural expressions, social habits, lifestyles, and cultural traditions historically spread by the different communities overlooking the "*Mare Nostrum.*"

The specific definition of "Mediterranean diet" was coined around the 1950s by the American physiologist Ancel Keys who was the first to identify, through the "Seven Countries Study," the relationship existing between the traditional diets of some Mediterranean populations and their low incidence of CVD [2].

Nutritional Model

Features of the Mediterranean Diet

The MD does not represent a strictly regimented nutritional plan, in the commonly recognized definition of the term "diet." Instead, it could be best described as a particular "nutritional model" featuring a unified collection of specific common characteristics. The traditional Mediterranean nutritional model is mainly based on the regular consumption of olive oil (as the main source of added fat), plant-based foods (unrefined cereals, vegetables, fruits, legumes, nuts, seeds, herbs, and spices), a moderate amount of fish, dairy products, eggs, and poultry, a low-to-moderate intake of alcohol (mostly red wine, with the imbibing of other alcoholic beverages not being common in the traditional MD), and limited consumption of red and processed meat, sweets, and highly processed foods [1, 3].

Each of the regions of the Mediterranean area developed its own recipes, food preferences, and restrictions as a result of the local differences in culture, climate, and religion [1, 3]. For instance, pasta consumption is significantly higher in Italy; the Spanish version is characterized by elevated fish and seafood intake; while total fat consumption is higher in Greece than in Italy [3]. Also, the food serving numbers vary among the different Mediterranean countries: from 3 to 9 per day for vegetables, 0.5–2 for fruits, 1–13 for cereals, and up to 8 for olive oil. Despite this, the nutrient profile of the different MDs does not vary significantly, since, in most cases, choices from different food groups complement each other [1].

The macronutrient profile of a traditional MD is characterized by roughly 55–60% of carbohydrates (with simple sugars representing less

Fig. 16.1 The Mediterranean diet pyramid. Serra-Majem L, et al. [8]

than 10%), 10–15% of protein, and 30–35% of fat (mostly monounsaturated [MUFA] and polyunsaturated [PUFA] fats). Nowadays, many Mediterranean countries' nutritional guidelines have lowered the lipid recommended intake to 20–35%, following World Health Organization (WHO), Food and Agriculture Organization (FAO), and European Food Safety Authority (EFSA) recommendations [4–7]. Traditionally, the typical serving sizes of a MD are frugal and moderate [8]; indeed, because of the major public health challenges of overweight and obesity and the widespread adoption of sedentary lifestyles, this aspect of the diet should be further encouraged. Mounting evidence, in fact, has demonstrated that moderate energy restriction, without malnutrition, exerts many beneficial health effects [9].

The abovementioned characteristics are combined in the "Mediterranean Diet Pyramid," a worldwide recognized nutrition guide (Fig. 16.1) [8].

The Mediterranean Diet Pyramid

Food pyramids are graphic visual nutrition guides that represent the relative amounts of each food group to be ingested in order to maintain a healthy diet. The portion sizes and the number of servings per day/week are also indicated. Food groups whose consumption is emphasized are located at the bottom of the pyramid while foods whose consumption should be restricted are located at the top. The MD pyramid was updated in 2020 (Fig. 16.1) [8].

The base of the pyramid highlights regular physical activity, adequate rest, conviviality, biodiversity, seasonality, traditional/local/eco-friendly food products, and culinary activities. Moreover, portion sizes should be based on frugality and moderation. Daily consumption of an adequate amount of water is recommended [8].

The food groups whose intake is suggested at every meal, such as vegetables, fresh

fruit, extra virgin olive oil, bread, pasta, rice, and other cereals (preferably whole grains), are located on the first level of the pyramid. Moving upward, we see foods that can be consumed daily, including spices and aromatic herbs (which contribute to salt reduction and contain important micronutrients and bioactive compounds), olives, nuts, and seeds, as well as legumes and low-fat dairy products. Legumes, combined with cereals, deliver higher quality proteins, fiber, and healthy fats (MUFAs and PUFAs), representing a valid alternative to meat. Fish should be eaten more than twice a week, while a moderate intake of poultry (maximum 2 portions per week) and eggs (2–4 portions) is also recommended. Finally, red and processed meat, sweets, and highly processed foods, located at the top of the pyramid, must be rarely consumed. Wine and other alcoholic beverages are also allowed in moderation, respecting social beliefs and traditions [8].

In summary, the MD is a nutritional pattern rich in fiber, MUFAs, PUFAs, and plant-derived bioactive compounds (polyphenols, carotenoids, etc.). These substances are, most likely, responsible for the beneficial health effects of this dietary pattern.

Effects on Health

Until the early years of the twentieth century, there was no compelling evidence that diet and lifestyle could play a role in preventing human diseases. Ancel Keys was the first to demonstrate that eating habits can influence health status globally, and, in particular, the occurrence of CVD. In 1957, he started the project known as "The Seven Countries Study" [10], which comprised 16 cohorts of individuals, aged 40–59, from seven different countries (USA, Finland, Netherlands, Italy, former-Yugoslavia, Greece, and Japan), enrolling more than 12,000 persons [10]. This work showed that consumption of saturated fatty acids (SFAs) is strongly correlated with severe coronary heart disease (CHD) and an increased risk of death, while a high intake of MUFAs and flavonoids is associated with a lower incidence of CHD mortality [11]. Altogether, these data demonstrated, for the first time, that the traditional MD is associated with a reduced risk of developing CVD [12]. Since then, much more evidence has confirmed the beneficial effects of the MD on global health and lifespan: several epidemiological studies, physio-pathological studies, and meta-analysis of prospective cohort studies (including more than 1.5 million subjects) have shown that adherence to the MD leads to a significant reduction in overall mortality (8%), mortality due to CVD (10%), cancer occurrence and progression (6%), and incidence of Parkinson's and Alzheimer's diseases (13%) [13–18].

How to Evaluate Adherence to the Mediterranean Diet

It is important to bear in mind that the protective role of the MD against the development of several NCDs can vary between countries, mainly because of the differences in food intake [3]. Therefore, several so-called adherence scores have been developed in order to better ascertain the degree of adherence to the MD. These scores are composite structures, which combine the amount of dietary components, foods, and nutrients consumed, in order to evaluate the association between the quality of diet and its effects on health [19].

The "Mediterranean Diet Score" (MDS-1) was the first index created to study adherence to the traditional Greek MD [20]. It is comprised of eight components: (1) high ratio of MUFAs to SFAs; (2) high intake of cereals, including bread and potatoes; (3) high intake of vegetables; (4) high intake of fruits and nuts; (5) high intake of legumes; (6) moderate intake of milk and dairy products; (7) moderate alcohol intake; and (8) low intake of meat and meat products. A score between 0 and 1 is assigned to each of these items based on its nutritional quality and frequency of consumption. The medians of the sample of subjects, specific for sex, are used as cut-off points. If the intake of a component is higher than the sample median for the protec-

tive components (fruits, vegetables, etc.) or if it is below the median for the non-protective components (meat, dairy products, etc.), 1 point is assigned. In the opposite situations, 0 points are assigned. Thus, the MDS-1 can range from 0 (minimal adherence) to 8 (maximum adherence). Generally, a score of 4 or more is associated with satisfactory adherence and better health implications [20].

The MDS-1 index is the most widely used score. However, more than 22 variants have been developed for use in different geographical populations. Several studies have established different MD indices and their relationship to the development of NCDs and overall mortality [21].

Cardiovascular Disease (CVD)

Since Ancel Keys' pioneering work, many studies have emphasized the protective effects of the MD on the risk of CVD [13, 22]. In particular, it has been shown that extra virgin olive oil (a rich source of MUFAs and phenolic compounds, with strong antioxidant and anti-inflammatory properties) together with walnuts, fish (rich in omega-3 fatty acids), dietary fiber, and phytosterols (with antioxidant activities) may exert an antiatherogenic function, which contributes to the cardioprotective actions of the MD [13, 22–24]. Reliable evidence has consistently indicated that following the MD results in better cardiovascular health outcomes including a reduction in blood pressure, the expression of markers of vascular inflammation, and the rate of ischemic stroke and CHD [22]. An umbrella review of meta-analyses of randomized controlled trials demonstrated that the MD, compared to other diets, had the strongest and most consistent beneficial effects on ameliorating cardiometabolic risk factors and anthropometric parameters [25].

Interestingly, the adoption of a Mediterranean-like nutritional pattern has been shown to also be beneficial in cardiac rehabilitation, a secondary prevention strategy employed to reduce recurrent cardiovascular events and to improve the quality of life in patients with CVD [26]. Large cohorts of patients with a history of CVD who followed a Mediterranean-like nutritional pattern decreased their risk of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and overall mortality [27].

Cancer

Research findings indicate that the MD also has a strong preventive effect on the development of many kinds of cancer. In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study this nutritional model was the most effective in reducing the overall cancer risk [28]. The Mediterranean lifestyle is particularly successful in the prevention of stomach, esophageal, colorectal, prostate, breast, and endometrial cancers [29–34]. This effect is probably due to the high amount of antioxidants and anti-inflammatory nutrients contained in many of the foods that are characteristic of this diet (legumes, fresh fruits, nuts, vegetables, fish, and extra virgin olive oil). These substances can exert a protective activity against cancer development and progression, preventing DNA damage, and reducing cell degeneration, proliferation, and metastasis [35].

Type 2 Diabetes (T2DM)

Findings suggest that the MD also has a beneficial effect in glycemic control, insulin sensitivity, and primary prevention of T2DM [36]. Epidemiological studies have shown that the MD is associated with a 20% reduced risk of diabetes. A possible explanation is that the diet attenuates inflammation and oxidative stress [37]. Comparable to the effects with CVD and cancer the impact exerted by the MD on T2DM could be attributed to its high antioxidant and anti-inflammatory properties, which are associated with decreased biomarkers of subclinical inflammation (a known risk factor for the development of T2DM) [38]. Dietary fiber is also of impor-

tance as it is believed to induce satiety, reducing caloric intake, preventing weight gain [39], and indirectly protecting against T2DM. Greater intake of total dietary and, particularly, cereal fiber were significantly and inversely associated with the risk of T2DM [40]. Moreover, water-soluble gel-forming fibers (β-glucan) cause a delay in glucose absorption hence decreasing both fasting blood glucose and insulin concentration [41].

Finally, unsaturated fatty acids (PUFAs and/or MUFAs), consumed instead of SFAs and trans fatty acids (TFAs), ameliorate insulin sensitivity [42].

Overweight and Obesity

Obesity is a chronic disease associated with several pathological conditions, including hypertension, dyslipidemia, CVD, alterations of glucose metabolism, T2DM, metabolic syndrome (MetS), and several types of cancer [43, 44]. A firm adherence to the traditional MD correlates with a reduction in body mass index (BMI), overweight, obesity, and the onset of MetS [45]. Accordingly, the latest World Cancer Research Fund (WCRF) report defined the MD as a nutritional pattern that helps maintain a healthy BMI [43] thus indirectly protecting against the development of 12 different types of cancer [44]. In addition, a hypocaloric version of the MD, combined with regular physical activity, is a safe approach to achieve stable weight loss [39].

Chronic Obstructive Pulmonary Disease (COPD)

COPD, the seventh leading cause of death worldwide, is a chronic pulmonary disease characterized by long-term breathing problems and progressive, not fully reversible, airflow limitation [46]. This pathology is influenced by many factors, including genetic susceptibility, environmental conditions, physical inactivity, history of smoking, and diet. Several studies have shown that following a MD, rich in fruits, nuts, vegetables, fish, and whole grains, is associated with a reduced risk of COPD. A likely explanation for this is that the richness of antioxidant and anti-inflammatory compounds, together with the paucity of processed meat, result in a modulation of the oxidative status and inflammatory processes occurring in the lung microenvironment [47, 48].

Osteoporosis

The MD may be effective in reducing bone loss and osteoporosis: some phenolic compounds found in the extra virgin olive oil (apigenin, luteolin, and ferulic, p-coumaric, and caffeic acids) have been suggested to be among the components responsible for the beneficial activity of the MD on bone health [49, 50].

Microbiota

The gut microbiota exerts several beneficial effects on health, including enhancing the host's response toward diseases, increasing the nutrient-exploitation capacity, neutralizing drugs and carcinogens, modulating intestinal motility, and establishing an important feedback with the central nervous system [51]. A healthy microbiota is therefore crucial for protecting against several pathologies, making the impact of nutrition on this ecosystem extremely important. Interestingly, the microbiome in people who follow a MD has elevated concentrations of short-chain fatty acids (SCFAs), derived from the fermentation of dietary fiber. These compounds promote the growth of the beneficial microbiota species Bifidobacteria and Lactobacilli and exert an anti-inflammatory and anticancer activity, in particular against the development of colorectal cancer [52]. More recently, it has been demonstrated that the MD, independent of energy intake, reduces the blood cholesterol level in patients with obesity and promotes healthier aging through the modulation of the gut microbiota [53, 54].

Aging

The regular intake of foods rich in antioxidant and anti-inflammatory substances can slow not only the onset of several pathologies but also delay the aging process, reducing oxidative stress, inflammation, and shortening of telomeres thus promoting healthy longevity [55].

The Healthy Aging: a Longitudinal study in Europe (HALE) is a cohort study that aimed to evaluate the association of specific diet and lifestyle with the mortality rate in an elderly population. The findings indicated that following the MD is associated with a reduction in overall mortality of more than 50%, even at an age between 70 and 90 [56]. Another study that generated valuable findings was the randomized trial NU-AGE (New Dietary Strategies Addressing the Specific Needs of the Elderly Population for Healthy Aging in Europe), which included 1296 European men and women aged 65–80 years. The results suggest that the MD improved both bone density and cognitive health [57].

Sustainability

A diet mainly based on foods derived from plants, when compared to other dietary patterns, especially the Western diet, is associated with a smaller water and energy footprint as well as less land usage and less greenhouse gas emissions. Hence, in order to achieve a sustainable and healthful environment it is essential to eat more plant-based foods and reduce the consumption of meat, animal products, and other processed and packaged foods (snacks, sweets, sweetened beverages, etc.), which are also unhealthy and poor in terms of nutritional value [58, 59]. For instance, by limiting the intake of meat to twice a week, it would be possible to reduce the individual environmental impact, generated by food consumption, by up to one-third [60].

The Barilla Center for Food and Nutrition has produced a version of the traditional Mediterranean food pyramid called the "Double Pyramid Model," in order to assess the impact that a MD has both on human health and the environment (Fig. 16.2) [59, 61]. This pyramid demonstrates that the foods recommended to be consumed most frequently are also those that have a less environmental impact, whereas the ones whose consumption, for health reasons, should be moderated are those with greater impact on soil use, water consumption, and CO_2 emission (Fig. 16.2) [59, 61].

In summary, a Mediterranean-like dietary pattern, compared to nutritional habits based on daily meat consumption, has a lower environmental impact. Accordingly, it is highly recommended for the well-being of our planet.

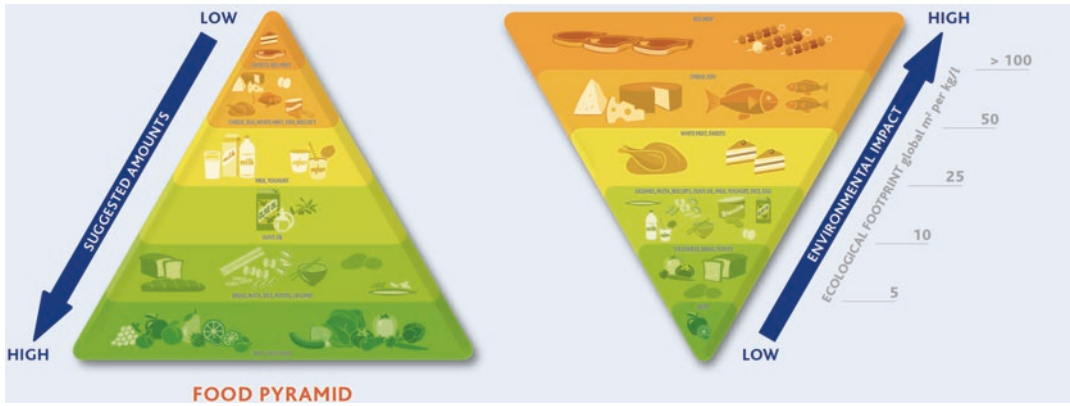

Fig. 16.2 The double pyramid model. From double pyramid: healthy food for people, sustainable food for the planet. Barilla Center for Food and Nutrition [61]

The Mediterranean Diet in Countries Beyond the Mediterranean Area

Even in other parts of the world, the Mediterranean-like eating pattern has been studied and, when feasible, recommended in order to counteract the incidence of noncommunicable diseases [62]. The adoption of a traditional MD can be particularly useful for Western populations, such as the United Kingdom and USA, whose poor diet quality became the primary cause of obesity, chronic diseases, and mortality [63].

For instance, the US Department of Health and Human Services and the US Department of Agriculture (USDA) have published "Dietary Guidelines for Americans," since 1980. These recommendations have been revised every 5 years. In the 2015–2020 version, the Mediterranean-style eating pattern was included, adapting the MD to American tastes and menus [64]. Moreover, many organizations, such as the Harvard School of Public Health [65] and Oldways [66], offer practical tools on how to adapt the traditional MD for Americans. A noteworthy example, created by nutrition experts at the Harvard School of Public Health (HSPH), is the Healthy Eating Plate, a visual guide that complements the healthy eating pyramid and represents a practical way to assemble a balanced and healthy meal based on the MD [67].

Several studies conducted in the USA have examined the effect of a Mediterranean-like diet on people's health, providing evidence of its efficacy in positively influencing the lipid profile in postmenopausal women [68] and reducing the risk of vascular events and death from all causes, including CVD and cancer [69], decreasing the rate of cognitive decline with older people [70], mitigating the metabolic syndrome (MetS) [71], and generally improving the quality of life, decreasing pain, disability, and depressive symptoms [72]. Of course, more research is needed, especially long-term trials such as the one called "Testing the Effects of a Mediterranean Dietary Pattern on Cardiovascular and Other Diseases in the United States," promoted by the National Heart, Lung, and Blood Institute [73].

Similarly, Australian researchers have studied the effect of the MD on people's health, highlighting many beneficial outcomes, including reduction in depressive symptoms, cardiovascular risk, and diabetes-induced mortality, as well as improvements in mental health, and glycemic control [74–76].

Finally, in a UK cohort and in large Eastern European urban populations (Czech Republic, Poland, and the Russian Federation) a greater adherence to the MD resulted in lower CVD incidence and mortality [77, 78].

Feasibility Issues

The abovementioned data paved the way for additional population-based and clinical studies designed to determine the effectiveness of the MD in non-Mediterranean populations. However, it is not always possible to adapt this diet to people living outside the Mediterranean area: in fact, studies might face several barriers, in terms of culture, economy, food availability (in particular, extra virgin olive oil), costs, etc. [79]. For that reason, it is crucial to seek new approaches to promoting healthy Mediterranean-like dietary behaviors beyond this geographical area. It would also be useful to identify a uniform evaluation score to quantify adherence to the MD in epidemiological studies and to discover which are the key components and molecular mediators responsible for its beneficial activities. Table 16.1 lists the major components of the Mediterranean diet and their effects on health. In the meantime, the adoption of a dietary pattern that shares major nutrients and characteristics of the MD should be globally encouraged and promoted, while respecting cultural and socioeconomic realities.

For instance, the New Nordic Diet (NND) is an example of a healthy alternative to the MD; it integrates cuisine and dietary habits from the five Nordic countries. The NND shares many char-

Table 16.1 Major components of the Mediterranean diet and their effects on health

Dietary components	Effects on health
Fiber and phytosterols (whole grains, legumes, vegetables, fruits, nuts, extra virgin olive oil)	1. Cardioprotective actions due to their antioxidant and antiatherogenic properties [57] 2. Prevention of cancer development and progression: protecting against DNA damage, counteracting cell degeneration, proliferation, and metastasis [35, 82] 3. Reduction of inflammatory biomarkers and increase of anti-inflammatory cytokines inversely associated with T2DM risk [38, 40] 4. Beneficial effects on microbiota health *via* the reduction of blood inflammatory markers [83] 5. Delay in aging processes and promotion of healthy longevity [55]
Fiber (whole grains, legumes, vegetables, fruit, nuts)	1. Induction of satiety, reduction of energy intake, prevention of weight gain [39]; delay in glucose absorption thus decreasing both fasting blood glucose concentration and insulin [40, 41] 2. 20% T2DM risk reduction [37] 3. Production of high concentration of SCFAs, with anti-inflammatory and anticancer properties, in particular toward colon cancer development [52]
Phytosterols (extra virgin olive oil)	1. Bone health improvement [73]
Unsaturated fats: MUFAs and PUFAs (extra virgin olive oil, nuts, seeds, omega-3 rich fish)	1. Cardioprotective activity due to their antioxidant, anti-inflammatory, and antiatherogenic properties [13, 23] 2. Prevention of cancer development and progression: protecting against DNA damage, counteracting cell degeneration, proliferation, and metastasis [35, 82] 3. Reduction of inflammatory biomarkers and increase in anti-inflammatory cytokines, inversely associated with T2DM risk [38] 4. Amelioration of insulin sensitivity [42] 5. Prevention of age-related cognitive decline [16, 17], Alzheimer's [15], and Parkinson's disease [84] 6. Beneficial effects on microbiota health *via* the reduction of blood inflammatory markers [83] 7. Delay in aging processes and promotion of healthy longevity [55]

acteristics with the traditional MD, such as high consumption of plant-based foods (fresh fruits, vegetables, legumes, whole grains, aromatic herbs, mushrooms, seaweeds), an abundance of MUFAs and PUFAs (from fish, nuts, seeds, and canola oil, rather than from extra virgin olive oil), and a low intake of red meat, processed foods, and sweets [80].

Finally, despite being characteristic of an Asian country the Japanese and Okinawan diets share many important features with the traditional MD, including a high intake of unrefined carbohydrates, a low glycemic load, high consumption of phytonutrients and antioxidants, a healthy fat profile (high in MUFAs and PUFAs, low in SFAs, and rich in omega-3 PUFAs), a low energy intake, and a moderate protein intake, mainly of plant and fish origin [81].

Conclusion

Despite the extensive epidemiological evidence supporting the many health benefits of the MD, this traditional dietary pattern is no longer followed as broadly as it was 50–60 years ago. The inhabitants of the Mediterranean area, in fact, have "westernized" their diet, which has become higher in energy-dense foods (processed food, refined grains, and food rich in sugars, SFAs, proteins from animal-derived sources, and alcohol) but poorer in substances that promote health (fiber, vitamins, minerals, omega-3 fats, PUFAs, MUFAs, phytochemicals, and antioxidants) [85]. Moreover, massive urbanization, development of automation technologies, and new patterns of transportation have led to a drastic decrease in physical activity, driving the global population toward increasingly

sedentary behaviors. Indeed, unhealthy diets and a sedentary lifestyle are considered, together with tobacco use and excessive alcohol consumption, among the factors that are primarily responsible for the development of NCDs [86].

In agreement with this, a significant increase in NCD burden has been observed in recent years. This is expected to rise even faster in the future, not only in the Mediterranean area but also worldwide. Because NCDs are responsible for the greatest share of early death and disability, those pathologies have a devastating impact on the global economy. Thus, investing in their prevention and management is an urgent ethical and economic requirement, which could avoid both many premature deaths and severe economic shortfalls. Following a healthy diet and a regular physical activity program are among the most cost-effective, affordable, and efficient strategies to prevent and manage the burden of those pathologies [87]. Indeed, efforts are required in order to encourage both Mediterranean and non-Mediterranean populations to adopt the MD, one of the healthiest dietary patterns for living.

In the meantime, further studies are needed in order to better understand the biological and physiological mechanisms that can explain how specific nutrients and bioactive compounds, characteristics of the Mediterranean diet, can modulate the key metabolic pathways involved in the development of NCDs.

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The DASH Dietary Pattern

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Pao-Hwa Lin, Crystal C. Tyson, and Laura P. Svetkey

Key Points

- Strong evidence supports the blood pressure lowering effect of the DASH dietary pattern and its long-term benefit on risk of hypertension and cardiovascular disease, including stroke.
- Observational evidence suggests that the DASH dietary pattern may be beneficial for kidney health and certain cancers.
- The Concordance of the US dietary intake with the DASH pattern is poor.
- Effective strategies for implementing the DASH dietary pattern are needed at the individual and population levels via avenues including health policy and food environment restructuring.

Introduction

The Dietary Approaches to Stop Hypertension (DASH) dietary pattern was first proven to reduce blood pressure (BP) in 1997 [1]. In this landmark randomized controlled feeding trial involving 412 participants, the DASH diet was shown to reduce both systolic and diastolic blood pressure (SBP/DBP) by 5.5/3.0 mmHg by 2 weeks and the effect was sustained for the remainder of the 8 weeks of feeding [2]. The BP reduction was greater among participants who were hypertensive at baseline compared to those with prehypertension (−11.6/−5.3 versus −3.5/−2.1, respectively), similar to the magnitude of one BP lowering medication. This dietary pattern was soon incorporated into the national guideline for BP control (JNC7) [3] and into the Dietary Guideline for Americans in 2005 [4]. The follow-up, large randomized controlled feeding trial (DASH-Sodium) further confirmed the BP effect of the DASH diet by showing that combining the DASH diet with sodium reduction led to BP reduction that was greater than each alone [5]. Many studies, observational and randomized controlled trials (RCT), have shown the benefit of the DASH diet not only on BP but also on risk for cardiovascular disease (CVD) and risk for other chronic diseases. This chapter summarizes research findings since 2017 on the health benefits of and practical suggestions for implementing the DASH dietary pattern.

Design of the Dash Dietary Pattern

Based on epidemiologic associations between nutrient consumption and BP, the DASH dietary pattern was designed to be rich in fiber, potas-

P.-H. Lin (✉) · L. P. Svetkey · C. C. Tyson
Duke University Medical Center, Durham, NC, USA

Department of Medicine, Nephrology Division, Duke University Medical Center, Durham, NC, USA
e-mail: pao.hwa.lin@dm.duke.edu; svetk001@mc.duke.edu; crystal.simpson@duke.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_17

sium, magnesium, and calcium, and, compared to the typical American diet, as well as being slightly higher in protein and lower in total fat, saturated fat, and cholesterol (Table 17.1) [6]. The resultant dietary pattern was high in fruits, vegetables, whole grains, moderately high in low-fat dairy, and seafood, includes nuts/seeds/legumes, and is reduced in meats, sweets, and sugar-sweetened beverages [7]. Even though the design of the DASH dietary pattern targeted the specific nutrients mentioned above, the totality of the food group pattern may have included other nutrients and/or food factors that also contributed to the BP effect. Previous research has shown that the DASH dietary pattern, being rich in fruits and vegetables, is also rich in antioxidants and this has been verified with markers of antioxidant activity and oxidative stress [8]. Further, a secondary analysis of the DASH trial showed that there were 44 known serum metabolites that differed significantly between those who consumed the DASH diet as compared to those who consumed the control diet [9]. These metabolites included an amino acid, 2 pro-vitamin factors, and 44 lipids. These findings suggest that the impact of the DASH dietary pattern may extend beyond the targeted nutrients and beyond BP.

Table 17.1 Comparison of DASH dietary recommendation to the national average intake of American adults

Based on 2100 kcal/day	DASH diet	Average intake of American adults [10–13]
Macronutrients, % of kcal unless otherwise noted		
Carbohydrate	55	47
Total fat	27	36
Saturated fat	6	12
Monounsaturated fat	13	13
Polyunsaturated fat	8	8
Protein	18	16
Cholesterol (mg/day)	150	300
Fiber (g/day)	31	17.3
Micronutrients, mg/day		
Potassium	4700	2633
Magnesium	500	307
Calcium	1240	949
Sodium	3000	3536
Food group, # servings per day unless otherwise noted		
Fruits	4–5	1.8
Vegetables	4–5	3.2
Whole grains	3–4	1
Dairy	2–3	1.5
Meat/seafood	≤6	4.8
Nuts/seeds/legumes	4–5/week	0.81/day
Fats	2–3	12.6
Sweets (use added sugar as an example)	≤5/week	6/day

Effect of DASH Diet on Blood Pressure and Hypertension

The BP lowering effect of the DASH diet has been repeatedly shown in different populations, cultures, and age groups. A significant inverse association was found between DASH adherence and BP in large cross-sectional studies of a Hispanic population [14], a Filipino cohort [15], a French cohort [16], and children of ages 4–18 [17–19]. Large prospective studies using data from the National Health and Nutrition Examination Survey (NHANES) [20] and Jackson Heart Study [21] showed that the higher the adherence to the DASH dietary pattern, the lower the BP, despite overall low adherence. A longitudinal study of 20,239 adults showed that a low adherence to the DASH diet was associated with 11.2% excess risk of incident hypertension in Black women [22]. A higher adherence to the DASH diet was associated with a lower risk for hypertension in both Black and white men and women in the CARDIA study [23]. Multiple meta-analyses also showed that adhering to the DASH dietary pattern was significantly associated with lower BP [24–26].

When RCTs tested behavioral interventions designed to help participants follow the DASH dietary pattern, the BP results varied depending on the degree of adherence [27–29]. In the ENCORE trial, the DASH alone arm lowered SBP/DBP by 11.2/7.5 mmHg while the control arm lowered BP by 3.4/3.8 mmHg ($p < 0.001$). When the DASH intervention was combined with a weight-loss intervention, the BP reduction was even greater (16.1/9.9 mmHg). In addition, when participants adhered more closely to

the DASH diet, there was a greater reduction in BP, independent of weight loss ($P \leq 0.01$) [30]. The PREMIER study also showed that a greater BP effect may be achieved when participants had better adherence to the different components of the behavioral intervention including the DASH diet, weight loss, sodium reduction, alcohol moderation, and physical activity [28]. These findings suggest a potential dose-response relationship between adherence to DASH and the BP effect [31].

The potential dose-response relationship is important, particularly in light of the low adherence achieved in many behavioral coaching studies and at the population level according to national surveys (Table 17.1). It is not surprising that when participants are coached to follow the DASH dietary pattern in a behavioral intervention trial, the adherence is not as high as in the original controlled feeding trials where all foods and beverages were provided for the entire study period. In many behavioral trials, participants were coached via group and/or individual sessions for an intensive contact schedule of weekly to monthly over 4–18 months. In the ENCORE trial, participants increased DASH adherence from a median score of 3.5 (maximum score of 10) at baseline to 6.5 following a 4-month behavioral intervention [30]. In the PREMIER trial, even though adherence to the DASH diet improved at 6 months, the overall adherence score was far from ideal and it relapsed at 18 months [32]. In the HIP behavioral trial, which delivered interventions to both the participants and to their providers, the DASH adherence score increased from a mean of 3.41 (maximum score of 9) at baseline to 4.09 at 6 months, and the increase relapsed slightly to 3.68 at 18 months [33]. These studies indicate the challenge in following the DASH dietary pattern fully and for the long term.

At the population level, despite many efforts by major organizations involved in population health, including the American Heart Association (AHA), the American Dietetic Association (ADA), and the US Department of Agriculture (USDA), in promoting a healthy diet, such as DASH, the average dietary intake of American adults remains unsatisfactory and, specifically, adherence to DASH is poor (Table 17.1). Analyses using data from the 1988 to 2004 NHANES showed that less than 1% of the US population was fully adherent to DASH, and only 20% achieved half of the recommended DASH target nutrient levels [34]. In addition, the 2007–2012 NHANES data showed that the average DASH adherence score was 2.6, far from the potential full score of 9 [35]. Thus, it is obvious that effective strategies that help individuals follow the DASH dietary pattern are urgently needed [31].

Implementation of DASH

Many studies have been conducted to test various behavioral theories in helping participants make lifestyle changes for BP control including following the DASH dietary pattern. A 6-month RCT showed that tailoring the intervention based on the transtheoretical model significantly increased compliance with the DASH diet among 533 adults with uncontrolled hypertension [36]. A comprehensive reminder system based on the Health Belief Model also helped hypertensive ischemic stroke patients in improving health behaviors for BP control [37]. The importance of mindfulness and self-regulation in modifying behaviors was demonstrated in a small study that reduced SBP by 6.1 mmHg ($p = 0.008$) at 1 year [38].

Much research has shown the importance of self-monitoring in lifestyle modification; however, self-monitoring is often tedious and challenging to maintain. Technology may be useful in helping individuals overcome some of the challenges. For example, after 4 weeks of using a self-monitoring device for measuring urinary sodium, participants in a RCT were able to effectively reduce the sodium/potassium ratio significantly [39]. The device seems to have motivated the users to avoid high salt intake and is a creative approach in enhancing motivation for behavior change. Development of mobile apps for self-monitoring dietary intake has also been shown to be promising in helping individuals make life-

style modification and follow the DASH pattern [31]. In a feasibility digital health intervention trial (DASH Cloud), an intervention that used a commercial tracking app with text messaging successfully increased the diet quality of the participants. Currently, an ongoing 12-month RCT is testing a mobile app that features self-monitoring and reminders on adherence to the DASH diet and on BP among adults with high BP (NCT03875768).

Additional research is needed to identify the most effective strategy or technology for lifestyle modification and to identify characteristics of individuals who may benefit from particular strategies. Since socioeconomic status and cultural background influence both diet and incidence of hypertension, they should be taken into consideration in designing lifestyle modification strategies [40].

Peer support and technology-enhanced BP monitoring have also been shown to be effective for hypertension control [41, 42]. Including community health volunteers was highly cost-effective against usual care in reducing BP in a 12-month study in Nepal [43]. Even though physicians play a significant role in patients' compliance with lifestyle recommendations [44], relatively few clinical recommendations for non-pharmacological strategies for hypertension control were given to 4000 hypertensive adult patients in a NHANES survey [45]. Lack of time and/or skill of the providers in addressing lifestyle modifications, or lack of resources in implementing effective strategies, may contribute to the challenges of implementing DASH.

Besides the need for developing effective strategies to help individuals make healthy dietary choices, the food environment also plays a critical role in shaping healthy eating for BP control. Restructuring the food environment may involve reformulating food products provided by food manufacturers and restaurants, either voluntarily or involuntarily as required by policies. Specific strategies can vary but the successful experience of sodium reduction in the UK may shed light on other areas of dietary modification [46]. From 2006 to 2014, the joint effort of the UK government in setting policy, clear targets for both the public and the industry, and the compliance of the food manufacturers and retailers to the salt reduction targets led to a reduction of salt intake in the UK by about 11%. Innovative strategies are needed to restructure the food environment so that more adherence toward the DASH pattern may be achieved at the population level.

Effect of DASH on the Risk of Other Chronic Diseases and Conditions

As can be expected from a healthy dietary pattern like DASH, numerous observational studies have shown associations between following the DASH diet and reduced risk of cardiovascular disease (CVD), and other chronic diseases and conditions including chronic kidney disease (CKD), metabolic syndrome, cancer, and mental health disorders. In a meta-analysis of 68 reports including 1,670,179 participants, diets of high quality as indicated by the Healthy Eating Index, Alternate Healthy Eating Index, and DASH scores resulted in a significant reduction of risk for all-cause mortality, CVD, cancer, type 2 diabetes, and neurodegenerative diseases [47].

DASH and Cardiovascular Diseases

High adherence to the DASH dietary pattern was significantly associated with a lower risk of coronary artery disease (CAD) in prospective studies with large populations, including the Million Veteran Program [48], the Singapore Chinese Health Study [49], and the Caerphilly Prospective Study [50]. A meta-analysis showed that each four-point increase in DASH adherence score (ranging from 8 to 40) was associated with a 5% reduction in risk of CAD (RR: 0.95; 95% CI 0.94–0.97) [51]. Analysis of the data from the ARIC trial also shows that a higher DASH adherence was associated with a lower risk of incident CVD, CVD mortality, and all-cause mortality

among 12,413 US adults [52]. Additional strong evidence of the CVD benefit of the DASH diet came from a meta-analysis of 15 unique prospective cohort studies, 4 systematic reviews, and meta-analyses of 31 unique controlled trials [53]. This analysis shows that greater DASH adherence is associated with lower incident CVD (RR: 0.80; 95% CI 0.76–0.85), Coronary heart disease (0.79; 95% CI 0.71–0.88), stroke (RR: 0.81; 95% CI 0.72–0.92), and diabetes (0.82; 95% CI 0.74–0.92) in prospective cohorts, and lower SBP (−5.2 mmHg; 95% CI −7.0 to −3.4) and DBP (−2.6 mmHg; −3.5 to −1.7) in controlled trials.

Even though RCTs could provide more definitive evidence than observational research, there is very limited RCT data with CVD or other disease outcomes. As such, in the absence of outcome trials, the strong associations between following the DASH dietary pattern and benefits on BP and other outcome markers from observational studies provide a strong rationale for recommending the DASH dietary pattern to promote cardiovascular health. In the ENLIGHTEN RCT, the DASH diet intervention lowered CVD risk significantly after 1 year of follow-up [54]. Overall, very few studies reported null association between DASH adherence and risk of CVD [55]. Thus, the AHA continues to recommend the DASH dietary pattern for cardiovascular health [56].

DASH and Kidney Diseases

Even though the high potassium and increased protein content of the DASH diet had raised concern previously regarding its safety among individuals with kidney disease, research findings have suggested otherwise [57]. In a pilot controlled feeding RCT, consuming the DASH diet for 2 weeks did not lead to clinically significant hyperkalemia or progression of CKD among adults with moderate CKD (estimated glomerular filtration rate (eGFR) of 30–59 mL/min/1.73 m^2) and medication-treated hypertension. A meta-analysis of prospective and 5 cohort studies showed that adherence to the DASH dietary pattern was associated with a lower risk of kidney disease [58]. In a cohort study of 2,403 individuals with chronic renal insufficiency, the most highly adherent tertile to the DASH diet was significantly associated with lower risk of CKD progression and all-cause mortality [59]. In addition, three systematic reviews and meta-analyses have shown that adherence to the DASH dietary pattern was actually associated with a significantly lower risk for developing CKD [60–62]. Adherence to DASH is associated with a lower risk of rapid decline in estimated eGFR ($p = 0.04$) [60]. Further, a greater risk of end-stage renal disease was found among individuals who had poor adherence to the DASH dietary pattern as compared to those with high adherence [63]. Altogether, these findings suggest that the DASH dietary pattern may be safe for CKD and may even be helpful in promoting kidney health.

DASH and Cancer

Although the DASH dietary pattern was not initially designed for the prevention or treatment of cancer, research has shown its potential benefit. The large prospective Sister Study of 50,884 US women showed that a high DASH adherence score was associated with a lower risk of breast cancer (HR: 0.78; 95% CI 0.67–0.90; p-trend = 0.001) [64]. Similarly, a prospective study of 3,450 breast cancer survivors found that DASH adherence was associated with a lower risk of total mortality and breast cancer-specific events [65]. In an Iranian study with 50,045 adults followed for 10.6 years, a higher DASH score was associated with a lower risk of gastrointestinal cancer mortality in men (HR: 0.55; 95% CI 0.30–0.99) and other cancer mortality in women (HR: 0.50; 95% CI 0.24–0.99) [66]. Three meta-analyses also showed that high adherence to DASH was associated with decreased cancer mortality [67, 68] and risk of colorectal cancer (CRC) [69]. In addition, a prospective study showed a strong dose-response association between increasing DASH adherence and decreasing risk of CRC [70]. However,

another analysis of two prospective studies found no association between adherence to the DASH dietary pattern and risk of CRC [71]. Even though the exact mechanism underlying such a potential association is unclear, the high antioxidant content of the DASH diet may play a role. This speculation is supported by previous studies. For example, a case-control study showed that the dietary antioxidant capacity is significantly and inversely associated with risk of CRC [72]. Another population-based case-control study also showed that low dietary antioxidant values were significantly associated with risk of CRC [73]. Further research is needed to clarify the role of the DASH dietary pattern in cancer.

DASH, Cognitive Function, and Mental Health

A growing body of research shows that a healthy diet, such as DASH, may play a beneficial role in cognitive function and mental health. In two large prospective studies (N = 16,144 women ≥70 years old; N = 16,948 adults 45–74 years old), a greater adherence to the DASH diet was significantly associated with better cognitive function [74] and a lower risk of cognitive impairment [75]. In addition, two large cross-sectional studies (N = 23,062 adults; N = 580 teenage girls) and two prospective studies (N = 4,949 and 709 adults, respectively) showed that greater adherence to DASH was significantly associated with a lower incidence or odds of depressive symptoms or recurrent depression [76–79]. Similarly, a cross-sectional study of 240 university students showed that a greater DASH adherence was associated with better mental health and less depression, anxiety, and stress [80]. Though not measuring DASH adherence specifically, a longitudinal study found that low fruit and vegetable intake (<1 portion/day) was a significant correlate of poor mental health across adolescence [81]. Taken altogether, this evidence suggests that a healthy eating pattern, such as the DASH pattern, may benefit cognitive function and mental health; however, more definitive future research is needed.

Practical Tips

Clinicians play a critical role in the care of patients' health and in promoting healthy lifestyles, including adopting healthy eating habits such as the DASH dietary pattern [27]. Even though time, training, and resources may be limited, simple and persistent effort can potentially produce a meaningful impact. The evidence-based 5 A's approach (Ask, Advise, Assess, Assist, and Arrange) [82] can be useful for assisting patients in following the DASH dietary pattern (Fig. 17.1). Clinicians may use the tool in Table 17.2 and follow this approach to (1) ask the patient to recall his/her own eating pattern, (2) advise the patient what DASH is, then to (3) assess the patient's readiness to change his/her eating pattern, (4) assist the patient in identifying a goal toward better DASH adherence and setting an action plan, and, lastly, (5) arrange a follow-up visit to provide accountability. Repeating this process has the potential to shift the patient's eating habits toward his/her goal.

The following lists a few additional tips:

- Utilize and share resources about the DASH diet with patients, e.g., pamphlets from the US government websites: https://www.nhlbi.nih.gov/files/docs/public/heart/dash_brief.pdf;

Fig. 17.1 Using the five A's approach in assisting patients to follow the DASH dietary pattern

Table 17.2 Step-by-step guide in following the DASH dietary pattern

Food groups (serving sizes)	Vegetables (1/2 cup cooked, 1 cup raw leafy greens)	Fruit (1/2 cup, 1 medium-sized fruit)	Dairy (1 cup milk/yogurt, 1 oz cheese)	Whole grains (1/2 cup cooked, 1 slice bread)	Meat/ seafood (3 oz cooked)	Nuts/seeds/ legumes (1/4 cup nuts/seeds, ½ cup legumes)	Sweets (1 serving of dessert, 8 oz sweet drink)	Example: fruit
1. How many servings of each of the food groups on the right do you usually eat in a day? Enter values, then circle one(s) that are different from the values listed in the next row								0.5
2. Recommended servings according to the DASH dietary pattern for someone consuming about 2000 kcal/day	4–5 per day	4–5 per day	2–3 per day	3–4 per day	2 or fewer per day	4–5 per week	5 or fewer per week	4–5 per day
3. Among the one(s) you circled, which food group(s) would you likely work on in the next month? Check all that apply								✓
4. What specific goal would you set for the food groups you checked in #3								Increase 1 per day
5. Write down actions that will help you achieve your goal								Go shopping for fruit on Tuesday
My next visit date/time:								

https://www.nhlbi.nih.gov/health-topics/dash-eating-plan

- Recommend a salt substitute in exchange for regular salt. Various brands are commercially available. Research has shown the effectiveness of using salt substitute in reducing salt intake and thereby lowering BP at the population level [83].
- Utilize more referrals to dietitians for personalized behavioral intervention—Find local dietitians in the Academy of Nutrition and Dietetics website: https://www.eatright.org/find-an-expert
- Utilize more referrals to affordable structured programs, such as the diabetes prevention program offered in YMCA centers across the USA (www.ymca.net).
- Integrate digital tools into treatment recommendations, especially for self-monitoring of dietary intake (e.g., MyFitnessPal).
- Model healthy eating behavior, e.g., if your healthcare setting provides snacks, put healthy snacks out; hang pictures of healthy foods; show healthy eating and lifestyle videos in the waiting area.

Modeling healthy lifestyles within the healthcare setting is an important aspect of helping patients to adopt a healthy lifestyle. How the clinician conveys the message of healthy eating with their patients can usually reveal to the patients how important the clinician thinks the message is to him/herself. Clinicians who make healthy eating a top priority at every visit and who consistently arrange for follow-up visits to keep patients accountable are likely to be successful at helping patients adopt healthy behavior.

Conclusion

The DASH diet is a well-studied dietary pattern with a clear definition of its content and design. Numerous studies have demonstrated its benefit in not only BP and hypertension control but have also shown the associations with reduced risk for CVD (including stroke), CKD, and cancer. This dietary pattern may also be beneficial for cognitive function and mental health; however, research in these areas is less well-established. Even though major health agencies in the USA and other countries have endorsed this dietary pattern for over 20 years, implementation remains a huge challenge and needs to be addressed from various angles including government policies, reformulation of products by food manufacturers, and individual or group coaching. Research is confirming that the dose-response association may be helpful in modifying implementation strategies so that goals are more practical and achievable. In addition, more effective strategies that incorporate tailored behavioral theories and technologies are urgently needed. Public policies that include and reenforce goals for the food industry to produce healthier products (e.g., with less salt in all processed foods and more vegetables in frozen meals) are critical for improving diet quality at the population level.

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The Vegetarian/Flexitarian Diet

18

Derek C. Miketinas and Catherine M. Champagne

Key Points

- Vegetarian diets are gaining popularity in the United States, although only a small fraction of the adult population follows some version of a vegetarian diet.
- Plant-based diets are heterogeneous in practice.
- Well-planned vegetarian and flexitarian diets can be healthy and reduce the risk of many chronic diseases.
- Unstructured vegetarian diets can be deficient in some nutrients like protein, omega-3 fatty acids, calcium, iron, zinc, vitamin B12, and vitamin D.

Introduction

Although vegetarian diets are among the most popular Internet searches globally, their practice within the United States remains low [1, 2]. People follow vegetarian diets for many reasons including ethical considerations, perceived health benefits, religious observance, and taste preferences. The Academy of Nutrition and Dietetics' position on vegetarian diets is that they are "healthful, nutritionally adequate, and may provide health benefits for the prevention and treatment of certain diseases" [3]. Nevertheless, these dietary patterns have implications for assessment, treatment, and counseling. This chapter will review vegetarian diets, their impact on human health, and clinical considerations.

Classifications and Overview

Vegetarian diets can be classified into several distinct categories that vary in the degree to which animal protein is restricted: flexitarian, lacto-ovo-vegetarian, pescatarian, and vegan. Each person might consider their vegetarian dietary pattern different from its classification within the literature. Therefore, it is important for the clinician to assess each patient's dietary patterns instead of relying solely on self-identified classifications. As with any diet, the goal is to emphasize consuming a wide variety of foods and food groups to ensure adequate nutrient intake while also avoiding an excess intake of calories and potentially unhealthy food components.

Flexitarian Diet

Flexitarian diets generally allow only for intermittent consumption of red meat and poultry. The

D. C. Miketinas (✉)
Department of Nutrition and Food Sciences, Texas Woman's University, Houston, TX, USA
e-mail: dmiketinas@twu.edu

C. M. Champagne
Pennington Biomedical Research Center, Baton Rouge, LA, USA
e-mail: Catherine.Champagne@pbrc.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_18

US News and World Reports listed the flexitarian diet as the second-best overall diet tied with the DASH Diet [4]. The flexitarian diet ranked third in healthy eating and first in weight-loss diets (tie). Flexitarian diets ranked sixth for best heart-healthy diets. The flexitarian diet is generally flexible, easy to follow, and offers many individualized meal plans. There are various benefits associated with the vegetarian diet; by including some meat (though significantly less than other eating plans), it may lead to improved overall health and lower chronic disease risk, and may be more acceptable to some, as opposed to completely eliminating meat from the diet.

Pescatarian Diet

Pescatarians exclude red meat and poultry but include seafood, fish, and other animal products like dairy and eggs. This dietary pattern is rich in animal sources of vitamin B12, calcium, vitamin D, and long-chain omega-3 fatty acids. Women who are pregnant or who may become pregnant should avoid larger fish with higher mercury levels such as flounder, ahi tuna, swordfish, and shark.

Lacto-Ovo-Vegetarian Diet

The lacto-ovo-vegetarian diet excludes red meat, seafood, and poultry but includes eggs, dairy, and other animal products. Those who follow this dietary pattern may overly rely on dairy consumption which could lead to excessive saturated fatty acid (SFA) intake, elevated calcium intake (which could affect iron absorption or interact with some medications), and may displace other important food groups.

Vegan Diet

Strict vegan diets exclude all animal products including, but not limited to, red meat, poultry, seafood, dairy, eggs, gelatin, and fatty acids derived from animals (e.g., omega-3 fatty acids from fish). Meeting nutritional needs can be difficult given the restrictive nature of this diet. Nutrients of concern include protein, iron, zinc, long-chain omega-3 fatty acids (DHA and EPA), calcium, and vitamins B12 and D.

Other Vegetarian Diets

Other forms of vegetarian diets have emerged, for example, raw food, fruitarian, and macrobiotic. These diets are extremely restrictive, potentially dangerous, and without scientific merit. Adherence to these diets should be discouraged.

Health Benefits of Vegetarian Diets

The Academy of Nutrition and Dietetics' Nutrition Care Manual considers vegetarian diets as preventative or therapeutic for the following disorders: cardiovascular disease (CVD), hyperlipidemia, coronary heart disease (CHD), hypertension, overweight and obesity, cancer, and type 2 diabetes [5].

Cardiovascular Disease (CVD)

Epidemiological studies report lower CVD risk among vegetarians compared to nonvegetarians. Vegetarians tend to have lower relative risks for CVD-related death, CHD, and cerebrovascular disease compared to nonvegetarians [6]. Historically, these findings were attributed to observed improvements in lipid profiles, blood pressure, and weight; however, more recent research has explored the impact of vegetarian diets on reduced oxidative stress in endothelial cells [7] as well as other potential pathways.

The tendency for observational studies to group nonvegetarian dietary patterns into a single category can be misleading, especially since the DASH and Mediterranean diets are nonvegetarian dietary patterns that have clinical evidence to support their efficacy for reducing CVD risk factors. Results from the CARDIVEG study showed comparable improvements in BMI and fat mass between calorie-restricted vegetarian and Mediterranean diets [8]. Interestingly, the Mediterranean diet resulted in greater reductions in triglycerides while the vegetarian diet resulted in greater decreases in LDL-c and serum B12; however, the vegetarian group's serum B12 was still within normal limits.

Obesity

Those who follow vegetarian, flexitarian, and vegan diets tend to have lower BMI, adiposity, and energy intake [9]. Vegetarian diets promote dietary habits conducive to weight loss such as consumption of high-fiber vegetables and grains and restriction of potentially energy-dense animal products. Although weight loss may not be a goal for every patient, weight maintenance can reduce patients' risk for other chronic diseases.

Cancer

Processed meat consumption has been associated with small increases in the risk for colorectal, breast, and bladder cancers. However, the relative risk estimates are modest, inconsistent, and likely confounded by other lifestyle characteristics. Furthermore, meta-analyses have reported inconsistent associations between increased processed and red meat intake and colorectal cancer type (distal, proximal, and rectal). Those with greater red meat intake also reported higher BMI, alcohol consumption, saturated fat, and total fat intake, while reporting reduced physical activity, fiber intake, and diet quality [10]. Improvements in lifestyle factors and diet quality may be driving the potential reduction in cancer risk observed in vegetarians; similar benefits have also been reported in those who adhere to the Mediterranean diet.

Randomized trials have not explored the use of therapeutic vegetarian diets to reduce mortality risk for cancer patients. Mixed results have been reported for the association between red meat consumption and cancer mortality. A recent meta-analysis of observational studies reported that total meat intake was associated with increased cancer mortality (RR = 1.12 per 100 g serving) but unprocessed red meat and processed meat consumption were not [11].

Type 2 Diabetes

Observational studies consistently report that vegetarians have a lower risk for diabetes compared to nonvegetarians [12]. This is also observed to a lesser extent in flexitarians and lacto-ovo-vegetarians. This risk reduction may be partly mediated by improvements in body weight.

The vegetarian diet is comparable to the Mediterranean and low-carbohydrate diets for reducing fasting glucose and HbA1c in patients with type 2 diabetes [13]. Following a vegetarian diet also results in improvements in insulin sensitivity and body weight reduction [14]. Patients with diabetes who follow a vegetarian diet may improve their LDL-c status thereby lowering their CVD risk.

Bone Health

Bone mineral density (BMD) of the lumbar spine and femoral neck tends to be lower in vegetarians compared to nonvegetarians; however, the differences appear to be clinically insignificant [15]. In studies that identified increased fracture risk among vegetarians and vegans, calcium intake better explained the association rather than vegetarian diet status [16]. The risk for low BMD, osteoporosis, and fractures can be decreased with adequate intake of calcium, vitamin D, protein, and vitamin B12.

Environmental Impact

Animal food production is responsible for approximately 30% of global greenhouse gas production, is a major source of water pollution, and requires massive amounts of freshwater to sustain [17]. As the global population increases and the effects of climate change become more pronounced, it is increasingly imperative that we follow healthier dietary patterns, reduce food waste, and adopt more sustainable food production prac-

tices [18]. Following a plant-based diet can help alleviate the environmental effects of climate change [19]. This topic is covered in proper detail in a Chap. 27 by Berardy and Sabate.

Health Benefits of Flexitarian Diets

In a recent review, Derbyshire [20] reported that there is a movement towards a semi-vegetarian diet that includes occasional meat consumption. The review included 25 studies with focuses on body weight, cancer, diabetes and metabolic health, other health outcomes, and diet quality. The potential health benefits associated with flexitarian/semi-vegetarian diets were weight loss, metabolic health, reduced risk for diabetes, lower blood pressure, and improved symptoms of irritable bowel disease. Limiting or excluding meat tends to reduce calorie intake, which may motivate those who seek weight loss or weight management.

All vegetarian diets are defined in one way or another by avoidance of animal products, completely or partially. Often however these diets do not differentiate between plant foods and products that are nutrient-dense versus nutrient-sparse. A plant-centered diet described by Choi et al. [21] measured using the A Priori Diet Quality Score (APDQS) would be flexitarian but focuses on the quality of plant foods as well as limiting animal foods.

Although there are many positive benefits of plant-based diets, the addition of animal products is a key component to acquiring high-quality protein, fatty acids, and other nutrients, such as bioavailable iron, zinc, and vitamin B12, in significant quantities relative to the proportion of energy. Draper et al. [22] studied the effects of vegan and animal meal composition on glucose and lipid responses and timing of meals. Glycemic and lipid parameters varied regardless of diet type, and both dietary patterns contained health-promoting and suboptimal nutrient combinations. The flexitarian diet is a healthy approach to meet nutritional needs while reducing overall meat consumption.

Nutrients in Vegetarian Diets

Protein

A common dietary concern for vegetarians is inadequate protein intake. On average, protein intake is typically lower among vegans (0.91 g/kg) and vegetarians (0.95 g/kg) compared to pescatarians (1.06 g/kg) and omnivores (1.14 g/kg). Although the average protein intakes of vegetarians and vegans are generally within the recommended range, the odds for inadequate protein intake for vegetarians are 4.2 and 5.3 times greater than for meat eaters (males and females, respectively) [9]. These numbers rise to 7.7 and 7.3 for vegans.

Plant-based protein sources contain essential amino acids necessary for human growth and function, albeit in lower amounts than animal protein sources. For example, legumes tend to have limited methionine content while having adequate lysine content; grains tend to have relatively low amounts of lysine (and threonine). These food groups are complementary proteins since, together, they provide a complete amino acid profile. Current recommendations state that complementary proteins do not need to be eaten together at a meal; however, emerging evidence indicates consuming complementary proteins together may increase methionine absorption and bioavailability [23].

The Institute of Medicine does not recommend separate protein requirements for vegetarians, provided they consume a variety of plant proteins. Plant-based, protein-rich foods include legumes (e.g., soy, beans, lentils, peas), nuts (almond, cashew, peanuts), and seeds (sunflower, pumpkin, flax). It should be borne in mind that some plant-based food products may have a relatively high content of nutrients that need to be reduced, like sodium and saturated fatty acids;

therefore, it is important to educate patients to choose healthier alternatives.

Carbohydrates and Fiber

The target range for total carbohydrate intake is 45–65% of energy, although humans can eat considerably less without significant concerns. Exclusion of some carbohydrate-rich foods, such as whole grains, enriched cereals, and starchy vegetables or fruit, can lead to inadequate intakes of some vitamins, minerals, and fiber. Vegetarians and vegans tend to report a slightly greater carbohydrate intake compared to meat eaters; therefore, nutrient-dense carbohydrate sources, like those high in fiber, should be encouraged.

The current recommendation for dietary fiber is 14 g/1000 kcal; this is approximately 21–25 g/day for non-pregnant women and 30–38 g/day for men. This is based on the amount of dietary fiber intake associated with a reduced risk for CVD. Dietary fiber has a myriad of health benefits beyond a reduction in CVD risk and should be emphasized in any diet. Adequate dietary fiber intake promotes satiety and normal GI function [24]. Moreover, dietary fiber intake has been associated with dietary adherence, weight loss [25], reduced diabetes risk [26], reduced risk for some cancers [27], and reduced risk for hypertension [28].

Fat

Current recommendations for total fat consumption are 20–35% of energy from total fat, between 11 and 17 g/day of linoleic acid (omega-6), between 1.1 and 1.6 g/day of alpha-linolenic acid (omega-3), and less than 10% of energy from saturated fatty acids. Total dietary fat intake is comparable across meat eaters, fish eaters, vegetarians, and vegans; however, the fatty-acid profiles vary significantly for vegans [9]. Although vegetarians have similar saturated fatty acid (SFA) and polyunsaturated fatty acid intake to meat and fish eaters, vegans have lower intakes of these nutrients.

Saturated Fatty Acids

SFA contain no double bonds on their carbon chain. Current recommendations limit consumption of SFA as overconsumption is associated with an increased risk for chronic diseases. In contrast, emerging research suggests that even-chain SFA are positively associated with chronic disease risk while serum levels of odd- and long-chain SFA are inversely associated with chronic disease risk [29, 30].

Coconut and palm kernel oils contain approximately 82 g SFA per 100 g of oil. All of the SFA from these oils are even-chain SFA. Two tablespoons of either coconut or palm kernel oil exceed the SFA recommendation for a person adhering to a 2000 kcal diet. Although these fats may have gained the reputation of being a "healthy food" in popular culture, their consumption should be limited to meet the recommendations.

Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids; they include alpha-linolenic acid (ALA) and the elongated versions of ALA: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Humans must consume ALA since it cannot be synthesized endogenously. Although humans contain the necessary enzymes to elongate ALA to DHA and EPA, this activity is limited and further suppressed by high linoleic intake (omega-6). Therefore, DHA and EPA must come from the diet (Tables 18.1 and 18.2).

While recommendations for intakes of DHA and EPA vary by professional organization, the Dietary Guidelines for Americans recommend 250 mg/day, which can be obtained from 8 oz per week of seafood. This recommendation is based on the observed decreased risk for cardiac deaths in those without preexisting CVD. Adequate omega-3 intake is also important for brain devel-

opment in infants and children, organ function, cellular membrane integrity and function, and hormone production. Omega-3 intake can also improve serum lipid parameters, suppress inflammatory responses, and lower blood pressure.

ALA intake is similar among vegans, vegetarians, and nonvegetarians. Vegetarian intake of EPA and DHA varies according to the inclusion of supplements and seafood whereas EPA and DHA intake is virtually nonexistent in vegans unless they take supplements. Although vegans and some vegetarians may have low EPA and DHA intake, there appear to be no associated health consequences.

Calcium

Calcium intake for lacto-ovo-vegetarians tends to meet or exceed recommendations [3, 9]. However, vegan men and women have 6.7 and 5.6 greater odds for inadequate calcium intake, respectively, in comparison with vegetarians [9]. Oxalic and phytic acids bind to calcium and inhibit its

Table 18.1 Sources of nutrients in vegan diets

Nutrient	Vegan sources	Amount per serving	Notes
Omega-3 fatty acids	Chia seeds	5.06 g (ALA)	Supplementation may be required. ALA is not efficiently converted to DHA and EPA in humans
	English walnuts	2.57 g (ALA)	
	Flaxseed	2.35 g (ALA)	
	Canola oil	1.28 g (ALA)	
	Soybean oil	0.92 (ALA)	
Calcium	Orange juice, calcium fortified	349 mg	Oxalate, phytate, low vitamin D intake, and drugs can reduce bioavailability and absorption
	Soy milk, fortified	299 mg	
	Tofu, made with calcium sulfate	253 mg	
	Breakfast cereals	130 mg	
	Greens, cooked (kale and turnip)	47–99 mg	
Iron	Breakfast cereals, fortified	18 mg	Non-heme iron absorption can be increased by vitamin C, retinol, carotenoids, and citric acid
	White beans	8 mg	
	Lentils	3 mg	
	Spinach	3 mg	
	Potato, baked	2 mg	
Zinc	Baked beans	2.9 mg	Phytic acid reduces zinc bioavailability. Zinc supplementation can impair tetracycline, penicillamine, and copper absorption
	Breakfast cereal, fortified	2.8 mg	
	Pumpkin seeds	2.2 mg	
	Cashews	1.6 mg	
	Chickpeas	1.3 mg	
Vitamin B12	Nutritional yeast, fortified	2.4 μg	Supplementation may be required. Aminoglycosides, antivirals, aspirin, ethanol, H2 blockers, metformin, oral contraceptives, and tetracyclines can increase risk of B12 deficiency
	Breakfast cereals, fortified	0.6 μg	
Vitamin D	Mushrooms, UV exposed	366 IU	Supplementation may be required. Risk for deficiency increases in older adults, bariatric surgery patients, people with obesity, and medications that inhibit fat absorption
	Soy milk, fortified	100–144 IU	
	Breakfast cereal, fortified	80 IU	
	Portabella mushrooms	4 IU	

Omega-3 fatty acid recommendations include alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA)

Table 18.2 Sources of nutrients in vegetarian diets

Nutrient	Vegetarian sources	Amounts per serving
n-3 fatty acids	Chia seeds	5.06 g (ALA)
	English walnuts	2.57 g (ALA)
	Flaxseed	2.35 g (ALA)
	Salmon	1.24 g (DHA); 0.35–0.59 g (EPA)
	Canola oil	1.28 g (ALA)
Calcium	Yogurt, plain	415 mg
	Orange juice, calcium fortified	349 mg
	Mozzarella	333 mg
	Sardines, with bones	325 mg
	Soy milk, fortified	299 mg
Iron	Breakfast cereals, fortified	18 mg
	Oysters	8 mg
	White beans	8 mg
	Lentils	3 mg
	Spinach	3 mg
	Tofu	3 mg
Zinc	Oysters	74 mg
	Crab, Alaska King	6.5 mg
	Baked beans	2.9 mg
	Breakfast cereal, fortified	2.8 mg
	Pumpkin seeds	2.2 mg
Vitamin B12	Clams	84.1 μg
	Fish (tuna, trout, salmon)	2.5–5.4
	Nutritional yeast, fortified	2.4 μg
	Milk	1.2 μg
	Yogurt	1.1 μg
	Breakfast cereals, fortified	0.6 μg
Vitamin D	Cod liver oil	1360 IU
	Fish (salmon and trout)	570–645 IU
	Mushrooms, UV exposed	366 IU
	Milk, fortified	120 IU
	Soy milk, fortified	100–144 IU

Omega-3 fatty acid recommendations include alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA)

absorption; foods high in these calcium chelators include spinach, greens, beans, and sweet potatoes. It is therefore important for vegetarians to consume calcium-rich foods (Tables 18.1 and 18.2) and avoid co-consuming foods high in chelating agents. Vitamin D status can also influence calcium absorption.

Calcium malabsorption can be caused by prednisone (and other glucocorticoids), cyclosporine, antibiotics, and sulfonamides, to name a few [31]. Anti-epileptics and lipase inhibitors (e.g., Orlistat) can impair vitamin D absorption, leading to secondary calcium deficiency. Calcium excretion can be increased by loop diuretics, corticosteroids, albuterol, antacids (containing aluminum), and other medications.

Vitamin D

Vitamin D is a fat-soluble vitamin that is important for calcium absorption in the small intestine, maintaining blood calcium and phosphorous concentrations, and for bone growth and remodeling. People can meet their vitamin D requirements with adequate sunlight exposure. Dietary sources of naturally occurring vitamin D are limited; rather, people must rely on fortified foods and dietary supplements if adequate sun exposure is unachievable (Tables 18.1 and 18.2). Factors that may impede adequate sunlight exposure include season, skin melanin content, clothing, sunscreen, length of the day, and other environmental factors (e.g., urban environments, air pollution, and cloud cover).

Inadequate vitamin D intake does not appear to differ between vegetarians and nonvegetarians. However, the following groups appear to have an increased risk for vitamin D deficiency: older adults, people who have certain medical conditions or are taking medications that inhibit fat absorption, people with obesity, and people who have had bariatric surgery. Although sun exposure is important for synthesis, sunlight exposure should be controlled to reduce the risk of melanoma.

Iron

Iron deficiency can result from poor intake as well as poor absorption. Iron absorption is affected by the amount consumed, the source of iron, and iron status. The two main forms of dietary iron include heme, which is easily absorbed and can be found in animal products, and non-heme, which is less bioavailable and can be found in plants and iron-fortified foods. The goal of persons who eat a vegetarian or vegan diet should be to promote the consumption of iron-rich sources (Tables 18.1 and 18.2) while co-consuming foods or beverages that have nutrients that enhance iron absorption: vitamin C, retinol, carotenoids, fructose, stearic acid, and citric acid. Phytic acid is the major phosphorous storage form in plants, representing 50–85% of total phosphorous; 250 mg of phytic acid can impair iron absorption by 80% [32].

Iron supplementation may be necessary to achieve adequate intake; however, certain drugs and nutrients can inhibit iron absorption. Antacids (containing magnesium hydroxide), cholestyramine, H2 blockers, tetracycline, neomycin, penicillamine, haloperidol, calcium, and zinc can decrease iron absorption [31]. Aspirin, NSAIDs, haloperidol, deferoxamine, and stanozolol can increase the risk of iron stores depletion. Normal serum iron ranges between 80 and 150 μg/dL (12–24 μmol/L) and should be monitored in patients at risk for deficiency.

Zinc

Animal products contain highly bioavailable zinc. Therefore, reliance on plant sources can lead to an increased risk of inadequate intake. Moreover, plant sources of zinc also tend to be high in phytic and oxalic acids, which bind to zinc and inhibit its absorption. The zinc requirement for vegetarians can exceed the RDA by as much as 50%. Compared to pescatarians, vegetarians have over 12 times greater odds of inadequate zinc intake [9]. Strategies to increase zinc bioavailability include leavening bread and soaking/sprouting beans, grains, and seeds to reduce their phytic acid content at the time of ingestion. Zinc-rich food sources for persons who eat a vegetarian or vegan diet are shown in Tables 18.1 and 18.2.

Although bioavailability and intake may be low among vegetarians and vegans, serum zinc levels tend to stay within a normal range (60–130 μg/dL). Only in instances of malnutrition, infection, burns, and liver disease are serum zinc levels likely to fall below the target range. Drug interactions with zinc supplementation also need to be considered.

Zinc supplementation inhibits the absorption of tetracycline and penicillamine [31]. ACE inhibitors can decrease zinc absorption while N-acetyl cysteine can increase zinc excretion in the urine. Copper absorption can be inhibited by zinc, leading to secondary copper deficiency; therefore, a zinc supplement should also include copper. Long-term zinc supplementation above the Tolerable Upper Limit (40 mg/day) could also lead to iron deficiency, impaired iron function, altered kidney function, and impaired immune function. High doses for medical treatment (short term) require monitoring; symptoms of toxicity include nausea/vomiting, diarrhea, dizziness, atherosclerosis, and renal failure.

Vitamin B12

Vitamin B12 (cobalamin) intake is especially important for neurological function, erythropoiesis, DNA synthesis, and the prevention of neural tube defects. Meat and fish eaters are not at risk for inadequate B12 intake. Vegetarians have slightly greater odds for inadequate vitamin B12 intake compared to nonvegetarians; however, men and women who follow vegan diets have 27 and 38 times the odds for inadequate B12 intake, respectively, compared to their vegetarian counterparts [9]. Although the frequency of inadequate intake is great for vegans, clinical manifestations of cobalamin deficiency may not be present. Vegetarians and vegans should be encouraged to consume foods fortified with vita-

min B12, such as cereals, yeast, and soy milk, or receive supplemental B12 to mitigate the risk of inadequacy. Tables 18.1 and 18.2 show food sources that supply vitamin B12 for persons who eat a vegetarian or vegan diet.

Drugs that increase the risk for B12 deficiency include (but are not limited to) aminoglycosides, antivirals, aspirin, ethanol, H2 blockers, metformin, some oral contraceptives, and tetracyclines [31]. Symptoms of B12 deficiency in adults include megaloblastic or macrocytic anemia, fatigue, poor cognition, tingling in the fingers, depression, macular degeneration, and hearing loss [3]. Tests for B12 status include serum B12, holotranscobalamin (Holo-TC), homocysteine, and methylmalonic acid.

Summary

Vegetarian diets are increasingly popular in developed countries due, in part, to a variety of health claims. Although vegetarian diets have been associated with a reduced risk of chronic diseases, omitting meat is neither necessary nor sufficient for health promotion and disease prevention. The DASH Diet and Mediterranean Diet are as effective as vegetarian diets for overall health promotion and disease prevention. The flexitarian diet is gaining in popularity and offers benefits associated with limited meat or poultry consumption. Carefully planned vegetarian diets are safe and nutritionally adequate; however, proper implementation of any diet requires patient education, monitoring, and evaluation to meet nutritional goals.

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Low-Carbohydrate Nutrition and Disease Prevention

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William S. Yancy Jr and Eric C. Westman

Key Points

- There exists minimal evidence from high-quality, randomized controlled trials that supports any one eating pattern for the prevention of disease or mortality.
- Observational research regarding low-carbohydrate nutrition and disease prevention is limited by the use of a "low-carbohydrate diet score" that is applied to populations containing few people who are restricting carbohydrate intake substantially.
- Observational research shows mixed results regarding the relationship between a low-carbohydrate eating pattern and risk for cardiovascular disease (CVD), type 2 diabetes, and certain cancers.
- Common themes in some of these studies are that plant-based low-carbohydrate patterns are associated with lower risk whereas high-glycemic index/load patterns are associated with higher risk.
- Randomized controlled trials of low-carbohydrate eating patterns (compared with control diets) have shown greater improvement in several intermediate risk factors, including blood pressure, serum HDL cholesterol, serum triglycerides, and hemoglobin A1c.
- There is a need for randomized controlled trials that investigate the relationship between low-carbohydrate eating patterns and disease incidence or mortality as a primary outcome.

Introduction

Dietary change has great potential for preventing health problems. Wide varieties of dietary changes have been recommended over many decades with opinions on some recommendations fluctuating over that time span [1]. Few recommendations however are based on solid evidence due to the difficult nature of studying diet in general and especially over long durations, which is necessary for prevention studies. Low-carbohydrate nutrition has been used for over a century for the treatment of obesity as well as many health issues that are associated with obesity and some that are not associated with obesity. Substantial research has supported the use of the low-carbohydrate eating pattern for many of these conditions [2], but research on low-carbohydrate nutrition for the prevention of health problems is more limited.

Because of the confounding that is inherently present in observational studies on nutrition and health, the gold standard for determining whether

W. S. Yancy Jr (✉) · E. C. Westman
Division of General Internal Medicine, Department of Medicine, Duke University Medical Center, Durham, NC, USA
e-mail: will.yancy@duke.edu; westm001@duke.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_19

a diet approach can prevent disease is a randomized controlled trial (RCT) [3]. To our knowledge, an appropriately powered RCT of a low-carbohydrate diet intervention with prevention of a particular disease as the primary outcome has not been performed. In fact, few such studies using any dietary approach have been reported [4]. Well-known examples include the Women's Health Initiative, PREDIMED, the Diabetes Prevention Program, and Look AHEAD [5–8].

Randomized Clinical Trials of Diet and Disease Prevention

The Women's Health Initiative randomized 48,835 women to either a very-low-fat diet (<20% of daily energy) or control, which was the maintenance of the baseline diet [3]. Over 6 years, there were reductions in fat intake, LDL-cholesterol, and diastolic blood pressure, and increases in intake of fruits and vegetables and grains in the intervention group compared to control. Further, secondary analyses noted that greater reduction in fat intake was associated with greater weight loss. Nevertheless, no differences were noted between the two groups in the incidence of coronary heart disease (CHD), stroke, or a composite of these that included revascularization or death related to CHD or stroke.

In the PREDIMED study, 7447 participants were randomized to either of two Mediterranean diet interventions (one supplemented with olive oil, the other with nuts) or a low-fat diet intervention [6]. At a median of 4.8 years, the Mediterranean diet arms experienced an approximate 30% relative reduction (0.6–1.0% absolute reduction) in the composite end-point of myocardial infarction, stroke, or death from cardiovascular causes. In addition to problems with randomization that were discovered and reported subsequent to the main findings, another major limitation of this study was that extra-virgin olive oil or mixed nuts were supplied to individuals in the two Mediterranean diet groups but no food was provided to low-fat diet participants. This could have enhanced adherence in the intervention groups compared with the control group while at the same time focusing changes on olive oil and nut intake instead of the full composition of the Mediterranean diet [9].

A third landmark prevention study with onset of diabetes as its outcome, the Diabetes Prevention Program, demonstrated that a low-fat, reduced-calorie diet plus exercise lowered the incidence of type 2 diabetes (T2DM) by ≈60%, with subsequent analyses demonstrating that weight loss was the strongest predictor (over fat intake reduction and increased physical activity) of diabetes prevention [8, 10]. These landmark studies highlight the limits to existing RCT evidence available on nutrition interventions and prevention of cardiovascular disease (CVD) and T2DM.

The Look AHEAD study was designed specifically to examine whether weight loss would reduce mortality and CVD outcomes in patients who had T2DM and elevated body mass index (BMI) [7]. While the study was terminated early on the basis of futility, post-hoc analyses showed that participants in the intensive lifestyle intervention group who lost 10% or more of their weight had a significant 20% reduction in the composite cardiovascular end-point compared with the control group. This demonstrates an inherent, yet necessary, limitation of "intent-to-treat" analysis because it is inevitable that a portion of participants will not lose weight and would not be expected to receive the potential benefits from weight loss [11].

In the absence of RCTs with disease incidence for outcomes, insight into the potential effectiveness of low-carbohydrate nutrition for disease prevention comes from observational studies and RCTs with intermediate outcomes.

Background and History of Low-Carbohydrate Eating Patterns

One of the first publications of a low-carbohydrate eating plan was a description of its use for weight loss by William Banting in 1863 [12]. Subsequently, a low-carbohydrate, high-fat diet has become a common method of weight management with many endorsements in the lay press from physi-

cians who have used it in clinical practice and support in the scientific literature [13–18]. In England, in fact, the term "banting" refers to losing weight by reducing sugar and starch in the diet.

Before effective medications were available, a low-carbohydrate, high-fat diet was also used to manage diabetes. As early as 1877, a medical textbook stated: "There are few diseases which present to the practitioner so clear an indication of what is to be done…a Diabetic should exclude all saccharine [sugary] and farinaceous [starchy] materials from his diet" [19]. In the early 1900s, leading authorities in diabetes used low-carbohydrate dietary plans for therapy, with Frederick Allen publishing several studies and Elliott Joslin successfully using a 70% fat, 10% carbohydrate diet [20, 21]. After the discovery of insulin in 1921, however, exogenous insulin administration became the mainstay of therapy, allowing for an increase in dietary carbohydrate for people with diabetes.

In 1921, the Mayo Clinic reported results from a series of patients with epilepsy treated successfully with a ketone-producing diet. The diet was coined as the "ketogenic diet" and became an effective alternative to fasting, which was previously touted for seizure control [22]. Similar to the history of diabetes management and insulin discovery, ketogenic diets were widely used for epilepsy until the development of antiepileptic drugs. Subsequently, the diet's use declined but resurged again in the 1990s after a case report of successful seizure control in a child and reports of the first prospective RCTs showing efficacy of the ketogenic diet for reducing seizure frequency in children [23, 24].

Nutritional guidelines for "healthy" Americans have traditionally recommended that individuals consume 45–65% of daily energy intake from carbohydrates, with a focus on those high in fiber. The average American diet consists of 2200 kcal per day, with approximately 33% of energy from fat, 16% from protein, and 50% from carbohydrates [25]. The percentage of energy from the macronutrients has varied over the years, related to guideline recommendations but also seemingly to scientific reports and popularity of certain dietary approaches (Fig. 19.1) [25–28]. It is noteworthy that the rise in intake of carbohydrates (as a percent of total energy) after 1976 corresponds to the rise in prevalence of obesity during the same years. Low-carbohydrate diets have commonly been defined as <40–45% of energy from carbohydrates with very-low-carbohydrate diets variably defined as <26% of energy from carbohydrates or <50 g per day depending on the review [29]. These eating plans emphasize protein from meat, poultry, fish, shellfish, eggs, cheese, and nuts; fats from animal and plant sources; and carbohydrates from non-starchy vegetables and certain fruits low in sugar such as berries or melon. They avoid starchy and sugary foods such as bread, pasta, rice, potatoes, certain fruits, sweets, and sweet beverages.

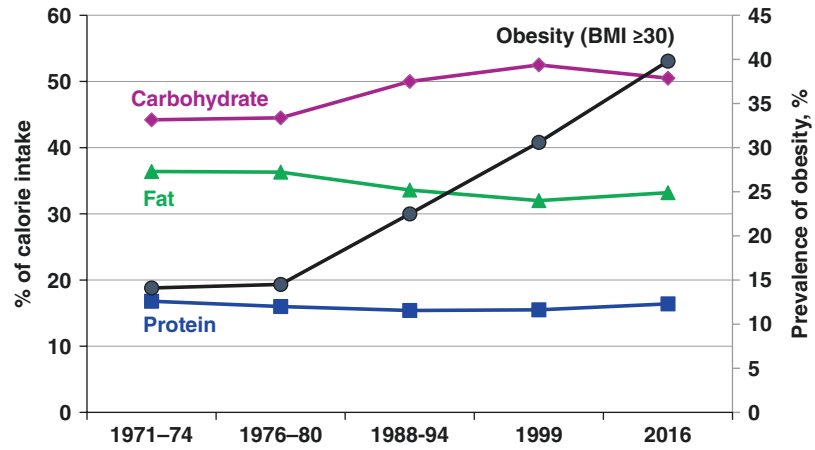

Fig. 19.1 Trends in macronutrient intake and obesity. Modified after references [26–28]

Observational Studies of Low-Carbohydrate Diet and Disease Prevention

Reduction or augmentation of risk related to low-carbohydrate eating patterns is most often assessed by performing secondary analyses to an existing observational study, typically a cohort study. In most scenarios, the researchers apply a "low-carbohydrate-diet score" to self-reported dietary intake data. Observational research is commonly used for many reasons to examine the relationship between nutrition and disease prevention. For one, it is very difficult to perform effective long-term RCTs of nutritional interventions due to the long duration of follow-up required and the difficulty participants have with adherence to dietary recommendations. Such studies also require large samples to detect effects. These requirements lead to substantial costs, which are not supported by any particular industry, and therefore governmental agencies or philanthropies are the primary sources of grant funding.

Observational studies of nutrition and disease prevention however are limited in several ways. They rely on self-reported dietary intake, which has been recognized by many experts as inaccurate and subject to recall bias regardless of whether the research is observational or experimental. In addition, observational research is subject to confounding, some of which can be controlled but it is likely that residual confounding remains. For example, in one rigorously performed study examining risk for CHD, women who consumed a lower carbohydrate dietary pattern were more likely to have a family history of heart disease and to smoke, less likely to take a multivitamin, and had a higher mean BMI and lower levels of exercise [30]. Based on these differences among a wide range of factors, it is also very possible for these participants to possess other high-risk attributes that were not measured. Evidence for this can be gleaned by comparing the relative risk for heart disease of animal fat intake in models adjusting only for age and smoking history versus the full multivariate models. In the models with age and smoking only, the relative risk was 1.36 for the highest animal fat intake decile with $p = 0.003$ for the trend across deciles. These numbers fell to 0.98 and $p = 0.66$, respectively, for the full multivariate models.

Cardiovascular Disease and Mortality

In observational research focused on low-carbohydrate nutrition and its relation to disease prevention, researchers typically derive a "low-carbohydrate-diet score," which has its own limitations. In the article just described, participants were ranked in deciles of protein, fat, and carbohydrate intake using self-reported food intake by food frequency questionnaire. Then, using a composite score from the three macronutrient rankings, those with the highest intakes of protein and fat and lowest in carbohydrate were considered to most closely follow a low-carbohydrate dietary pattern. One problem with this strategy is that the number of participants in the top decile of the low-carbohydrate-diet score was only 3693 in a total sample of 82,802, representing just 4.5% of the sample. The other more important issue is that the decile defining the lowest carbohydrate intake was defined as a carbohydrate intake of <29.3% of daily energy intake, with a mean intake of 117 g per day. In other words, this decile of individuals included a wide spectrum of carbohydrate intake that could range from nearly 0% of energy intake to almost 30% of energy intake. However, this contrasts with what is commonly considered a very-low-carbohydrate eating pattern: <10% of daily energy intake or <50 g per day of carbohydrate. Nevertheless, in this rigorously performed study, the low-carbohydrate-diet score was not related to the risk of CHD and, in fact, the best predictors of CHD were a high-glycemic index eating pattern or a low vegetable fat eating pattern.

Other studies have had variable results. Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, researchers examined 2226 participants with a baseline coronary artery calcium (CAC) score of 0 and found that carbohydrate intake as a percentage of total

energy was inversely associated with the risk of CAC progression (hazard ratio [HR] 0.73; 95% CI: 0.55–0.97) [31]. Similar to other studies, it found that an animal-based but not plant-based low-carbohydrate-diet (LCD) score was significantly associated with a higher risk of CAC progression. In another study using 24 h dietary recall data from 37,233 adults in the US National Health and Nutrition Examination Survey (NHANES), neither an overall LCD nor an overall low-fat-diet score was associated with total mortality, but the "healthy" versions of both scores (emphasizing high-quality carbohydrate, plant protein, and unsaturated fat) were associated with lower mortality and the "unhealthy" versions with higher mortality [32]. A similar study using data from 85,168 women in the Nurses' Health Study and 44,548 men in the Health Professionals' Follow-up Study found that overall LCD score was associated with a slight increase in overall mortality; the hazard ratio comparing highest to lowest deciles was 1.12 [95% CI: 1.01–1.24], but the *P* value for the trend across deciles was not significant [33]. Similar to other studies, the animal LCD score was related to higher risk whereas the vegetable version of the score was associated with decreased risk.

Type 2 Diabetes and Metabolic Syndrome

The LCD score has also been applied in observational studies to metabolic outcomes such as T2DM and the metabolic syndrome. Similar to studies with CVD and mortality outcomes, results have been variable depending on the population, outcome, and type of score used. For example, in 85,059 women in the Nurses' Health Study, the relative risk (RR) for T2DM incidence was 0.90 (95% CI: 0.78–1.04; *P* trend = 0.26) comparing the highest decile of LCD score with the lowest decile [34]. However, the relative risk was 0.99 for this comparison using an LCD score based on animal sources whereas it was 0.82 (95% CI: 0.71–0.94; *P* trend = 0.001) with a score based on plant sources. The study found that higher carbohydrate consumption and most prominently higher dietary glycemic load were also associated with T2DM incidence. In this study, mean carbohydrate intake was 29.6% of daily energy intake in the top decile of the total LCD score. In a subsample from this study focused on women with a history of gestational diabetes, HRs (95% CIs) for T2DM, comparing the highest with lowest quintiles, were 1.36 (1.04–1.78; *P* trend = 0.003) for overall LCD score, 1.40 (1.06–1.84; *P* trend = 0.004) for the animal-based score, and 1.19 (0.91–1.55; *P* trend = 0.50) for the vegetable-based score [35]. In a study of 40,475 men using the Health Professionals Follow-up Study, results were noticeably different [36]. Both the overall (HR 1.31; 95% CI: 1.14–1.49) and animal-based (HR 1.37, 95% CI: 1.20–1.58) LCD scores were associated with mild increased risk comparing high to low quintiles, whereas the plant-based score was not. Adjusting further for red and processed meat substantially reduced the relative risk for the animal-based score (HR 1.11; 95% CI: 0.95–1.30), providing additional evidence for the confounding that occurs in these studies.

Cancer

An LCD score has also been investigated for a possible relationship with risk of cancer. In a Swedish population study of 62,582 men and women, the low-carbohydrate, high-protein (LCHP) score was not related to cancer risk, except for a non-dose-dependent, positive association of moderate LCHP score with respiratory tract cancer in men [37]. There was also an inverse association of the LCHP score with colorectal cancer in women with high saturated fat intake and a positive association of the LCHP *vegetable*-based score with colorectal cancer. These findings underscore some of the inconsistencies of results with the lack of dose effect for respiratory cancers in men and the vegetable-based score being associated with higher risk of colon cancer, which is contrary to current paradigms regarding this type of cancer. In another analysis of the Nurses' Health Study, diet scores were calculated for both the low-carbohydrate and Dietary Approaches to

Stop Hypertension (DASH) eating patterns [38]. Across quintiles, the DASH score was associated with a lower risk of estrogen receptor-negative breast cancer (RR comparing extreme quintiles 0.80; 95% CI: 0.64–1.01, *P* trend = 0.02) but this effect was explained by higher intakes of vegetables and fruit. There also was an inverse association between the vegetable-based, LCD score and risk of ER cancer (RR 0.81; 95% CI: 0.65–1.01; *P* trend = 0.03) but no evident association using the overall and animal-based scores. Mean carbohydrate intake was actually not very low in the fifth (lowest carbohydrate) quintile of the overall LCD score, at 43.8% of energy.

Around the World

In studies of populations outside of the United States, where carbohydrate intake is traditionally higher on average, the LCD score has been associated variably with lower, no, or higher risk. For example, in an Iranian population, there was no association between the LCD score and risk of CVD outcomes in all participants (HR 0.93; 95% CI: 0.86–1.02) and women (HR 1.13; 95% CI: 0.94–1.36) but the score was associated with a *reduced* incidence of CVD in men (HR 0.89; 95% CI: 0.80–0.98; *P* trend = 0.028) [39]. In a Greek population of 22,944 adults, the LCD score associated with increased mortality by a ratio of 1.22 (95% CI: 1.09–1.36) [40]. A study of 77,319 Swedish men and women, however, did not find an association between the LCD score and mortality [41].

The LCD score was associated with an increased risk for T2DM in a Chinese population [42]. Similar to other studies, adjusting for important confounders greatly attenuated the risk—from RR 2.75 to RR 1.87 after adding socioeconomic status and physical activity to the initial multivariate model. Conversely, in a Japanese population of 64,674 adults, the overall LCD score was associated with decreased odds of T2DM in women (odds ratio [OR] for highest vs lowest quintile 0.63; 95% CI: 0.46–0.84; *P* trend <0.001), as was the animal protein-based score (OR 0.64; 95% CI: 0.48–0.87; *P* trend = 0.002). However, there was no association for the overall LCD score in men nor with the plant-based LCD score in women or men [43]. Similar results were reported in a separate cohort of Japanese adults, with an inverse association between LCD score and CVD mortality and overall mortality in women but not men [44].

In summary, observational evidence suggests that lower carbohydrate intake is generally associated with reduced or neutral risk for major disease outcomes and mortality, with risk commonly being lower if foods are vegetable-based, and risk being neutral or sometimes higher if foods are animal-based. However, the use of observational research, while benefiting from the opportunity to examine long-term data, is limited because of inherent confounding and wide ranges of carbohydrate intake in the lowest carbohydrate intake groups of the populations studied.

Intermediate Outcomes in Clinical Trials

A large number of clinical trials of LCD plans examining intermediate outcomes have been performed, especially in the past 20 years. The research has examined a spectrum of outcomes. The overall impression of this research is that of disease improvement and/or risk reduction, which has led to wider adoption by people and clinicians seeking risk reduction, intensified research regarding health effects, and increasing support in clinical guidelines [29, 45].

Cardiovascular Disease Risk Factors

For a number of reasons, the most commonly studied risk factors in clinical trials of low-carbohydrate diet approaches are related to CVD. Starting in the 1960s, Ancel Keys found relationships between fat intake and CVD mortality after carrying out studies of observational design. This spurred the "diet-heart" hypothesis that has since been questioned [46–48]. Contributing to the diet-heart hypothesis, experiments in animals showed increased ath-

erosclerosis, while RCTs in humans showed increased serum LDL-cholesterol levels in the setting of increased saturated fat intake. These findings led to widespread recommendations at first to generally reduce fat intake with later refinement to specifically reduce intake of saturated and *trans*-unsaturated fats and to replace fat intake with increased carbohydrate intake. However, subsequent observational research has demonstrated that higher intake of saturated fat does not increase risk and may in fact decrease risk [49–51]. Further fine-tuning of this research with RCT evidence suggests that replacing saturated fat with unsaturated fat may be associated with lower CVD risk [52], but this finding may need to be further specified based on evolving evidence, including evidence for varied responses depending on characteristics such as activity level and genetics [53].

Despite the updated knowledge in this area, concerns remain about a possible increased CVD risk related to the high-fat content of low-carbohydrate eating patterns. As a result, blood pressure and serum cholesterol levels are frequently reported in clinical trials of these dietary patterns. This has led to a substantial accumulation of evidence and the carrying out of meta-analyses. The majority of these meta-analyses have summarized RCTs comparing the effects of a low-carbohydrate eating pattern to a control diet, typically a low-fat eating pattern. One meta-analysis however studied the before/after effects of low-carbohydrate eating, which is meaningful because it shows the expected effects for someone changing from a "usual" diet rather than comparing to a prescribed (low-fat, low-calorie) diet that most people are not already following [54]. This helps move the conversation away from "What is the best diet for everyone?" to "What are potential diet options for individuals?", which can be later refined to "What is the best diet tailored to the individual's risk profile?"

The before/after meta-analysis focused on RCTs of author-described LCDs with at least 3 months duration of follow-up and at least 100 overweight/obese adults completing the study follow-up [54]. The authors found 23 publications related to 17 clinical trials fitting these criteria, with a total of 1141 participants following the LCD counseling; this ranged from 20 g per day to 40% of daily calories. The main findings were that the following risk factors improved significantly from baseline: weight (−7.04 kg), BMI (−2.09 kg/m [2]), waist circumference (−5.74 cm), systolic/diastolic blood pressure (4.81/−3.10 mmHg), plasma triglycerides (−29.7 mg/dL), HDL-cholesterol (+1.73 mg/dL), hemoglobin A1c (−0.21%), and plasma C-reactive protein (−0.22 mg/L). In contrast to expectations with an LCD, plasma LDL-cholesterol (−0.48 mg/dL) did not change significantly in participants who were overweight/obese and who were actively losing weight.

The various systematic reviews/meta-analyses of RCTs of low-carbohydrate eating patterns have mostly generated similar results and contributed importantly to our knowledge of the effects of dietary change on serum lipid profiles. The consistent findings are that low-carbohydrate eating patterns lead to greater improvements in fasting serum triglyceride and HDL-cholesterol whereas low-fat eating patterns lead to greater improvements in LDL-cholesterol [55–60]. One [59] of these meta-analyses noted a greater decrease in diastolic blood pressure, whereas another [58] reported a greater decrease in systolic blood pressure, with a low-carbohydrate eating plan compared with a low-fat plan. One meta-analysis additionally calculated 10-year ASCVD risk and found that the risk score was lowered more effectively by a low-carbohydrate than by a low-fat eating plan [60]. In this analysis, the low-carbohydrate eating pattern led to highly significant between-group improvements in HDL-cholesterol (+5.1 mg/dL, $p < 0.0001$) and triglycerides (−28.8 mg/dL, $p < 0.0001$) whereas the low-fat eating pattern led to greater improvement in LDL-cholesterol (−8.6 md/dL, $p = 0.0008$). These results were similar using Bayesian analysis with additional benefit from low-carbohydrate plans on systolic blood pressure (−2.3 mmHg, 95% CI: −4.4, −0.2). These changes led to significant mean differences in ASCVD score favoring the low-carbohydrate

pattern in four subpopulations ranging from −0.10 (95% CI: −0.20, −0.01) in lower risk White adults to −0.76 (95% CI: −1.38, −0.14) in higher risk Black adults.

While the LDL-cholesterol may change more favorably in low-fat/high-carbohydrate eating patterns, an LCD has been shown to shift the LDL sub-fractions to a less atherogenic pattern, evidenced by fewer small, dense LDL particles [61–65]. For example, in one RCT, LDL-1 (large) increased from 9.7 to 20.0% whereas LDL-3 (small, dense) decreased from 7.9% to 1.7% with a carbohydrate-restricted diet; the change in both parameters was significantly more favorable than the changes that occurred from a low-fat diet [64]. The increase in LDL-1 may explain why standard lipid profiles can show an increase in LDL-cholesterol when, in actuality, the overall change in LDL sub-particles related to low-carbohydrate eating fits a lower risk state. Combining these changes with the favorable changes seen in serum triglycerides, HDL-cholesterol, insulin, and glucose, and in blood pressure point to a reduction in risk for heart disease with an LCD.

With the burgeoning prevalence of obesity and T2DM worldwide, interest in prevention and reversal of diabetes has gained attention. The carbohydrate content of a meal is the biggest driver of postprandial glycemia so it follows that carbohydrate restriction can be a powerful strategy for reducing hyperglycemia. RCTs in patients with T2DM have in fact shown low-carbohydrate eating plans to be more effective compared to higher carbohydrate eating plans at lowering hemoglobin A1c and reducing diabetes medication [31, 66–70]. In one meta-analysis that included 23 RCTs, the mean difference for hemoglobin A1c was −0.47% (95% CI: −0.60, −0.34) at 6 months and −0.23% (95% CI: −0.46, 0) at 12 months [66]. Other meta-analyses have also demonstrated improvements in glycemic control, and a network meta-analysis of 56 trials ranked the LCD approach as the best out of 9 dietary approaches (surface under the cumulative ranking curves or SUCRA: 84%) for lowering hemoglobin A1c.

In RCTs that are not focused on people with T2DM and may therefore give more specific information regarding the prevention of T2DM, improvements in glycemia are less pronounced because there is less scope for improvement. In meta-analyses of weight-loss RCTs not focusing on T2DM, low-carbohydrate eating patterns did not significantly impact fasting serum glucose in comparison with the control diet [56–58]. Some studies that included but did not focus on patients with T2DM found glycemic improvements in the subset of those patients but not in the overall sample [71–74]. Effects on serum insulin levels or other markers of insulin sensitivity have been mixed [72, 74–79] but favored low-carbohydrate eating patterns when statistical differences occurred [62, 80, 81]. No RCTs have been designed to adequately answer the question of whether a low-carbohydrate eating pattern can prevent T2DM. One study reported this outcome in a sample of patients with prediabetes enrolled in a commercial program focusing on low-carbohydrate nutrition: 52% achieved normoglycemia (hemoglobin A1c <5.7%) without medication at 2 years while only 3% developed T2DM [82].

Very few trials have examined intermediate outcomes for cancer in human beings following a low-carbohydrate eating plan. According to Warburg's hypothesis in 1924, reducing carbohydrate intake has the potential for making cancer cells less viable. This is based on the finding that tissues from many types of cancer ferment sugar for energy in the absence of oxygen whereas healthy cells rely primarily on oxidative phosphorylation but can additionally generate energy from other pathways such as fatty acid oxidation [83]. Therefore, reduction in carbohydrate intake could potentially "starve" cancer cells and thereby prevent their growth [84]. Consistent with this hypothesis, high-glycemic index eating patterns have been associated with a modestly higher risk for several cancers, including cancer of the breast, endometrium, prostate, ovary, colon, bladder, and kidney [85]. As a result, low-carbohydrate ketogenic diets have been studied in patients with a wide variety of cancers, albeit in only a few ($n = 6$) studies with very small sample sizes and therefore no clear evidence for effectiveness [86]. On the other hand, one ran-

domized crossover study examined intermediate colorectal cancer outcomes and found that, compared with a high-protein/moderate-carbohydrate diet, a high-protein/low-carbohydrate diet led to a decrease in fecal cancer-protective metabolites and increased concentrations of potentially hazardous metabolites [87]. This finding is limited in that it used surrogate outcomes, the duration of intervention was short (4 weeks), and the sample was small ($N = 17$) and consisted of men only.

Summary and Conclusion

A large volume of observational studies has examined the relationship between a low-carbohydrate eating pattern and the incidence of CVD, T2DM, and cancer. These studies have generated varying results and have important limitations; the primary limitation is that participants grouped in the lowest carbohydrate eating category do not represent a very-low-carbohydrate intake compared with plans that are used clinically. On the other hand, RCTs have provided substantial evidence with intermediate outcomes suggesting reduced risk for CVD and T2DM. Findings on cancer are very limited as this is a relatively new area of research interest. While there are many additional attributes of low-carbohydrate eating patterns that could contribute to disease prevention, including weight management, reduced inflammation, and improved physical function, mood, and energy, we will ultimately need large RCTs with disease outcomes to definitively tell us whether this diet strategy has an overall net benefit. This chapter may help move the conversation away from "What is the best diet for everyone?" to "What are potential diet options for individuals?" which can be later refined to "What is the best diet tailored to the individual's risk profile?"

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20

Trends in Dietary Recommendations: Nutrient Intakes, Dietary Guidelines, and Food Guides

Maria Morgan-Bathke, Kelsey McLimans, and Norman J. Temple

Key Points

- The Dietary Reference Intakes (DRI) are a set of reference values for nutrients. They are used in the USA and Canada.
- The DRI values include—Estimated Average Requirements (EAR), Recommended Dietary Allowances (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Levels (UL). DRI tables also include Estimated Energy Requirements (EER).
- The purpose of the DRI is to provide an estimation of the nutrient intake that will meet the needs of most individuals and groups within a specific population.
- The European Union uses a set of values known as Dietary Reference Values. These are similar to the DRI.
- The United Kingdom also uses a set of values known as Dietary Reference Values. However, these values have major design differences compared to the DRI.
- Many countries publish sets of dietary guidelines that are aimed at the improvement of population diets. Some include quantitative recommendations that focus on nutrients while other sets of dietary guidelines are based entirely on foods.
- The version used in the USA is the Dietary Guidelines for Americans.
- Many countries publish food guides that are written for the general public, such as MyPlate which is used in the USA.

M. Morgan-Bathke · K. McLimans
Department of Nutrition and Dietetics, Viterbo University, La Crosse, WI, USA
e-mail: memorganbathke@viterbo.edu; kemclimans@viterbo.edu

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

Introduction

The Recommended Dietary Allowances (RDA) are the recommendations for nutrient intakes in the USA. The first edition of the RDA was published in 1943 and has been revised at regular intervals since then [1]. The Dietary Reference Intakes (DRI) is a development that grew out of the RDA. It is based on reports published between 1997 and 2004 [2]. The DRI are reference values that provide estimates of nutrient needs for planning and assessing the diets of healthy people [3, 4]. The various tables provide guidelines for the intake that healthy individuals should consume across the lifespan. These reference values are based on data and scientific judgment. The DRI include the RDA, Adequate Intakes (AI), Tolerable Upper Intake Levels (UL), and

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_20

Estimated Average Requirements (EAR). These tables are used in the USA and Canada and are intended to assist clinicians, dietitians, and the general public in planning and assessing dietary intake of healthy individuals.

Other resources have also been developed that are more user-friendly for the general population. These include food-based dietary guidelines and food guides. In the USA, the Dietary Guidelines for Americans and MyPlate make recommendations for food selection by consumers. These guides are designed to be consistent with the DRI values. Other countries have their own versions of these guides.

The Dietary Reference Intakes

The different sets of values are intended for close to all healthy individuals. However, the studies that provide the data on which the DRIs are based are sparse in many cases. In particular, there is little data available on the dietary needs of youth and children. Because of these limitations in the available data, scientific judgment is also involved in establishing the DRIs.

Values of RDA and AI are given for 14 vitamins and 15 minerals. Values are also given for energy, carbohydrates, protein, dietary fiber, and water. Also included are n-3 and n-6 polyunsaturated fats. Tables are broken down by age and sex. Specific recommendations are given for women who are pregnant or lactating. The tables can be seen on the website shown in ref. [5].

Estimated Average Requirement

The EAR is the nutrient intake value that is estimated to meet the requirement of half of the healthy individuals in a group [3]. It is commonly utilized to assess a healthy individual's dietary intake. Similarly, the EAR can be used to determine the prevalence of an inadequate intake within a group. However, it is important to note that in order to fully assess the dietary status, it is necessary to obtain clinical, biochemical, and anthropometric data.

Recommended Dietary Allowance

The RDA is the average daily dietary intake required to meet the nutrient requirement for 97–98% of healthy individuals in a group [3, 4]. It is most useful for planning dietary intake for individuals. The RDA values vary based on age. Because of limitations in the available data, the RDA values are not universally agreed upon [2].

Adequate Intake

Adequate Intakes (AI) are reported as a goal intake when there is insufficient evidence to support RDA values [3, 4]. AI are often used for infancy and pregnancy as research is more difficult at those life stages. For infants, AI are based on the average intake of a particular nutrient for healthy breastfed infants. Adult AI are often based on more limited scientific studies.

Tolerable Upper Level Intake

The UL is the highest level of daily nutrient intake that are unlikely to pose risks or adverse health effects to most healthy individuals within a group [4]. The main purpose of the UL is to inform the public of the risks associated with excessive nutrient intake.

In 1998 the Institute of Medicine developed a risk assessment model specifically for nutrients in order to quantify the UL [6]. This dose-response assessment is built upon three toxicology concepts: no-observed-adverse-effect level, lowest-observed-adverse-effect level, and uncertainty factor.

Estimated Energy Requirement

An important inclusion in DRI tables is Estimated Energy Requirements (EER). Unlike nutrients, there is no RDA for energy. This is because of the multitude of factors that play into an individual's energy needs. Guidelines are available that show energy requirements required for healthy indi-

viduals [4]. These guidelines take into account age, sex, weight, height, and level of physical activity. Available equations include infants and young children, both boys and girls 3–8 and 9–18 years of age, male and female adults, and pregnant and lactating women.

Indirect calorimetry is considered the gold standard for determining calorie requirements for an individual. The method involves the measurement of oxygen use and collection of exhaled carbon dioxide [7]. However, indirect calorimetry is typically limited to special circumstances, such as research labs, as it is labor intensive and more costly than using predictive equations.

Acceptable Macronutrient Distribution Ranges

The Acceptable Macronutrient Distribution Ranges (AMDR) is the distribution of energy intake between the three macronutrients—carbohydrates, protein, and fat—including breakdowns for n-3 and n-6 fatty acids. The AMDR value for each macronutrient is presented as an acceptable range of energy intake. The values are as follows: 45–65% for carbohydrates, 10–35% for protein, and 20–35% for fat. After determining an individual's EER, one can utilize AMDR to determine a range of calories for each macronutrient.

While the RDA and EAR values are aimed at preventing deficiencies, the AMDR has a goal of preventing chronic diseases. Thus, if an individual consumes a macronutrient outside of their AMDR range, they may be at increased risk for developing chronic disease.

Limitations of the DRI

As stated above, the DRI apply only to healthy people. Appreciably different levels of nutrients may be required by individuals with particular diseases, especially malabsorptive or inflammatory diseases.

One notable limitation of the EER formulas is the difficulty in obtaining an accurate estimation of physical activity. It is also necessary to gather accurate height and weight data which may be difficult in some community settings. In addition, these equations are not appropriate for hospitalized patients or patients in disease states who may require significantly more calories.

There is often a discrepancy between AMDR percent protein intake and an estimate using EAR/RDA based on g/kg body weight. However, studies have shown that in healthy individuals the RDA method sets a minimum for protein consumption, and there is little evidence of harm from consuming above the RDA while still within the AMDR range [8]. Similarly, the RDA for carbohydrates is set as a minimum to prevent deficiency symptoms whereas the AMDR is set for optimal carbohydrate intake [9].

General Guidelines for Diet Assessment of Individuals

In general, the RDA should be used when determining if an individual is at risk for nutrient deficiencies. If an individual is consuming above the RDA value for a particular nutrient, he/she typically does not need to decrease his/her intake unless it is above the UL.

Because the diets of most people vary widely from day to day, there is likely to be a significant error if conclusions about the diet are drawn from a single day's diet record. For that reason, a reasonably accurate assessment of the diet requires that it is recorded over several days.

How the DRI Is Used

The DRI is used widely in research and serves as the basis for developing nutrition public policy. DRI values are utilized to create dietary guidelines, food guides, tracking nutrition-related public health programs, and create educational programs. The DRI forms the scientific foundation for federal food programs, including nutrition labeling, requirements for school meals, and the design of supplemental food packages for the Women, Infants, and Children (WIC) program.

Recommendations for Nutrient Intakes in Other Countries

Other countries have developed systems for making recommendations on nutrient intake. Here we look at two examples.

European Union

The 28 member countries of the European Union (EU) have designed a set of recommendations for nutrient reference values that state the estimated needs of healthy people. These values are known as Dietary Reference Values (DRV) [10] and have many similarities with the DRI. They can be used for planning and assessing diets. They can also be used as the basis for information on food labels and for establishing dietary guidelines.

The DRV include the following sets of values:

Average Requirement (AR). This gives the intake of a nutrient that meets the daily needs of half of the population. This corresponds to the EAR of the DRI.

Population Reference Intake (PRI). This gives the intake of a nutrient that meets the daily needs of the great majority (97.5%) of the population. As a general rule, the PRI is calculated as the AR plus twice its standard deviation (SD). This corresponds to the RDA of the DRI.

Adequate Intake (AI). When there is insufficient evidence to determine the PRI, an estimate is made. This corresponds to the AI of the DRI.

Reference Intake range for macronutrients (RI). These are typically set for total fat and total carbohydrates based on their relative contribution to total energy intake. These values are similar to the AMDR

Tolerable Upper Intake Level (UL). This is the maximum amount of a nutrient that can be consumed safely over a long period of time. It corresponds to the UL of the DRI.

The above sets of values of the DRV guide professionals on the amount of a nutrient needed to maintain health in an otherwise healthy individual or group of people. However, DRV are not intended to be nutrient goals or recommendations for individuals. The DRV are used by policymakers in the EU in order to formulate recommendations on nutrient intake for consumers. The DRV are also used as the basis for information on food labels and for establishing dietary guidelines. Such guidelines can help consumers make healthy dietary choices.

The United Kingdom

The Scientific Advisory Committee on Nutrition (SACN) is the expert group in the UK that formulates recommendations on nutrient intake [11]. The SACN reports to the Department of Health.

The UK recommendations are known as the Dietary Reference Values (DRV). Although the name is the same as the one used by the EU for their recommendations, as described above, there are important differences in design. The DRV were originally set in a 1991 report. These recommendations took a new approach by defining a range of values for each nutrient to reflect variability in requirements within the population. The various sets of values are broken down by age, gender, and life stage. Nutrient recommendations are stated as Lower Reference Nutrient Intake (LRNI), EAR, and Reference Nutrient Intake (RNI); these represent the lower limit, mean, and upper limits, respectively, of nutrient requirements in a population. We now look at these terms in more detail:

- The DRV are based on the assessment of the distribution of nutrient requirements for **healthy people in a population**. The DRV are intended primarily to provide a comparator for nutrient intakes of groups only. They are not intended to be recommendations or goals for individuals.
- The EAR is the mean requirement of a group for a particular nutrient or for energy. About half the population will usually need more than the EAR and half less.
- The RNI is the amount of a nutrient (calculated as mean EAR + 2SD) which is sufficient for almost all individuals in a group (97.5%). It therefore exceeds the requirement of most

people; habitual intakes above the RNI are almost certain to be adequate.
– The LRNI is the amount of a nutrient or energy (calculated as mean EAR—2SD), which is sufficient for only a few individuals in a group (2.5%) who have low needs. Habitual intakes below the LRNI by an individual will almost certainly be inadequate.

Although the criteria for determining the above values have not always been backed by strong evidence, it was judged to be the best possible and set a framework for amendments as new information from research becomes available.

Safe intake. This is an additional category. It is used where there is insufficient evidence to set an EAR, RNI, or LRNI. The safe intake is the amount judged to be adequate so that there is no risk of deficiency while at the same time, there is no risk of excessive intake.

In most respects, the UK version of the DRV is similar to both the American DRI and the EU version of the DRV. However, there are several notable differences. A prominent difference is the LRNI.

The DRV also provides guidelines for the intake of macronutrients, including free sugars (referred to as "nonmilk extrinsic sugars"), monounsaturated fatty acids, and *trans* fatty acids. Guidelines are also given for alcohol and dietary fiber. These guidelines are more wide-ranging than the AMDR that are used in the USA and that were discussed above.

The DRV can be used for several diverse purposes: yardsticks for surveys (RNI), in guidance of dietary composition (RNI), for food labels (RNI), and to provide a general guide in assessing the adequacy of an individual's diet (LRNI/RNI).

Dietary Guidelines

Around the world, different agencies publish sets of dietary guidelines that are aimed at the improvement of population diets. In highly developed countries, the primary goal is to reduce the impact of chronic disease.

Dietary guidelines fall into two distinct groups:

- Some include several quantitative recommendations that focus on nutrients, such as setting a target for sodium of <2000 mg/day. Recommendations of this type are most useful for health professionals. However, the aim is that the advice filters down to the general population.
- Other sets of dietary guidelines are based entirely on foods rather than nutrients; they are therefore referred to as food-based dietary guidelines (FBDG). They are written in clear simple language, are nonquantitative, and can be understood by the general public.

Dietary Guidelines That Include Both Qualitative Advice and Quantitative Recommendations

First, we examine some examples of dietary guidelines that include a mix of both qualitative advice and quantitative recommendations. In each case, the lion's share of the advice is qualitative and requires no expert knowledge to understand ("eat less sugar"). The quantitative recommendations, by contrast, are intended mainly for health professionals.

Dietary Guidelines for Americans

The Dietary Guidelines for Americans (DGA) are produced jointly by the US Department of Agriculture (USDA) and the US Department of Health and Human Services (HHS) [12]. A revised version is released every 5 years. The current version covers the period 2020–2025. The recommendations include dietary advice for people of all ages and all stages of their lifespan. The DGA is adaptable to diverse cultural food patterns.

The large majority of the document is in the form of qualitative advice that can be readily understood by the lay public. But the DGA also includes quantitative recommendations that are mainly intended for health professionals; these are as follows:

- **Limit saturated fatty acids** to less than 10% of calories;
- **Limit added sugars** to less than 10% of calories;
- **Limit sodium** to less than 2300 mg/day for half of the adult population but to less than 1500 mg/day for persons aged over 51 and persons at risk; and
- **Limit alcoholic beverages**, if consumed, too, at most, two drinks per day for men and one drink per day for women.

The Health Eating Index (HEI) measures adherence to the DGA [13]. Scores range from 0 to 100, with 100 being the best possible score. The USDA has a website that explains how diets are scored [14].

Researchers at the Harvard T.H. Chan School of Public Health are critical of the DGA [15, 16]. Here are some of their key points.

- The DGA fails to encourage the consumption of healthy protein sources like beans, nuts, fish, or poultry in place of red meat and processed meat.
- The DGA continues to recommend three servings per day of dairy foods even though there is no convincing evidence that this is beneficial to health. The recommendation for low-fat and fat-free dairy products does not state what will happen to the fat naturally present in milk. Because of its economic value, much of it will likely be used in the manufacture of other foods. This means that the consumption of low-fat and fat-free dairy products does not really lower the fat intake of the general population but rather shifts the fat from one food to another.
- The DGA says nothing about the environmental impacts of their dietary targets. In particular, the relatively large amounts of meat and dairy foods recommended have serious impacts on climate change and cause other damaging environmental footprints. The production of animal-based foods tends to have higher greenhouse gas emissions than plant-based foods. In this regard, red meat (especially beef) and dairy foods caused the most damage.

American Heart Association Recommendations

Several professional bodies in the USA publish dietary recommendations. Among the most well-known are those from the American Heart Association (AHA) which, not surprisingly, have a focus on the prevention of cardiovascular disease [17]. Much like the DGA most of the document consists of general dietary advice that can be readily understood by the lay public. In addition, there are also several quantitative recommendations intended for health professionals. The most recent version of the recommendations, published in 2017, includes the following:

- "If you need to lower your blood cholesterol, reduce saturated fat to no more than 5 to 6 percent of total calories."
- "aim to eat no more than 2,300 milligrams of sodium per day. Reducing daily intake to 1,500 mg is desirable."

The recommendation for alcohol is the same as that given in the DGA.

Canada's Dietary Guidelines

The Canadian Dietary Guidelines, published in 2019, resemble the DGA in several respects. The document states that it is intended for health professionals. Almost the entire document consists of qualitative advice that can be readily understood by the lay public [18]. But the document does include three quantitative recommendations as follows:

- **Limit saturated fatty acids** to less than 10% of calories;
- **Limit free sugars** to less than 10% of calories;
- **Limit sodium** to less than 2300 mg/day.

World Health Organization Recommendations

The World Health Organization (WHO) publishes updated dietary recommendations. Here, we look at documents published in 2019 [19] and 2020 [20]. While these documents present general dietary advice, they also include quantitative recommendations intended for health professionals.

- Total fat should be less than 30% of calories. The document states that the reason for this recommendation is to "avoid unhealthy weight gain." This recommendation was common in the USA in the past but disappeared some years ago. Current guidelines in the USA are more liberal: the Acceptable Macronutrient Distribution Ranges (AMDR) suggests that fat can be in the range of 20–35% of energy. The DGA makes no recommendation for the total intake of fat.
- Intake of saturated fatty acids and *trans* fatty acids should be less than 10% and 1% of calories, respectively. At the same time, there should be a shift away from these fats and to unsaturated fatty acids.
- Intake of free sugars should be less than 10% of calories. A further reduction to less than 5% of calories is suggested.
- **Limit sodium** to less than 2000 mg/day.

Food-Based Dietary Guidelines

The other type of dietary guidelines is based almost entirely on foods; quantitative recommendations are kept to a bare minimum. Statements such as "**Limit saturated fatty acids** to less than 10% of calories" are excluded. Dietary guidelines of this type are referred to as food-based dietary guidelines (FBDG). They are written in clear, simple language and are intended to be user-friendly for the general public. A typical recommendation is "eat five servings a day of fruit and vegetables." FBDG are culturally sensitive and are adapted to the customary dietary pattern of the target population [21, 22]. Based on these principles FBDG used in developing countries often contain statements along the following lines: "Drink lots of clean, safe water," "Foods consumed should be safe and clean," and "Use only iodized salt." More than 100 countries worldwide have developed FBDG [22].

An illustrative example we can look at the FBDG used in Germany:

- Enjoy a variety of foods.
- Eat plenty of cereals, preferably whole grain, and potatoes.
- Vegetables and fruits—eat "five-a-day."
- Eat milk and dairy products every day; fish once or twice a week; and meat, sausages, and eggs in moderation.
- Eat small quantities of fat and high-fat foods.
- Eat/use sugar and salt only occasionally and in moderation.
- Drink plenty of fluids, at least 1.5 L every day.
- Do not overcook your meals.
- Allow plenty of time for eating and enjoy mealtimes.
- Watch your weight and stay active.

Food Guides

Many countries publish food guides [23, 24]. These are written for the general public. They typically center on a colored diagram or poster that describes what the diet should look like. They are, in essence, FBDG in a graphical format.

Food Guides in the United States

The food guide used in the USA has undergone major changes over the past two decades. Until 2005, the official guide was the Food Guide Pyramid. As the name implies, the design was based on a pyramid with a wide base depicting the foods to be eaten in largest quantities (grains). The narrow top covered fats, oils, and sweets. The pyramid was accompanied by a one-page document that had a very user-friendly design. It was a simple matter to look at this one-page document and determine how many servings should be eaten from each food group, much as one reads a TV guide.

In 2005, the Department of Agriculture (USDA), the agency in charge of the food guide, decided that it was time to go online. This decision resulted in the launch of MyPyramid. As far as we are aware, this was the world's only food guide that required the use of Internet. The user typed in his or her age, sex, and physical activity and was then given personalized diet recommendations. While the food guide looks, at first glance, to be a perfect fit for the internet age, it

was met with much criticism. The first and most obvious problem was that a computer places a barrier between the user and the food guide. This is because millions of ordinary Americans are willing to read a simple, printed food guide, but either cannot or will not use a website for this purpose.

A serious criticism of MyPyramid is that the USDA made too many concessions to the lobbyists from the food corporations [25]. The primary goal of the food industry and its lobbyists is that the food guide should be friendly to the commercial interests of the food industry. At the heart of the problem lies the fact that the USDA has a serious conflict of interest: on the one hand, it must advise the population how best to eat a healthy diet, but at the same time it must support the commercial needs of farmers and of food producers, which often means minimizing suggestions that people reduce their consumption of meat and ultra-processed foods.

The USDA responded to these complaints and in 2011 it scrapped MyPyramid. In its place, they went over to a simple pictorial design called MyPlate [26]. This food guide is in the form of a plate with food sectors (Fig. 20.1). The area of the plate given to each food group indicates what proportion of the diet should come from that food group, much like the old Food Guide Pyramid.

Fig. 20.1 MyPlate [26]. Reprinted from US Department of Agriculture. https://www.ChooseMyPlate.gov/

However, MyPlate places little emphasis on how many servings should be eaten from each food group; this is a radical departure from the design of the Food Guide Pyramid and MyPyramid. It should be noted however that recommendations for serving sizes are included on the MyPlate website. This new food guide is elegantly simple. Quite a few other countries have adopted a similar dinner plate design.

However, the criticisms regarding whether the food guide is promoting the healthiest diet have not gone away. Nutrition experts from the Department of Nutrition of the Harvard School of Public Health have been highly critical of successive versions of the food guide. They have produced their own version of MyPlate [27]. This is called the Healthy Eating Plate. While similar in design to MyPlate, it differs in some details and claims to be based on the best evidence of the diet composition associated with the lowest risk of chronic disease.

Food Guides in Other Countries

A variety of designs for food guides are used around the world [23, 24]. There is a clear trend towards the adoption of a plate design similar to MyPlate. In 2019, Canada went down this road with the publication of a completely new version of Canada's Food Guide [28]. Unlike the previous version, the new version of Canada's Food Guide does not specify the number of servings from each food group. The UK also uses a variation of a plate design known as the Eatwell Guide [29]. Quantitative recommendations are kept to a bare minimum. Australia and Sweden have also adopted this design for their food guides.

While increasing numbers of countries have adopted a plate design, other countries are still using a design modeled on a pyramid. For example, the food guide used in Japan is shaped to resemble a spinning top; it is called the Japanese Food Guide Spinning Top [22]. Similarly, the Chinese food guide has a shape similar to a pagoda. China has also developed two auxiliary graphics: the Balanced Diet Abacus and the Balanced Meal Plate [22].

Food Guides: Comments

When we look at the food guides used in different countries, we see a variety of designs being used. However, several clear trends have emerged. The two most obvious trends are seen in MyPlate (USA), Canada's Food Guide, and the Eatwell Plate (UK). First, these food guides have now adopted a plate design. Second, these food guides pay little attention to the number of servings of each food group. The rationale for this is that the quantity of food that people eat is determined to a large extent by their appetite. It is not realistic to tell people how much food they should eat. Instead, the food guide should focus on the balance between the different *types* of food in the recommended diet rather than the *amount*.

Another trend to have emerged in recent years is that several food guides, including the ones used in the USA and Canada, now recommend that a larger part of the diet should come from fruit and vegetables than from grains. The newer revisions of the American, Canadian, and UK food guides have put much more emphasis on whole grains rather than refined grains. However, these food guides still allow for the consumption of modest amounts of refined grains.

Food guides are moving in the direction of placing less emphasis on the consumption of meat, especially red and/or processed meat. This is part of the trend of encouraging a diet that is dominated by foods of plant origin. Food guides normally place meat, fish, and beans in one food group and milk and other dairy foods in another. But the most recent version of Canada's Food Guide has merged these foods into one food group; this broad food group is known as "protein foods." This implies that the designers of the food guide do not consider that calcium intake from milk is of critical importance in the diet.

There are several other important differences between the various food guides. One is in the placement of fruit and vegetables. Roughly half of the food guides separate fruit and vegetables into two food groups. This has been the case with the different versions of the American food guide as well as the food guides used in Germany, Sweden, and Australia. The other half of food guides combine these foods into one food group. This is the case in Canada, the UK, China, Korea, and Mexico. Which design makes more sense?

Findings from prospective cohort studies strongly indicate that fruit and vegetables are protective against cardiovascular disease (including both coronary heart disease and stroke) and cancer while also reducing all-cause mortality [30]. This evidence also suggests that the benefit from eating these foods can be obtained by eating either fruits alone or vegetables alone. However, a consideration of phytochemicals points in the opposite direction. These substances may be protective against various diseases including cardiovascular disease, cancer, and diabetes. There are major differences between different types of fruits and vegetables in their content of phytochemicals [31]. These findings suggest therefore that the diet should include a wide variety of fruits and vegetables so that it supplies a wide variety of phytochemicals.

Looking at this evidence as a whole a reasonable conclusion is that food guides should combine fruit and vegetables into one food group while also encouraging people to eat a variety of both fruit and vegetables. This advice is consistent with an optimally healthy diet. An additional advantage of this approach is that the food guide will then be as simple as possible. This food guide design is used in the UK, Switzerland, and the Netherlands.

Food guides also vary in their placement of potatoes. They are included with other vegetables in the USA, Canada, Japan, and Australia, with grains in the UK, Germany, and Mexico, while in Sweden potatoes and root vegetables are given their own group.

There is mixed evidence regarding the relationship between the consumption of potatoes and health. Findings from prospective cohort studies suggest that potatoes have a weak association with weight gain [32] but no association with risk of CHD, stroke, colorectal cancer, or all-cause mortality [33]. They are also a major contributor of phytochemicals, supplying a quarter of the phenolics in the American diet [31]. Overall, boiled and baked potatoes have fairly little association with risk of disease in contrast

to the clearly beneficial effects of most other vegetables. But potatoes may pose some health risk when eaten as French fries as they appear to increase the risk of type 2 diabetes and hypertension [33].

Based on this evidence food guides should place potatoes in the fruit and vegetables group. Placing potatoes in the same food group as grains is likely to cause confusion for many consumers. A prudent recommendation is that intake of potatoes should be much less than that of other foods in the fruit and vegetables group and that they should be eaten as boiled or baked potatoes rather than as fries. It must be stressed that the supporting evidence for this conclusion is far from solid and that much more research is needed.

Another inconsistency is in the placement of legumes (i.e., beans, peas, and lentils). MyPlate allows these foods to be counted with either "protein foods" or with vegetables. The UK food guide also follows this flexible approach. In Canada, by contrast, legumes are included in the "protein foods" group (i.e., meat, fish, nuts, and milk) but are excluded from the fruit and vegetable group. This schism in the placement of legumes reflects the fact that they are a low-fat, protein-rich alternative to meat but are also a good source of fiber and various nutrients such as folate.

In theory, there should be an optimal design for food guides. The ideal food guide should be consistent with current knowledge of nutrition science. In particular, people who follow the food guide will substantially reduce their risk of chronic disease. Another major goal is that if the recommendations are followed, then the diet will almost certainly provide all nutrients in amounts that meet RDA recommendations. One notable exception to this rule is vitamin D as it is sunshine, rather than food, that is the dominant source. For that reason, many health authorities recommend a supplement of the vitamin for people who may be at risk of having a low blood level.

A diet recommended by a food guide should be environmentally and culturally friendly. It needs to be acceptable to different ethnic groups and to those who follow a vegetarian/vegan diet. At the same time, the food guide must be user-friendly and designed so it has the highest chance of persuading readers to follow the advice. Another design challenge with food guides is that many highly processed foods contain mixtures of diverse foods, or their derivatives, along with several additives. Accordingly, placing these foods in a food guide can lead to confusion. Achieving all these objectives is clearly a tall order. The design of food guides seems to be a neglected area of research.

One essential rule in the design of food guides is that the folks in charge must be impervious to food industry lobbyists. As was mentioned earlier, the US food guide is under the control of the USDA which is closely associated with food corporations, including the meat industry. This makes it much easier for food industry lobbyists to influence the design of the food guide. Most countries, such as Canada and the UK, have avoided this problem by simple means of handling the design of the food guide to the health department. The designers of the most recent version of Canada's Food Guide went one step further by excluding the food industry from any involvement.

Summary

This chapter has described three distinct sets of recommendations. Each type is intended to serve a distinct purpose.

Many countries publish sets of recommendations concerning the intake of various nutrients as well as energy. The DRI, which is used in the USA and Canada, and the tables used in the European Union and the UK each consist of several subsets of recommendations. While the details differ, each set of tables states the recommended intake for different sections of the population as well as the safe maximum intake. The overall goal is to achieve two distinct objectives: achieve a diet that is adequate in each nutrient so that there is *no risk of deficiency* and also achieve an *optimal intake for health.* There has been endless debate over the last several decades regarding how to achieve these objectives.

Another type of dietary recommendation is known as dietary guidelines. In some cases,

most of the advice is qualitative (such as "eat less sugar") while also including quantitative recommendations that focus on nutrients. The Dietary Guidelines for Americans is a well-known example. Recommendations of this type are mainly intended to be used by health professionals. Other sets of dietary guidelines give advice on foods only while quantitative recommendations are kept to a bare minimum and include only those that are easy to understand. These are known as food-based dietary guidelines and are intended for the general public.

Food guides, such as the MyPlate, are directed at the general population and for that reason are intended to be easily understood and highly flexible. There are also numerous differences between the guides in the placement of different foods; for example, combining fruit and vegetables into one food group or separating them into two groups. More research is clearly needed into how to optimize the presentation of the guides so that users are persuaded to consume a healthy diet.

Clearly, guidelines must address the key nutritional issues of their target population. In developed countries, the focus is primarily on the prevention of chronic diseases. But in less developed countries malnutrition is still a widespread problem. However, such chronic diseases as obesity and type 2 diabetes are becoming rapidly more prevalent in many less developed countries and dietary recommendations must stay abreast of these changes in population health.

As diets continue to evolve around the world and nutrition science continues to progress, the various types of dietary recommendations will also need to evolve. One conclusion is inescapable: this entire field will be the scene of considerable debate, controversy, and research for years to come.

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Food Labels: Sorting the Wheat from the Chaff

21

Karen M. Gibson and Norman J. Temple

Key Points

- Food labels provided the information needed to guide the selection of foods that will help individuals meet nutrition and health goals.
- Recent changes in the format for back-of-package labels necessitate the reinterpretation of food label information.
- Different designs for front-of-package food labels are discussed.
- Health claims on food labels are regulated by the FDA.
- This chapter explains how to best utilize the information provided by food labels.

Developed countries have regulations that specify what information must be stated on food labels. Millions of people use food labels to assist them in making healthier food choices. This was demonstrated by Shangguan et al. [1] in a systematic review of studies carried out in many countries. But labels are only useful if consumers properly understand how to use them. Unfortunately, the ease of comprehension leaves much to be desired [2]. The focus of this chapter is on various types of information that are presented on food packages, both back-of-package (BOP) labels and front-of-package (FOP) labels.

The Nutrition Facts Label

The labels described in this section appear on the back of food packages. For that reason, they are known as back-of-package (BOP) labels. These labeling regulations only apply to food that is sold in packages, such as cans or cardboard boxes, whereas many foods that are not packaged by the manufacturer, such as fresh meat and fish, do not require a label.

The Design of Nutrition Facts Label

Regulations require that nutritionally important nutrients or food components found in a food must be listed on the Nutrition Facts Label [3, 4]. A new design of the label was introduced in the USA and Canada in 2020. Figure 21.1 shows a typical example of the new format of the label.

The label focuses on nutrients that are associated with certain chronic diseases or with nutrient deficiencies. By law, the new version of the food label must contain the following information:

K. M. Gibson
Department of Family and Consumer Sciences, Carson-Newman University, Jefferson City, TN, USA
e-mail: kgibson@cn.edu

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_21

Nutrition Facts

4 servings per container

Serving size 1 1/2 cup (208g)

Amount per serving

Calories **240**

	% Daily Value*
Total Fat 4g	**5%**
Saturated Fat 1.5g	**8%**
Trans Fat 0g	
Cholesterol 5mg	**2%**
Sodium 430mg	**19%**
Total Carbohydrate 46g	**17%**
Dietary Fiber 7g	**25%**
Total Sugars 4g	
Includes 2g Added Sugars	**4%**
Protein 11g	
Vitamin D 2mcg	10%
Calcium 260mg	20%
Iron 6mg	35%
Potassium 240mg	6%

* The % Daily Value (DV) tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.

Fig. 21.1 Example of the nutrition facts label. (Figure reprinted from FDA https://www.fda.gov/food/food-labeling-nutrition/changes-nutrition-facts-label)

- List of ingredients arranged in descending order by weight (main ingredient first).
- Serving size (using a standardized serving size), plus the number of servings per container. For packages that contain more than one serving, the label states the nutrition information per serving as well as per package.
- Amount per serving of the following: total calories, fat, total fat, saturated fat, trans fat, cholesterol, sodium, total carbohydrate, dietary fiber, total sugar (including added sugar), protein, vitamin D, potassium, calcium, and iron. These quantities are also listed for the whole package of foods that are typically consumed in one sitting. However, if the food has a negligible amount of a particular food component, then it may be omitted from the label.
- The sugars listed on the label include naturally occurring sugars (such as those in fruit and milk) as well as those added to a food or drink. If added sugars are listed as one of the first few ingredients, this is an indication that the food has a high content of sugar. Other names for added sugars include corn syrup, high-fructose corn syrup, fruit juice concentrate, maltose, dextrose, sucrose, honey, concentrated or organic cane juice, and maple syrup.
- If the product is making a claim for a particular nutrient, information for that nutrient must be included.

The new label has several refinements compared to the design used prior to 2020. The serving size and the number of servings per container are in larger, bolder type. Serving sizes have been adjusted based on more recent consumption data. As a result, the nutrition information provided for each serving more realistically reflects what people actually eat and drink. Changes have been made to the nutrients that must be included. Added sugars are now listed. Vitamin D and potassium are now included because Americans often fail to obtain the recommended amounts. By contrast, the inclusion of vitamins A and C is no longer required because deficiencies of these vitamins are now uncommon, but they can be listed by manufacturers voluntarily.

Serving size is one of the most important items on a food label. This is stated in familiar units, such as cups or pieces, followed by the metric amount, such as the number of grams. In general, serving sizes are standardized to make it easier to compare similar foods. For example, the serving size for all ice creams is two-thirds of a cup and all soda beverages is 12 oz. Some exceptions to this rule are discussed below. The serving size indicated on a food label is intended to reflect the amount a person typically consumes on one occasion rather than how much they *should* consume. But many people may consume signifi-

cantly larger servings. It is also important to understand that the serving size is not a recommendation of how much to eat or drink. Another source of possible confusion is that the serving sizes on food labels are not always the same as those of the diabetic exchange plan.

When looking at the serving size, consumers need to compare the size listed with the amount they actually eat. In the sample label in the figure, for example, one serving of this food equals two-thirds of a cup. But if the consumer eats a larger amount, that obviously increases the calories and the quantity of nutrients. Similarly, the servings given to customers in restaurants are often considerably larger than the serving sizes used on food labels. This can result in people greatly underestimating their intake of food calories. [Note: In this chapter, we use the word calories for consistency with actual food labels. However, in the rest of this book, calories are abbreviated as kcal.]

Most consumers have a hard time interpreting the significance of the quantity per serving of various nutrients and fiber. Is 240 mg of sodium and 280 mg of potassium good or bad? To overcome this problem BOP labels also state the amount present of several substances as a percentage of the recommended daily intake. For this purpose, food labels in the USA and Canada use a term known as Daily Values (DVs). DVs are shown on the sample label (bottom of Fig. 21.1). They reflect dietary recommendations for nutrients and dietary components that have important relationships with health. The DV for a nutrient represents the percentage contribution one serving of the food makes to the daily diet for that nutrient based on current recommendations for healthful diets.

The DVs cover several food components including cholesterol, sodium, potassium, calcium, iron, and dietary fiber as well as carbohydrate and fat. A %DV for protein is only listed if the food is meant for use by infants or children. Not all nutrients have a %DV listed. Amounts are shown based on a 2000 calories diet.

The DVs are based on the following daily allowances:

Total fat: maximum of 65 g
Saturated fat: maximum of 20 g
Carbohydrates: 300 g
Fiber: 25 g; 12.5 g per 1000 calories
Cholesterol: maximum of 300 mg
Sodium: maximum of 2400 mg
Potassium: 3500 mg
Vitamin D: 5 μg (200 IU)

A lower DV is generally desirable for saturated fat, cholesterol, and sodium; a DV of 5% or less is a good indicator. A higher DV is generally desirable for dietary fiber, potassium, calcium, iron, and vitamin D, with 10% or more representing a good source, while a DV of 20% is considered high. There is much debate regarding what should be seen as a desirable intake of total fat and total carbohydrate; this issue is discussed in other chapters.

The above explanation for DVs may seem rather confusing. However, DVs are quite easy to use in practice. The "%Daily Value" helps consumers easily see whether a food contributes a little or a lot of a nutrient.

Why BOP Food Labels Can Cause Confusion

A closer look at BOP labels reveals some important design flaws. First, the quantity per serving of nutrients and fiber is not arranged in a logical order. Food components that many people consume in excessive amounts are interspersed with others that are often lacking in the diet. For example, sugar is placed next to fiber while sodium is next to potassium.

Another problem with BOP labels is that similar products often use different serving sizes. This can make it difficult for consumers to make accurate comparisons. For example, two cans of sardines may have the same content of salt. But if the serving size on one is double the other, then the BOP label will state that one has twice as much sodium per serving as the other. This problem has been observed in Canada. A similar problem is seen in the USA with serving sizes for cereals.

These are based on density, usually 28–30 g. Those cereals like granola that are denser may have a serving size of 0.25 cups whereas less-dense cereals, such as cornflakes, may be 1.25 cups.

Using the Nutrition Facts Label

Let us now summarize the key rules for reading labels:

- Read the list of ingredients.
- Learning all the rules is ideal, but most people do not have the inclination for that. The next best thing is to focus on four key numbers: calories, sodium, saturated fat, and dietary fiber. Start by figuring out reasonable targets for each of these. For an active adult man who is well motivated to keep himself healthy, appropriate targets are 2500 calories, 1800 mg sodium, 20 g saturated fat, and 38 g fiber; for a sedentary adult woman, the numbers are 2000, 1800, 20, and 25, respectively.
- For each food determine these four values. This must be based on the amount actually eaten. The user may well consume more than the serving size shown on the label; a label that states that the package contains 2 servings may, in reality, be only one serving for some consumers but 3 servings for others. The food can then be evaluated based on either the actual amounts or the percentages. As a simple litmus test, if the numbers for these four values are consistent with a healthy diet, then everything else will probably fall into place.

Lastly, we will look at how the calorie content of food is calculated. We will use the food label shown in Fig. 21.1 as an example. Fat contains 9 calories/g, while carbohydrate and protein each have 4. So, one serving of the food has 72 calories as fat (8 times 9), 148 as carbohydrate (37 times 4), and 12 as protein (3 times 4). This adds up to 197 calories. The small difference from the number on the label is because of rounding errors. Knowing how to make these calculations can be useful. For example, examination of a food label followed by a quick calculation may reveal that half the energy in a cake comes from fat.

While reading food labels can be very informative, many people may wish to know the total nutrient and energy content of their diet. People can obtain this information at the following website: http://www.nutritiondata.com. A Canadian website can be found by doing a Google search for "nutrient value of some common foods." This provides detailed information on the nutrition content of large numbers of foods.

Front-of-Package Food Labels

The Design of Front-of-Package Food Labels

Front-of-package (FOP) labels inform the buyer of the brand name and the type of food, such as Quaker Oats. A recent trend is the use of additional front-of-package (FOP) labels. These have a simple design and are intended to enable shoppers to select healthy foods much more quickly and easily than is the case with BOP labels. For that reason, FOP labels are potentially of much greater value than BOP labels for helping shoppers to make healthy choices. Let us suppose that a shopper is in a supermarket and wishes to buy breakfast cereals. The time spent evaluating each of the choices on offer is typically no more than a few seconds. Few people can evaluate a BOP label in such a short amount of time. Even if the shopper is especially diligent and carefully reads the BOP labels, he or she is likely to end up being confused by the information. This is especially the case with older adults and those with less education. FOP labels are intended to overcome this problem.

A variety of designs for FOP labels are now in use around the world. The effectiveness of different FOP labels was recently reviewed by Temple [5].

FOP labels are of two distinctly different types:

- Nutrient-specific labels. These present information on a small number of substances, most

commonly saturated fat, sugar, and sodium (or salt). The total amount of fat is often included.

- Summary labels. These use an *algorithm* to translate the components of the food into a single value that denotes how healthy or unhealthy the food is. This value is expressed in a very simple manner such as stars or a tick. The calculation is based on multiple components of the food such as saturated fat, sugar, sodium and other minerals, vitamins, protein, dietary fiber, as well as some ingredients in the food such as fruits, vegetables, and whole grains.

A major difference between the two types of FOP labels is that while nutrient-specific labels focus on substances that are harmful when consumed in excess, summary labels cover a spectrum from the most healthy foods to the most unhealthy foods.

Here are some examples of nutrient-specific labels. One British-designed system is based on traffic lights or multiple traffic lights (MTL; the abbreviation used here) [6]. It has been adopted by several countries. Colored circles are placed on the package and indicate if the food has a high (red), medium (orange), or low (green) content of fat, saturated fat, sugar, and salt (Fig. 21.2). The label also indicates the actual quantity of these substances per serving.

Another design is the Guideline Daily Amounts (GDA) label. The label states the amount of these substances per serving as well as of energy (Fig. 21.3). The amounts are also stated as a percentage of an adult's reference intake. The label is used in Mexico. The GDA, or slight variations of it, are also known as Facts Up Front [7], Reference Intake label, and Daily Intake Guide.

A recently developed FOP label is health warnings. The label is usually a simple statement such as "high in sugar" or "high in sodium" (Fig. 21.4). This style of label is comparable with health warnings on cigarette packages. The design was developed and first used in Chile. In 2016 that country mandated the use of health warnings for foods high in sugar, fats, salt, or calories [8]. This FOP design is now attracting much interest in several other countries [9], especially for use on containers of sugar-sweetened beverages. Some countries employ the label for foods rich in saturated fat. Brazil, Uruguay, Canada, and several US states and cities have

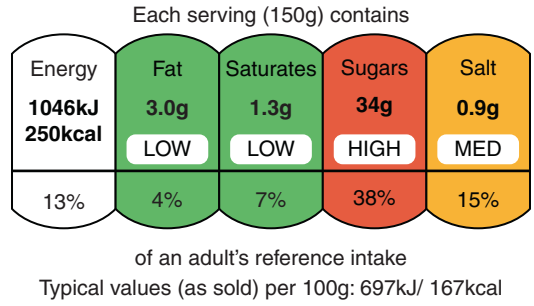

Fig. 21.2 Example of multiple traffic lights food label. (Figure reprinted from Food Standards Agency (UK) https://www.food.gov.uk/safety-hygiene/check-the-label)

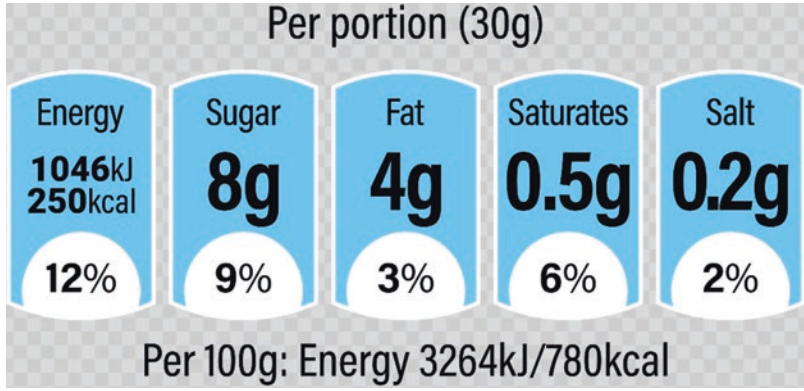

Fig. 21.3 Example of Guideline Daily Amounts food label. (Figure reprinted from Shutterstock with permission)

Fig. 21.4 Examples from Chile of warning labels for foods high in sodium and sugar. At the bottom of each label, it states Ministry of Health

Fig. 21.5 Example of Nutri-Score food label. (Figure reprinted from Shutterstock with permission)

taken steps to implement this public health strategy. One obvious limitation of this design is that it focuses on the harmful aspects of a food while providing no guidance as to which foods are most healthy.

We now examine examples of summary labels. Nutri-Score is an elegantly simple FOP label. Also known as 5-CNL (5-Color Nutrition Label) the label depicts the estimation of the overall health value of the food as a letter from A (healthiest) to E (least healthy). The label shows all five letters, each in a different color, but the one indicating the value of the food is expanded (Fig. 21.5). Components of the food that are included in the score include saturated fat, sugar, sodium and other minerals, vitamins, protein, dietary fiber, n-3 fatty acids, fruits and vegetables, and whole grains [10]. Nutri-Score was developed in France where it is used on many food products. It has also been adopted by Belgium and Spain.

Another summary label is called Guiding Stars [11, 12]. The label denotes the health value of the food with zero, 1, 2, or 3 stars. A notable design flaw of this FOP label is that shoppers can deduce a zero star rating only from the absence of stars. The label was designed in the USA and its use is mainly confined to that country, though it was also adopted by Loblaws, a supermarket chain in Canada.

Australia and New Zealand have developed their own version of Guiding Stars. This is known as the Health Star Rating [13]). The label displays from half a star to five stars. In a variation

of this design, the label may include additional information such as the quantity of energy, saturated fat, sugar, and sodium.

The simplest summary FOP label displays only a symbol such as a tick. The symbol is added to the food package if the food is deemed to be healthy. Different versions of this label have been developed by countries around the world. One version adds a tick to indicate that the food is considered to be heart healthy. Another version, named Choices, was developed in the Netherlands in 2006 [14]. It has been adopted in many other countries. The Nordic countries (Sweden, Denmark, and Norway) use a variation of this design known as the Keyhole or the Nordic Keyhole [15]. It was originally developed in Sweden in 1989. As the name indicates, the symbol depicts a keyhole.

Designs that use a symbol such as a tick or a keyhole have inherent flaws. First, all foods are forced into one of two groups, which is a gross oversimplification of the reality of food composition and its effect on health. The second flaw was also seen with Guiding Stars, namely that the absence of a symbol implicitly indicates that the food is relatively unhealthy but most shoppers are unlikely to notice this.

How Effective Are Front-of-Package Labels?

Much research has been done in an effort to determine the effectiveness of FOP labels. This research strongly suggests that FOP labels can be fairly successful at improving the ability of shoppers to distinguish between more healthy and less healthy foods. The designs for FOP labels that appear to be most successful are MTL (multiple traffic lights), warning labels, and Nutri-Score. Labels that include stars were much less successful. As might be predicted, the most successful designs are the ones that are easiest for shoppers to understand and which include the use of color.

Research studies have also investigated whether FOP labels lead to shoppers having an increased intent to buy healthier foods. Many studies reported positive findings. Warning labels were the only FOP design to display success in most studies. By contrast, MTL, Nutri-Score, and labels that included stars had a much lower frequency of success.

Taking these studies as a whole the FOP label design that appears to be most successful is warning labels. This is followed by MTL and Nutri-Score. However, we must be very cautious before making any firm conclusions. This is because the studies have two major weaknesses. First, there is a lack of consistency in the findings. For example, in three studies out of ten, MTL labels were clearly successful at persuading shoppers that they should buy healthier foods, in two studies the label was only weakly effective, while in five studies the label appeared to have no positive effect. The explanation for these inconsistent findings probably lies in differences in the details of the different studies, such as the country where the study was conducted, the types of food tested, and the characteristics of the subjects recruited for the study (gender, age, education, and so forth).

The second weakness of the studies is that they were all conducted in an artificial setting, mostly by showing images of food packages on a computer screen. Subjects typically spent less than 1 h involved in the experiment. We cannot say with any confidence that because a person states that they would buy a particular food product after being shown images on a computer screen, they would make the same food selection week after week while shopping for their family in a real supermarket. However, we do have some evidence from studies carried out in real-world supermarkets. But, unfortunately, only a handful of such studies have been carried out. Here we focus on what appear to be the two most reliable studies carried out in supermarket chains. In each case Guiding Stars labels were attached to the shelves adjacent to foods. In both studies, sales in stores that used the labeling system were compared with sales in stores that did not. The studies had a duration of 6–7 months.

The first study was carried out in Canada and included a wide variety of foods [16]. There was

an increase in the mean star rating of 1.4%. The other study was in the USA and focused on sales of ready-to-eat cereals [17]. Sales of cereals with no stars fell by 2.6% while sales of cereals with one, two, and three stars increased by 1.15%, 0.89%, and 0.54%, respectively. The combined results of the two studies suggest that Guiding Stars caused a shift to healthier varieties of food by about 1.5–2%.

The key conclusion from these studies is that FOP labels or shelf labels may achieve a small degree of success in persuading shoppers to buy healthier foods rather than less healthy foods. The magnitude of the change was, at most, a mere 2%. This is hardly a stellar success. But these findings must be viewed cautiously for the following reasons. First, few studies have been carried out. Second, we have very little evidence regarding whether warning labels would achieve greater success. This may well be the case as the evidence cited earlier suggests that this FOP label design appears to be the most effective. Studies of the effectiveness of MTL and Nutri-Score are also needed.

The review of FOP labels carried out by Temple provides much additional information (4).

Health Claims on Food Labels

Many food products include a health claim that is displayed prominently on the front of the food package. There are about a dozen health claims that have been authorized by the US Food and Drug Administration (FDA). These claims are intended to inform shoppers that the food—as part of an overall healthy diet—may reduce the risk of a specific health problem. The claims are based on evidence about the food itself or that the food has a high or low amount of particular nutrients or other substances. In making this determination, the FDA carries out an extensive review of the scientific literature. The health claims are authorized if there is a significant scientific agreement (SSA) among experts that the claim is supported by the totality of the available scientific evidence that the substance affects the risk of disease.

Here is a list of the approved health claims for food labels:

- Sodium and hypertension
- Calcium, vitamin D, and osteoporosis
- Folic acid and neural tube defects
- *Dietary lipids and cancer
- Fiber-containing grain products, fruit, and vegetables and cancer
- Fruit and vegetables and cancer
- *Dietary saturated fat and cholesterol and risk of heart disease
- Fruit, vegetables, and grain products that contain fiber, particularly soluble fiber, and risk of heart disease
- Soluble fiber from certain foods and risk of heart disease
- Plant sterol/stanol esters and risk of heart disease
- Dietary noncariogenic carbohydrate sweeteners and dental caries

The two claims marked with * are based on evidence that is now widely seen as questionable. As new evidence emerges, the FDA will review all the claims and update the approved list as necessary.

Other health claims are termed “qualified” as the supporting evidence is less strong than is the case with the above health claims. Accordingly, the phrasing allowed by the FDA must include a “qualifier” that dilutes the claim. These health claims are authorized based on an Authoritative Statement by Federal Scientific Bodies. Examples of this type of health claim are as follows:

- Whole grain food and risk of heart disease and certain cancers
- Whole grain foods with moderate fat content and risk of heart disease
- Potassium and the risk of high blood pressure and stroke
- Fluoridated water and reduced risk of dental caries

- Substitution of saturated fat in the diet with unsaturated fat and reduced risk of heart disease.

In addition to "health claims," food labels may also contain nutrient content claims. These words now have strict definitions as listed below:

- Free: synonyms include "zero," "no," "without," "trivial source of," and "dietarily insignificant source of"
- Low: synonyms include "little," "few" (for calories), and "contains a small amount of," "low source of"
- Reduced/less: synonyms include "lower" (and "fewer" for calories)

Using Labels to Make Misleading Implicit Health Claims

Food marketing is very sophisticated but can often be misleading. Sugar-sweetened beverages are widely seen as unhealthy and that is where we see the most egregious examples of misleading labels. In North America, only pure fruit juice can be called "juice." However, there are several imitation juice products that contain no more than 20% actual juice; many contain none at all. These pseudo-juice products are, in reality, sugar solutions with added colors and flavors. Despite being little different from cola drinks, they have names that suggest real fruit, such as fruit beverage, fruit nectar, and fruit cocktail.

In 2000 a new product appeared called VitaminWater. It comes in a variety of formulations. This beverage contains roughly 5.5% (5.5 g/100 mL) sugar, about half the concentration found in Coca-Cola, plus vitamins and assorted other substances. The manufacturers have succeeded in achieving the best of each world: consumers have the taste of a sugary beverage while the product's name conveys an implicit message that it is healthy.

A similar example is provided by Sunny D. The name is highly suggestive of sunshine and of the vitamin D that the body produces when exposed to sunshine. The label has images of fruit. In reality, the main ingredient (after water) is sugar; it also contains a lesser amount of fruit juice. Many other food products also have large colored images of fruits on their labels. For example, some brands of fruit juice consist mainly of cheap fruit juice, such as apple juice, but with a small amount of berries. The image will typically display the reverse of this, namely large brightly colored images of berries. This problem occurs in the USA and Canada. In the UK, by contrast, many food labels state how much of some or all of the ingredients are present in the food.

What these examples demonstrate is that consumers need to be vigilant in order to avoid being deceived by deceptive labels, such as products with misleading names or the presence of misleading images. There is a strong case for enhanced regulation so that the information that appears on the front of food packages is both honest and easy to understand.

Food Labels and the Environment

Another possibly valuable addition to food labels is information on whether the food is environmentally friendly. For example, foods derived from plants would receive a more positive score than those containing red meat as the former foods are responsible for far less production of greenhouse gases and other forms of environmental damage. Similarly, fish from an endangered species would receive a low score. A FOP labeling system along these lines was launched in 2021 in the UK and the European Union [18]. Foods are given a score from A to G, which is similar to Nutri-Score. The scoring is based on a combination of four measures: emission of greenhouse gases, water usage, water pollution, and biodiversity.

Conclusion

Well-designed food labels are potentially of much value in helping shoppers to select healthier foods. The ideal combination is a clear, simple

FOP label combined with more detailed nutrition information in the BOP label. This will allow shoppers to quickly peruse the FOP label in order to make a quick decision regarding whether the food is healthy while also providing detailed information, by examining the BOP label, if consumers desire this. With respect to the design of BOP labels used in the USA, there is plenty of room for improvement.

There is still much to be learned regarding the best design of FOP labels and to what extent they are effective at persuading shoppers to buy healthier foods. Our best currently available evidence suggests that warning labels achieve the most success followed by MTL (traffic lights) and Nutri-Score. However, warning labels are limited in the information they provide as they have a narrow focus on the harmful aspects of a food. Other designs, by contrast, such as MTL and Nutri-Score, indicate both which foods are unhealthy and which are most healthy.

Another dimension of labels is the inclusion of environmental scores. This aspect of food labeling is still in its infancy but, hopefully, rapid progress is around the corner.

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Health Promotion and Nutrition Policy by Governments

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Norman J. Temple

Key Points

- Health promotion campaigns of various types have been conducted: in communities, at worksites, and in physician offices.
- The most common targets have been smoking, exercise, and people's diets, such as the intake of fruits and vegetables.
- The aim has most often been to reduce excess weight, lower blood cholesterol, blood pressure, and blood glucose, and prevent coronary heart disease (CHD).
- The results of these campaigns have been mixed. Some have achieved very little while others have met with moderate success. Typically, target outcomes have been improved by a few percentage points and this should reduce the risk of CHD by about 5–15%.
- In light of this limited success of health promotion programs, government policy initiatives are needed to improve population health.
- This includes reducing the food content of *trans* fatty acids and salt and the use of taxes and subsidies to adjust the price of various foods so as to shift consumption patterns to healthier foods.
- Other policy measures should include restrictions on the advertising of unhealthy food, especially to children.
- I propose a comprehensive action plan (strategic nutrition) that covers all the key topics including health promotion and action policies by governments.
- Policy measures along these lines are likely to meet with resistance from food corporations.

Introduction

It has been well established for many years that lifestyle—diet, tobacco use, exercise—has a major impact on the causation and prevention of a spectrum of diseases. These diseases have been referred to by different names, including Western diseases, noncommunicable diseases, and chronic diseases of lifestyle (CDL). The major CDL include most forms of cardiovascular disease (CVD) (including coronary heart disease (CHD), stroke, and hypertension), obesity, type 2 diabetes, and several major types of cancer.

Because of the strength of the evidence linking lifestyle with risk of CDL, combined with the enormous potential of a healthy lifestyle to improve population health, the importance of a healthy lifestyle is now widely accepted by those working in medicine and public health. The general population has heard this message countless times. However, there is a world of difference

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_22

between awareness of the facts and their translation into preventive action.

While the focus of this chapter is on nutrition in relation to health promotion and government policy, we also examine other areas, especially smoking and exercise. This is necessary because many health promotion campaigns have taken a broad lifestyle approach and simultaneously tackle nutrition, exercise, and smoking.

The high prevalence of CDL across the Western world has created immense pressure on healthcare systems. This crisis is most severe in the United States where the cost of health care now exceeds $3.8 trillion and accounts for almost 18% of GDP. This level of spending has brought about a great strain on both public and private finances. Unless drastic measures are taken, this spending is likely to continue its seemingly unstoppable increase in coming years. One factor driving this is that millions of baby boomers are now moving into their 60 s and 70 s. Another major factor is that the epidemic of obesity that has swept the world since the 1970s is now precipitating other disorders such as type 2 diabetes. Compounding these problems, the relentless cost inflation of medical treatment has shown little sign of being brought under control.

Health Promotion Campaigns

During the 1970s, the intimate connection between lifestyle and health became increasingly clear. As a result, many people assumed that the next step was to disseminate this information to the public and exhort lifestyle changes, action that would, hopefully, bring about widespread adoption of healthier lifestyles. Here we look at various types of health promotion campaigns, most of them focused on risk factors for CVD.

Campaigns in Communities

A number of community interventions have used the mass media combined with various other methods to reach the target population. We shall start in the early days of health promotion. Three major projects were carried out in the USA during the 1980s. Their aims were to lower elevated levels of blood cholesterol, blood pressure, and body weight, to cut smoking rates, and to persuade more people to take exercise. Each program lasted 5–8 years and succeeded in implementing its intervention on a broad scale, involving large numbers of programs and participants. In the Stanford Five-City Project, two intervention cities in California received health education via TV, radio, newspapers, other mass-distributed print media, direct education, and schools [1]. On average each adult was exposed to 26 h of education, achieved at the remarkably low cost of $4 per person per year (i.e., about 800 times less than total healthcare costs). A similar project was the Minnesota Heart Health Program which included three intervention cities and three control cities in the Upper Midwest [2]. A third project was the Pawtucket Heart Health Program in which the population of Pawtucket, Rhode Island, received intensive education at the grassroots level: schools, local government, community organizations, supermarkets, and so forth, but without involving the media [3]. In total, the three studies included 12 cities.

An analysis of the combined results of the three studies painted a disappointing picture [4]. Improvements in blood pressure, blood cholesterol, BMI, and smoking were of very low magnitude and were not statistically significant; the estimated risk of CHD mortality was unchanged. These results are mirrored by two other community projects that took place at around the same time [5, 6].

In contrast to these studies, other community projects have achieved much success. A pioneering study for heart disease prevention was conducted in North Karelia, a region of eastern Finland which had an exceptionally high rate of the disease [7]. Indeed, Finnish men had the distinction of having the highest mortality rate in the world for CHD. The intervention began in 1972 before much health information had reached the population. Nutrition education was an important component of the intervention. Over the next few years, CHD rates in North Karelia fell sharply. Between 1972 and 2007, CHD mortality in middle-aged men fell by an astonishing 80% [8]. This can be largely explained by changes in risk factors: serum cholesterol declined by 22% while

sharp decreases were also seen for blood pressure and smoking. An intensive educational campaign spread to the rest of Finland leading to a national drop in CHD rates [9]. Two other European studies carried out in the 1980s and 1990s also achieved some success [10, 11].

Two community campaigns carried out in the 1990s are of particular interest because each was narrowly focused on changing only one aspect of lifestyle and used paid advertising as a major intervention strategy. The 1% Or Less campaign aimed to persuade the population of two cities in West Virginia to switch from whole milk to low-fat milk (1% or less) [12]. Advertising in the media was a major component of the intervention (at a cost of slightly less than a dollar per person) together with supermarket campaigns (taste tests and display signs), education in schools, as well as other community education activities. Low-fat milk sales, as a proportion of total milk sales, increased from 18% to 41% within just a few weeks. The intervention campaign was repeated in another city in West Virginia; this time only paid advertising was used [13]. Low-fat milk sales increased from 29% to 46% of total milk sales. An Australian campaign also used paid advertising as a major component [14]. The goal was to increase consumption of fruits and vegetables. Significant increases in consumption of these foods were reported (fruits by 11% and vegetables by 17%).

Another area where campaigns have been narrowly focused on trying to change just one aspect of lifestyle has been those attempting to increase levels of exercise. Several dozen interventions have tried to persuade people to engage in more walking. A systematic review of these concluded that people can be encouraged to walk more by interventions tailored to their needs, targeted at the most sedentary or at those most motivated to change, and delivered either at the level of the individual or household or through group-based approaches [15]. By this means, interventions can potentially increase walking by up to 30–60 min/week on average. Several dozen interventions have also been attempted to increase exercise levels among children and adolescents [16]. Results have been mixed. The authors of a systematic review concluded that: "For adolescents, multicomponent interventions and interventions that included both school and family or community involvement have the potential to make important differences to levels of physical activity and should be promoted." [17].

Pennant et al. [18] carried out a systematic review that assessed the effectiveness of community programs for the prevention of CVD. They included several of the studies discussed above. They only included those interventions that targeted the whole population living within a defined geographic area. Their conclusions are similar to the comments made above. Overall, systolic blood pressure was reduced by 2.9 mmHg, total cholesterol level by 0.01 mmol/L, and smoking prevalence by 1.7%. The estimated decrease in 10-year CVD risk was 9.1%. This is relative risk, meaning the proportion of cases prevented. The estimated decrease in absolute risk was 0.65%, indicating that one case of CVD would be prevented in 10 years for every 150 people in the target population. The authors of this review were unable to identify factors that made program success more likely.

A notable feature of the studies reviewed by Pennant et al. [18] is that almost every one of them was done before the year 2000 (35 were carried out between 1970 and 2000 but only one between 2000 and 2008). This suggests that in the field of health promotion, the hare has been replaced by a tortoise!

Worksite Health Promotion

Other interventions have applied health promotion to worksites. Different ways have been tested in attempts to encourage workers to eat a healthier diet. For example, worksite canteens have displayed prominent labels to inform employees which foods are healthiest. Canteens have also increased the availability of fresh fruit and vegetables.

A pioneering project of this type, which started in 1976, was carried out in Europe by the World Health Organization. The project was conducted over 6 years in 80 factories in Belgium, Italy, Poland, and the UK with the aim of preventing CHD [17, 19]. The trial involved 61,000

men and achieved modest improvements in risk factors (1.2% for plasma cholesterol, 9% for smoking, 2% for systolic blood pressure, and 0.4% for weight); these were associated with a 10.2% reduction in CHD.

Another worksite project, the Treatwell program, took place in New England around 1990 [20]. Employees were encouraged to increase their intake of fiber and reduce their fat intake. Compared with the control sites, the program had no effect on fiber intake but fat intake fell by about 3%. A few years later the research team carried out a new study (Treatwell 5-a-Day study) and reported that they succeeded in increasing employees' intake of fruits and vegetables by 19% (0.5 serving/day) using an approach that targeted employees and their families [21].

The above reports represent a small selection of the many interventions that have taken place at the worksites. Our best evidence is that these types of interventions can often achieve a modest improvement in the diet [22, 23]. The American Heart Association reviewed the subject [24]. With respect to nutrition programs, the reviewers concluded that they: "… are generally effective in favorably modifying dietary practices consistent with current recommendations and in reducing major cardiovascular risk factors such as overweight/obesity, hypercholesterolemia, and hypertension." One of their conclusions regarding worksite interventions overall is that they lead to a reduction in absenteeism and improved productivity.

Health Promotion in the Physician's Office

In 1994, two British studies reported the effects of health promotion activities carried out by nurses in the offices of family physicians. The aim was to improve cardiovascular risk factors. Each study was a randomized trial aimed at cardiovascular screening and lifestyle intervention. Both studies achieved only modest changes despite intensive intervention. The OXCHECK study reported no significant effect on smoking or excessive alcohol intake but did observe small significant improvements in exercise participation, weight, dietary intake of saturated fat, and serum cholesterol [16, 25]. The Family Heart Study achieved a 12% lowering of risk of CHD (based on a risk factor score) [26]. Similar findings came from an American study where patients were given mailed personalized dietary recommendations, educational booklets, a brief physician endorsement, and motivational counseling by phone. After 3 months the intervention group had increased its consumption of fruits and vegetables by 0.6 serving/day but there was no change in intake of red meat or dairy products [27].

Wilcox et al. [28] reviewed 32 intervention studies carried out in a medical setting. They concluded that:

> Overall, these interventions tended to produce modest but statistically significant effects for physical activity or exercise, dietary fat, weight loss, blood pressure, and serum cholesterol…. Whereas small by conventional statistical definitions, these findings are likely to be meaningful when considered from a public health perspective.

A variation of the above trials is the targeting of patients at high risk of CHD, probably the most cost-effective form of intervention [29]. A study from Sweden exemplifies this approach. Subjects at relatively high risk of CHD received either simple advice from their physician or intensive advice (five 90-min sessions plus an all-day session) [30]. The intensive advice had a modest impact; it reduced the risk of CHD by approximately 6%. Two highly successful randomized controlled trials, one in the USA and one in Finland, were carried out on overweight subjects with impaired glucose tolerance, the goal being to prevent the progression to type 2 diabetes [31, 32]. The interventions consisted of physical activity and dietary change. In both studies, the estimated risk reduction was about 58%. In general, interventions focused on high-risk subjects have been more successful than other interventions [33].

The major deficiency of the high-risk approach, as Rose [34] has pointed out, is that it only affects a minority of future cases: the 15% of men at "high risk" of CHD account for only

32% of future cases. Therefore, to achieve a major effect on CHD it is necessary to target the entire population. This logic also applies to other diseases related to diet and lifestyle, such as stroke and cancer.

Internet-Based Health Promotion

In recent years, many health promotion programs have been developed that use the Internet for delivering information. This is a diverse field with programs targeting exercise, diet, obesity, and smoking. Promising findings have been reported from many interventions [35–38].

Health Promotion and the Individual

What the above projects demonstrate is that appealing to individuals to change their lifestyles will be effective in some instances but not in others and can therefore be frustratingly difficult. While some projects have achieved a moderate degree of success, typically progress has amounted to no more than a few percentage points. This might be expected to reduce the risk of CVD (including CHD) by about 5–15%. While this is certainly beneficial, it will not affect the majority of people at risk. Thus, exhortations to the individual, whether via the media, the internet, in the community (including in schools), at the worksite, or in the physician's office, are most unlikely to turn the tide of the chronic diseases of lifestyle.

More research is required to determine why different health promotion projects have achieved such varying levels of success. Would campaigns be more successful if the focus was on one lifestyle change rather than many? Is paid advertising the best means to utilize scarce resources?

Food Advertising

Children are on the receiving end of an enormous amount of food advertising, the vast majority of which is for unhealthy foods or for fast-food restaurants. Such advertising is often successful in inducing children to consume the advertised foods [39] In particular, these adverts induce children to consume more snacks, sweetened beverages, and fast food [40, 41]. Moreover, exposure to such advertising is associated with the risk of obesity in children and adolescents [41, 42].

The case is therefore strong for a ban on advertising unhealthy foods where children are a major target. In order to make this policy effective, the ban would have to cover all programs being shown late into the evening as a great many children are still watching TV at that hour. As far as is practical, this policy needs to be extended to other forms of marketing. There is evidence that such bans can be effective. According to one analysis a ban on TV advertising in the USA would lead to a roughly 19% decrease in the number of children and adolescents eating two or more fast-food meals per week and would lead to a modest decrease in obesity rates [43]. Many jurisdictions have implemented this policy and have banned adverts that encourage young people to eat unhealthy food.

This policy can be seen as the mirror image of health promotion in that it removes disease promotion.

Is the Population Adopting a Healthier Lifestyle?

The limited effectiveness of health promotion is confirmed by another line of evidence. From the 1970s onwards enormous amounts of dietary information and advice have been disseminated to the populations of all Western countries. People have been exposed to many thousands of TV programs, articles in newspapers and magazines, and books. Governments have made dietary information, such as food guides, widely available. Food packages now carry labels that provide nutrition information on the food. Yet, despite all this effort relatively little progress has been made in persuading the general population to follow the recommended dietary changes. This

is demonstrated by the findings from surveys of the American diet [44].

It is true that a few positive trends have been seen. Americans reduced their sugar intake during the period 1999–2012. But with most other aspects of the national diet, the rate of progress has been underwhelming. For example, despite being strongly encouraged to eat more fruit, only 21.5% of Americans eat one or more servings of whole fruit each day. Similarly, Americans still eat about five times more refined grains than whole grains. The failure of decades of dietary advice to persuade the population to adopt a healthier diet is exemplified by the following findings. Almost 60% of calorie intake in both the USA and the UK comes from ultra-processed foods. These consist of mixtures of such ingredients as sugar, refined flour, and added fats, plus much salt [45, 46].

A similar story emerges when we look at exercise. Only about half of American adults have heeded the advice to engage in regular physical activity, with little sign of much improvement in recent years [47].

Changes in the prevalence of obesity serve as a barometer for lifestyle. The USA has been struck by an epidemic of obesity that started in the 1970s. Between 1976–1980 and 1988–1994 obesity among adults jumped from 14.5% to 22.9% [48]. This then climbed to 30.5% in 1999–2000 [49] and to 42.4% in 2017–2018 [50].

The evidence presented in this chapter compels the following conclusion: vast numbers of Americans largely ignore the advice to lead a healthy lifestyle. This applies not only to health promotion but also to other strategies that have the goal of persuading people to adopt a healthier diet (as well as other aspects of lifestyle).

"Education, advice, and encouragement" is a convenient term that covers diverse approaches, including health promotion, that aim to persuade people to adopt a healthier lifestyle [51].

A note of caution is warranted. There are some examples of education, advice, and encouragement that have achieved significant success. One prominent example is the previously mentioned health promotion campaign carried out in North Karelia, Finland.

Why Are People Resistant to Education, Advice, and Encouragement?

Most readers of this chapter probably have a mindset that health is of great importance and that everyone should therefore try their best to follow a healthy lifestyle. But, clearly, the majority of the population gives their health a much lower priority. How can we explain this?

Myriad factors influence people's behavior besides concerns about how to protect health. Social factors, such as housing, employment, and income, also shape people's attitudes, as does their education. Advertising directly affects what people want while prices and income determine whether they can afford it. We are also creatures of habit and custom; resistance may therefore be expected when lifestyle modification demands changes in longstanding behavior and goes against fashion or peer pressure. We must also bear in mind that individuals have little control over many aspects of their physical environment, such as pollution, food contamination, and where and what kinds of foods are sold. It is probably naïve therefore to expect dramatic results from interventions that merely exhort the individual to lead a healthier lifestyle. In other words, a strategy that aims to improve population health by using education, advice, and encouragement is likely to be of modest value but is unlikely to lead to a major improvement in population health.

This frustrating problem can be stated as follows: you can lead a horse to water, but you cannot make it wear a swimsuit.

Government Policy

The Case for Action Policies

Attention is now turned to an alternative strategy designed to improve the nutrition quality of the diets consumed by the population, namely interventions carried out by direct action by governments. This strategy is referred to here as action policies. Without a doubt the implementation of well-planned action policies by governments can

be a very effective tool for improving the national diet and population health. I presented these arguments in a recent paper [51].

Action policies by governments in the area of public health have a long history. Many such policies were implemented in the nineteenth century and achieved great success. Deadly infectious diseases, such as cholera and typhoid, were brought under control by such measures as providing the population with safe drinking water as well as sewage disposal. This approach continued in the twentieth century with many new policies that were designed with the goal of improving health and safety. For example, in recent decades it became compulsory for cars to be fitted with seat belts and for these to be used by anyone riding in a car. Smoking in many public places was prohibited.

Until the 1970s hazardous amounts of lead were present in various consumer products, including gasoline and paint. Governments in many countries, including the USA, forced major reductions or removal of lead from these products. In the case of lead in gasoline, there was strong opposition from the petroleum industry. Fortunately, governments resisted this pressure. These measures greatly reduced the amount of lead that entered the environment, including the air. Testing of American children revealed that their blood concentration of lead fell by at least 75% between the late 1970s and the early1990s [52, 53].

This strategy has been applied to the field of nutrition. Many regulations have been implemented over the decades in the area of food safety. Likewise, it became compulsory for particular micronutrients to be added to some foods, such as the addition of vitamin D to milk and of thiamin to bread. In 1996 the USA and Canada implemented a policy that mandated the addition of folic acid to grain products. The goal was to correct the low intake of the vitamin in pregnant women and thereby prevent spina bifida in infants. This policy and the others mentioned above have generally achieved a high degree of success. Moreover, the policies, in most cases, are highly cost-effective.

Examples of Action Policies

Removal of *Trans* Fatty Acids from Foods

Here is an example of an action policy in the area of nutrition. Around the years 2010–2018, the USA and Canada implemented a policy that forced food manufacturers to remove *trans* fatty acids from foods. Other countries implemented similar policies but with more modest targets [54]. The rationale for this policy was the discovery that consumption of these fats significantly increases the risk of CHD [55]. These unnatural fats are formed during the production of hydrogenated fats. Until their removal, major food sources included hard margarine, cakes, doughnuts, cookies, and deep-fried foods.

Reducing the Salt Content of Processed Food

Salt is another substance in food where a strong case can be made for an action policy so as to reduce intake. The populations of the USA and most other Western countries consume about 50%–100% more than the recommended amount [56]. Strong evidence documents that this excessive intake increases the risk of hypertension [57, 58] and cardiovascular disease [58, 59]. This indicates that a reduction of one-third in the salt content of food could help prevent many thousands of cases of cardiovascular disease [60, 61].

The only practical way to achieve that goal is to greatly reduce the salt content of processed food as that is the source of roughly 75–80% of dietary salt [62]. One strategy is a voluntary action by industry, a policy adopted by the UK [63]. In the 7 years following the implementation of the campaign (2001–2008) salt intake by adults in the UK fell by about 10% [64]. This is clearly far less than the required one-third reduction in salt intake. An action policy approach (i.e., setting mandatory limits on the salt content of processed food, similar to that adopted to reduce the food content of *trans* fatty acids) would have achieved the required reduction in salt intake in a mere few years.

Action Policies in Schools

Schools in North America are fertile ground for action policies. For example, vast numbers of schools have vending machines that sell unhealthy foods or beverages. Evidence reveals that when action is taken to improve the food environment in schools, such as by ensuring that vending machines stock only healthy foods and that meals served in schools are of high nutritional quality, students then consume a healthier diet [65]. Some jurisdictions in the USA and in other countries have implemented concrete policies in order to achieve these goals. For example, in 2011 Spain banned unhealthy food from schools [66].

A study that is worthy of attention is Romp and Chomp [67]. This was a community-wide, multisetting, multistrategy intervention conducted on 12,000 young children in Australia from 2004 to 2008. The goals were to reduce the prevalence of obesity by improving diets and encouraging children to engage in more exercise. The intervention achieved much success. The investigators summarized the situation after the policy had been implemented as follows:

> Early-childhood settings in the intervention areas are now places in which fruit, vegetables, and water are promoted and packaged snacks and sweet drinks are restricted or discouraged. Driving these changes has been the implementation and enforcement of effective policy, cultural changes within organizations, and capacity-building with early-childhood teachers and caregivers. The consistency and continued reinforcement of messages across the community was a key factor in the success of the intervention, in addition to the capacity building of a willing and influential group of gatekeepers (early-childhood workers). Utilizing capacity-building and policy-based strategies also increases the potential of the intervention to benefit future cohorts of children.

Taxes and Subsidies as Tools to Improve Population Diets

It is well known that when the price of a product is increased, sales go down. Economists refer to this phenomenon as price elasticity. Many studies have demonstrated that this rule applies to tobacco and alcohol. It also applies to food as the following example illustrates. When fruit in a supermarket is starting to become overripe, the store will lower the price in order to sell the product quickly. As a rule, a change in food prices of around 10–15% will significantly affect sales [68].

This rule can be put to good use in order to achieve an impact on the national diet [69]. This means manipulating food prices as follows:

1. subsidies can be applied to healthy foods, such as fruit, vegetables, and wholegrain cereals, in order to lower the price, and
2. a tax can be added to less healthy choices, such as white bread and sugar-sweetened beverages (SSB), so as to increase the price

If the level of subsidies and taxes are carefully regulated, then the cost to the government should be minimal as money spent on subsidies will be canceled out by the extra revenue from taxes. Similarly, there should be no overall effect on food prices.

It is in relation to SSB that this strategy has attracted most attention. Indeed, several cities in the USA and 40 countries have either formulated or implemented plans for a tax on SSB. It has been estimated that a 10% tax on these drinks will reduce consumption by around 10% [70, 71]. The findings from a study in the UK suggest that an even greater impact on the sales of unhealthy foods could be achieved by directing the tax to solid sugar-rich snacks, such as chocolate, cookies, and cakes [72].

Food Prices and Socioeconomic Status

The question of food prices is especially important in relation to people who have a low socioeconomic status. Many studies have demonstrated that people on a low income have the least healthy diets. They also tend to have the poorest health and the highest rates of obesity. This is a complex issue with multiple factors at work. But one important factor that pressures poorer people to eat a less healthy diet than do more affluent people is that healthier diets are generally more expensive than unhealthy diets [73]. For example, obtaining calories from fruits and vegetables is much more costly than buying calories from foods rich in added sugar [74]. Likewise, a study

in Belgium concluded that buying food energy in the form of unprocessed or minimally processed foods costs more than twice as much as buying it from ultra-processed food (1.29 vs 0.55 euros per 100 kcal) [75].

These findings lend extra weight to the argument that making healthy foods more affordable will improve the national diet and thereby improve population health.

Another strategy that can help poorer people to obtain healthy foods is to distribute vouchers that can be exchanged for healthy foods. These are often referred to as "food stamps" in the USA. Implementing this action policy would require little more than a change in the rules governing how the food vouchers can be used.

Strategic Nutrition

Many experts on health policy have made proposals similar to those stated above. But the large majority of previous proposals have been narrowly focused. In 2016, I published a paper with a comprehensive action plan—"strategic nutrition"—that covers *all* the key topics [76].

Strategic nutrition is, in essence, a combination of education, advice, and encouragement, including health promotion, as well as action policies by governments. The goal of this plan is to foster an environment that supports healthy choices in diet and other aspects of lifestyle.

Strategic nutrition includes the following:

1. Providing subsidies so as to encourage consumption of healthier foods combined with adding taxes on unhealthy foods.
2. The stricter regulation of adverts for unhealthy foods. Of most importance adverts for unhealthy foods ("junk food") should be banned when the target audience is children.
3. The design of food labels needs to be improved so that they are more user-friendly and encourage the selection of healthier foods (see Chap. 21).
4. Improved design of food guides. As far as possible they must be scientifically accurate while also being easy to read and understand (see Chap. 20).
5. Setting strict limits on the food content of unhealthy substances such as salt.
6. The government should, where reasonable, exert pressure on schools and other institutions under government control so that they provide healthy food. This approach can also be a guiding principle for government programs that provide food assistance to people on low incomes.
7. There is a need for an agency that provides accurate information to the general public, as well as to the media and to health professionals. This will help counter the enormous amounts of false and misleading statements that appear continually in TV adverts, magazines, books, and in social media.
8. Health promotion campaigns need to be expanded. There is a need for a new class of health professional who specializes in carrying out health promotion. The person would have expertise in nutrition. Key skills include motivational techniques that help persuade people to adopt a healthier diet. These skills would extend to related lifestyle areas including adopting an exercise program and smoking cessation. Practitioners might work in schools, workplaces, gyms, and senior centers.
9. Stricter regulation is needed in the marketing of dietary supplements. This is because large quantities are sold but few are of proven value (see Chap. 31). More checks should be carried out so as to determine the actual composition of supplements as they often do not contain what is stated on the label.
10. The ideal government department to coordinate and implement this action plan is the department of health. However, the proposals clearly affect several other government departments.

This plan opens up a path to a major advance in public health. The World Cancer Research Fund International made similar proposals with a plan known as NOURISHING [77].

Some Signs of Progress

Latin America is one region of the world where encouraging progress is being made. The governments of several countries, including Mexico, Peru, Chile, Colombia, Brazil, and Uruguay, have passed laws and implemented policies that are intended to reduce the consumption of unhealthy foods, especially by children [78]. Actions include limiting advertising that is directed to children for unhealthy foods and the sale of those foods in schools and adding a tax to unhealthy foods.

Policies advocated in this chapter have come together in campaigns that have focused on curbing the obesity epidemic. An excellent—but, alas, rare—example of the implementation of a broad strategy comes from an intervention carried out in France [79]. Children in schools in two towns were given nutrition education. This program was launched in 1992 and expanded somewhat after 1997 to the adult population of the towns. From 1999 there was even wider community activity in support of more physical activity and a healthier lifestyle. At the same time, there was much media interest. The BMI of children aged 5–12 years was measured in 2004 and compared with two other towns that received no intervention. The findings revealed that the children in the intervention towns had a lower BMI (15.7 vs. 16.5) and a lower prevalence of overweight or obesity (7.4% vs. 19.4% in boys; 10.4% vs. 16.0% in girls). This is a remarkable degree of success.

Another noteworthy broad-based program is the Amsterdam Healthy Weight Programme [80, 81]. This program is scheduled to run from 2013 to 2033 and aims to reduce childhood overweight and obesity in Amsterdam.

The Question of Cost-Effectiveness

Despite being limited in its impact, health promotion is, nevertheless, of much value. This extends to considerations of cost. Because minor changes in the lifestyle of millions of people can make valuable contributions to public health, expenditure on health promotion is cost-effective [82, 83]. The evidence is especially strong with health promotion at the worksite. This was demonstrated by a review carried out by the American Heart Association. As interventions at the worksite can bring about a reduction in absenteeism and improved productivity, nutrition programs can be highly cost-effective, saving employers several dollars for each dollar invested [24].

Compared with health promotion, action policies carried out by the government can have a large impact at a relatively modest cost. As a result, they can be highly cost-effective. This was clearly demonstrated with analyses of the cost and health benefits of policies that reduce the food content of *trans* fatty acids and salt [84, 85].

Barriers to the Implementation of Strategic Nutrition

The food industry profits enormously from the sale of highly processed food. For that reason, food corporations and their lobbyists endeavor to construct barriers to the implementation of effective policies of the type proposed here. These corporations are emulating the game plan developed decades ago by the tobacco industry. That industry strongly opposed all efforts to increase taxes on cigarettes and to implement policies that curtailed smoking in public places. The tobacco industry achieved much success over many years by being utterly unprincipled and utilizing a large budget, much of it used for contributions to political parties and lobbyists.

Here is an illustrative example of recent actions by food corporations. As mentioned above several jurisdictions in the USA and elsewhere have attempted to add a tax on sugar-sweetened beverages (SSB) in order to reduce sales. Food corporations that manufacture SSB have vigorously opposed these taxes for the obvious reason that such taxes are likely to lower sales [86]. It is therefore of utmost importance that those advocating for pro-health policies are resolute.

The pressure exerted by the food industry in the protection of its financial welfare is further explored in Chap. 30.

Final Comments

It is the environment around us that plays a major role in determining the lifestyles and the health of the general population. The word "environment" here refers to the many factors that affect our behavior and our diet. Factors of major importance include food composition and food prices. From this, it follows that in order to achieve a major reduction in the numbers of people affected by the chronic diseases of lifestyle, it is essential that policies are implemented so as to change the environment. In other words, we need to radically change the current environment from one that encourages people to follow an unhealthy lifestyle and then, inevitably, to develop diseases, and instead create an environment that fosters enhanced health for the population. Achieving this requires important changes in a range of government policies, regulations, and laws.

The philosophy discussed here need not stop at nutrition: what applies to nutrition certainly applies to other areas of lifestyle, especially to smoking. Exercise also lends itself to policy initiatives. What is the point in telling people to exercise if there is a lack of appropriate facilities? What is the point in telling people to cycle if the roads are too dangerous for bikes? What is needed is a comprehensive view of human health that takes all such factors into consideration.

As the century unfolds people may look back with incredulity on today's world where narrow commercial interests and government laissez-faire predominate while the national health flounders.

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Part V

Emerging Trends

Food Synergy: A Paradigm Shift in Nutrition Science

23

David R. Jacobs, Jr. and Norman J. Temple

Key Points

- A major focus of nutrition science has centered on identifying the various macronutrients, vitamins, and minerals and then investigating their mode of action.
- Many associations between diet and risk of disease are best understood by looking at food as a whole and not merely as a collection of individual nutrients and other bioactive substances.
- Because of the limitations of epidemiology, it is extremely difficult in many cases to identify the substances in food that account for protection against disease. This is especially the case with phytochemical-rich plant foods, including fruit, vegetables, nuts, legumes, and whole-grain cereal foods.
- More research into foods and dietary patterns is needed.
- The findings can be directly translated into dietary recommendations. They also serve as a scientific anchor point to which studies of food components must conform.

This chapter critically evaluates approaches to explaining the nature of the relationship between diet and disease. Most research historically has focused on studying single substances: macronutrients, micronutrients, as well as the many other bioactive substances present in food, either beneficial or harmful. Here we argue the case for turning our attention to food as a whole and to dietary patterns. The constituents of foods and patterns act in concert to influence health. This concept, known as food synergy, defined as an additive or more than additive influences of foods and food constituents on health, is a powerful tool to help explain many nutrition-related diseases and how best to prevent and treat them. Many ideas in this chapter were stated some years ago by one of us (DJ) [1–5]. Other authors endorse this concept [6–8].

The Concept of Nutrient Deficiency Diseases

Up until the 1950s, a major focus of nutrition science centered on identifying the various vitamins and minerals and then discovering their mode of

D. R. Jacobs, Jr. (✉)
Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA
e-mail: Jacob004@umn.edu

N. J. Temple
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_23

action [7]. The underlying philosophy can be summarized as follows:

1. There is a simple cause-and-effect relationship between deficiency of a nutrient and the associated specific disease.
2. Each nutrient deficiency disease can be explained in terms of the role played by that nutrient, especially in the areas of biochemistry and physiology.
3. The nutrient deficiency can be prevented (and often reversed) by giving that nutrient in an isolated (pure) form.

Classic examples are vitamin C in relation to scurvy and iron in relation to anemia. This concept is still very much alive and is seen in the vitamin and mineral chapters of every textbook used in college nutrition courses. The concept can be applied not only to vitamins and minerals but also to protein and essential fats.

In recent years the concept has shown its continuing value in several areas. Folate illustrates this well. Research has firmly established that supplementary folic acid (a form of folate) is protective against neural tube defects (NTD), a group of congenital disorders that include spina bifida [9]. While NTD cannot be characterized as a vitamin-deficiency disease in the mother, it seems clear that a low maternal intake of folate creates a deficiency condition in the fetus that hinders normal development of the nervous system thereby allowing the condition to emerge [10]. As a result of this discovery, mandatory addition of folic acid to refined grain products started in 1998 in the USA and Canada.

The relationship between single substances and disease risk extends well beyond disease protection by micronutrients; there are many other bioactive substances in food, either beneficial or harmful. Sodium (as salt) is an especially clear example of this. A high intake of the mineral, which is the case for the great majority of the population, plays an important role in the causation of hypertension ([11, 12]; see Chap. 9) and cardiovascular disease (CVD) [12, 13]. Strong evidence also suggests that salt significantly increases the risk of stomach cancer [14]. Jacobson described the practical and political issues, and some limited success, in working towards salt reduction by the food industry [15]. *Trans* fatty acids are another example. This type of dietary fat adversely affects multiple cardiovascular risk factors and increases the risk of coronary heart disease (CHD) [16, 17]. Another bioactive substance in food is alcohol. High intakes cause multiple harmful effects. The adverse effect of the alcohol itself is almost certainly the cause of higher disease rates in heavy drinkers. But as explained in Chap. 12 evidence has emerged over recent decades that alcohol lowers the risk of CHD and possibly several other conditions. The active ingredient could be alcohol itself, but the production of alcoholic beverages extracts many phytochemicals from the plant from which it is made, such as barley or corn [18], and these might explain the epidemiologic associations. The small amount of alcohol in a single drink could be beneficial or adverse, but if it is adverse, the simultaneous provision of phytochemicals may provide a net benefit up to a certain amount drunk. In fact, this interplay between the alcohol and phytochemical constituents of alcoholic beverages is a good example of food synergy.

In many respects, this reductionist approach to nutrition, called nutritionism by Scrinis [19], has not provided satisfactory answers to nutritional questions. Of special note, as discussed below, are studies in which nutrients were derived from food intake, found to be "protective" observationally (e.g., [20]), then used in higher doses as supplements in clinical trials. The purified nutrients in relatively high dose did not work as predicted according to reductionist logic.

Food Synergy: An Alternative Paradigm

The Emergence of the Concept of Food Synergy

A strong argument has been made that to properly explain the many associations between diet and risk of disease we should view food as a

whole, and not merely as a collection of individual nutrients and other bioactive substances. Over the past couple of decades, this concept has emerged as an alternative concept to the one discussed above that focuses on individual nutrients and bioactive substances in food. In a nutshell—figuratively (and literally in the case of nuts)—food synergy has provided a better explanation for many nutrition-related diseases and how best to prevent and treat them. This represents a paradigm shift in our understanding of nutrition science.

Compelling support for food synergy comes from examining complex dietary patterns in relation to disease risk. The following examples illustrate this.

The Mediterranean Diet

One such dietary pattern that has been much studied in relation to CHD is the Mediterranean diet. This diet and its effects on health is discussed in detail in Chap. 16. While this diet varies from country to country around the Mediterranean, major features include a relatively high intake of vegetables, fruit, legumes, nuts, fish, cereals, and olive oil. Conversely, the diet is typically low in meat, especially red meat, such as beef and pork, and processed meat.

Mente and colleagues carried out a systematic review on the relationship between diet and risk of CHD [21]. They examined some 26 nutrients, foods, and dietary patterns for the strength of the associations seen in cohort studies. They reported that of all the associations with risk of CHD, either positive or negative, the strongest one was for the Mediterranean diet. The diet has the following attributes: first, it manifests strong protection against the risk of CHD; and second, it has a complex nutritional composition, rich in phytochemicals but low in saturated fat, heme iron, and many other substances found in meat. It appears highly likely that multiple dietary components and multiple pathways are responsible. Based on this it can be reasonably argued that this diet–disease association provides strong support for the food synergy concept. Indeed, the large, long-term PREDIMED randomized controlled trial found that the Mediterranean diet protects against total CVD [22].

The Alternate Healthy Eating Index

Another healthy eating dietary pattern is the Alternate Healthy Eating Index, as revised in 2010 [23]. Findings from the Nurses' Health Study showed that middle-aged women adhering to this dietary pattern have a much reduced risk of death from CVDs, from cancer, and from all causes combined [24], as well as other outcomes such as physical function impairment [25].

The A Priori Diet Quality Score

A novel index based only on foods is the A Priori Diet Quality Score [26]. It was formulated as the sum of ranks of food groups that had been judged to be favorable or unfavorable for health by knowledgeable persons experienced in nutrition and nutritional epidemiology. It was reported as being related to reduced odds for myocardial infarction [26], CVD [27], changes in intermediate risk markers [28, 29], common carotid intima media thickness, mediated by waist circumference [28], incident diabetes [30, 31], and loss of kidney function [32].

Western Dietary Pattern

Just as every movie with a hero also needs a villain, so a healthy dietary pattern needs an unhealthy one. That role is played by the "Western" pattern. Such a diet is high in red meat, processed meat, refined cereals, French fries, and desserts. A publication from the Nurses' Health Study linked this dietary pattern to an elevated risk of death from CVDs, cancer, and all causes combined [33].

Meat and Health

The above dietary patterns are wide-ranging. The meat content of these dietary patterns is just one factor among many. However, there has been much interest for many decades regarding the relationship between meat consumption and health. Vegetarian diets have been advocated by many people over the years as a healthier alternative to a meat-based diet. The most compelling evidence supporting the strong health benefits of a reduced intake of meat comes from a cohort study of half a million middle-aged and elderly Americans [34]. The findings clearly show that consumption of red meat and processed meat are associated with a higher risk of death from CVDs, from cancer, and from all causes combined.

The Seventh-Day Adventist religion includes scriptural mandates to eat a vegetarian diet. Findings from the Adventist Health Study 2, in which many participants ate a vegetarian diet, observed lower all-cause mortality for vegetarians [35], and that in this population both ultra-processed food and red meat consumption are associated with excess total mortality [36].

There are several possible food constituents that might explain these results, including saturated fat, iron, and various amino acids, and a low intake of phytochemicals. The researchers in this study did adjust their hazard ratios for many confounding variables. This is important as meat consumption in this population is associated with a generally poor diet and unhealthy lifestyle. Many nutritional factors are probably involved in the connection between meat and risk of death from diverse causes. Accordingly, meat consumption should best be viewed from the perspective of food synergy.

DASH Diet

This diet was developed as a treatment for hypertension [37]. Key features are a generous intake of fruit, vegetables, and low-fat dairy products, combined with a reduced intake of meat, and therefore saturated fat. As described in Chap. 17 this food synergy approach has proven effective as a treatment for hypertension [37].

Food Synergy and Disease

In each of the above cases, we see strong evidence that the relationship between diet and disease risk is best explained by focusing on foods rather than substances present in food. This applies to both prevention and treatment. It also applies both to dietary patterns and to single food groups, such as meat. Our best explanation lies in the great complexity of food and dietary patterns, the thousands of different substances present, and the many pathways that connect food with the etiology of disease.

Food Synergy: A Research Perspective

The Limitations of Epidemiology

The evidence considered above supports the case for food synergy as an explanation for many diet–disease associations. However, there is a separate line of argument that also supports the food synergy concept. Nutrition research methods have limited power to identify which nutrients or other bioactive substances in a complex food are likely to be responsible for particular health benefits or for increasing the risk of particular diseases. The reasons for this were explained in Chap. 1 by the authors of this chapter. The major problem is that nutrients and other bioactive substances are not distributed randomly in foods. Instead, they are mostly associated with each other. In other words, focusing on one substance causes confounding due to the presence of many other substances. This problem is especially acute with the multitude of substances found in fruit and vegetables and other phytochemical-rich plant foods. These include folate, vitamin C, potassium, fiber, and, of course, a great many phytochemicals, many of which have been little studied or not even identified. Because of this, it is unlikely that epidemiological studies will ever be able to determine, for

example, whether lycopene prevents prostate cancer or if alpha-carotene prevents colon cancer.

Cereal fiber and whole-grain cereal foods pose a similar challenge and an interesting counterpoint. This was illustrated in a study by Jacobs et al. [38]. They observed that dietary fiber from whole-grain cereals has a stronger protective association with disease than does the same amount of fiber from refined cereals. The proposed explanation is because of the phytochemicals present in whole grains. This indicates that epidemiological studies cannot even state with confidence whether dietary fiber really has an independent protective association with disease risk, beyond its direct effect in the large intestine. However, the suggestion is that there is something of health value in the whole grain, which is a conclusion about a food, rather than a nutrient.

We see therefore that the problem of confounding makes it extremely difficult to identify which nutrients or other bioactive substances deserve the credit for the health benefits of fruit, vegetables, and whole-grain cereals.

One obvious way to circumvent this problem is to carry out randomized clinical trials (RCTs) on single substances. However, these are extremely costly and usually take several years. They are only appropriate therefore when dealing with dietary components where there is already strong supporting evidence. Besides, as argued in depth in Chap. 1 on research design, the many differences between drugs and foods heavily influence research design. One must be very careful when undertaking an RCT on a single substance derived from food to be clear about whether it is even possible to answer the question being asked about the health implications of a single nutritional substance. As well, one must consider whether the findings from that RCT would help elucidate what food people should eat. We will now illustrate these points with some examples.

The saga of antioxidants provides perhaps the best illustration of the limits of epidemiology. It was discovered that beta-carotene (derived as a weighted average of beta-carotene-containing foods) was inversely related to lung cancer [20]. Subsequent epidemiological studies led to the widely held view that beta-carotene may be effective as a chemopreventive agent against a range of cancers [39]. At around the same time epidemiological evidence linked two other antioxidant vitamins—C and E—with protection against disease. Vitamin C was reported to have a negative association with risk of cancer [40] while several cohort studies observed that intake of vitamin E has a modest protective association with risk of CHD [41]. Following these findings all three antioxidant vitamins were studied as disease preventatives; this involved administering these substances in a purified form at doses typically several times higher than the RDA. The results of long-term RCTs on beta-carotene appeared in the mid-1990s and these have consistently shown that supplements are ineffective for the prevention of cancer [42]. Likewise, supplements of vitamin E have little or no preventive action against CHD [21]. Findings for all three antioxidants were actually adverse: an increase in total mortality of about 2–5% [43]. The likely explanation for these findings is that the negative associations seen in epidemiological studies were entirely due to confounding by or interaction with phytochemicals and other substances that are found in the same foods as the antioxidant vitamins.

It is very likely that there is a complex food synergy at work in all the examples discussed above. In other words, the true reason that fruits, vegetables, and whole-grain cereals are protective against cancer and CHD is because of a complex interaction induced by a wide variety of nutrients and other bioactive substances. But let us suppose for one moment that the active ingredients are limited to a mere three or four phytochemicals. Because of the limitations of epidemiology, as explained above, it is extremely difficult to identify these substances with any confidence. For that reason, it hardly matters if the actual number of anticarcinogenic phytochemicals is 3 or 300. In contrast, a finding that a certain food or dietary pattern influences health is feasible, informative for future thinking, and of great practical value.

The limitations of epidemiology are also shown by studies investigating the relationship between homocysteine, folate, and CHD. Several epidemiological studies had revealed that blood homocysteine levels are correlated with risk of CHD and other CVDs [44, 45]. As supplements of folic acid (the form of folate used in supplements) are effective at lowering the blood homocysteine level [46, 47], it was hypothesized that this intervention will therefore be protective against CHD. Separate from this, epidemiological studies had indicated that dietary intake of folate has a strong inverse association with risk of CHD [21]. Indeed, in the systematic review carried out by Mente et al. [21], based on the findings from cohort studies, of all the nutrients, foods, and dietary patterns examined, folate had one of the strongest associations with risk of CHD. However, when the results of RCTs appeared, contrary to expectations, results showed no indication that folic acid supplements prevent CHD [21, 46], and some RCTs have even suggested adverse effects on cancer and other diseases ([47, 48]; see Chap. 10). The lesson here is that the studies that attempted to explain the association between blood homocysteine levels and risk of CHD did not confirm a simple, critical, causal role for homocysteine. The protective association between folate and CHD is most likely explained as one more case of confounding. In other words, folate is present in the same foods as the substances in foods that are protective against CHD. These supplement studies do not necessarily imply no value for folate when obtained from foods, because nutrients obtained from (whole) foods are in natural balance, certified by evolution.

The Limitations of Mechanistic Research in Explaining the Effects of Food on Health

Some might argue that what cannot be achieved by epidemiology can be accomplished by laboratory-based research with the goal of explaining disease in terms of its causative mechanisms. For example, studies of the biochemical action of diverse phytochemicals on the processes of carcinogenesis will (supposedly) help identify which ones are potentially chemopreventive and should therefore be tested in RCTs. Similarly, while epidemiological research has provided indications that particular vitamins prevent CHD (and, therefore, by implication, also help prevent atherosclerosis), this can be firmly established by studies of the processes of atherosclerosis at a cellular level.

Chapter 1 explained the serious limitations of mechanistic research on nutrients, often referred to as reductionism. We will illustrate this by returning to two of the antioxidant vitamins discussed above. Many studies were carried out during the 1980s that investigated the effects of beta-carotene on body systems possibly related to cancer. This included studies of antioxidant action [49] and immune function [50, 51]. However, the dubious relevance of these studies to the relationship between diet and cancer became obvious when RCTs demonstrated that supplemental beta-carotene does not prevent human cancer. Likewise with vitamin E. Here, the focus of research was on the ability of vitamin E to retard the oxidation of LDL [52]. But as vitamin E has shown little or no effectiveness in preventing CHD, it is hard to discern the practical value of mechanistic research.

Future Research Directions

There is nothing intrinsically wrong with an approach that searches for the roles of specific molecules. But there is much to be said for seeking findings about foods or food patterns; this is because this can generate valuable information that answers nutritional questions. It is not necessary to reduce foods to constituents in order to understand that diet does affect health and to formulate policy for better eating. We should take a food synergy perspective, think foods first [4], working on the assumption that as we have little idea which substances are involved, the only practical approach is to assume that all nutrients and other bioactive substances in phytochemical-rich plant foods play a role in giving protection

against cancer, CHD, and other chronic diseases. Even if there are simple reductionist answers to nutritional questions in generally well-nourished people, due to practical circumstances of solving the immensely complex problem of interacting food constituents, we are unlikely to make major progress in the near future based on a strategy that centers on a reductionist approach.

What is the best way for researchers to design investigations in order to achieve a better understanding of how to maintain health? Based on the arguments presented here, the answer lies in a two-stage strategy. First, epidemiological studies are required to identify which dietary patterns or foods have an apparent cause-and-effect relationship with disease. Such studies are quite reliable for that purpose. In the second stage, RCTs need to be carried out in order to test either whole diets or individual foods.

Carrying out such RCTs presents serious challenges. These would need to be long term. Moreover, blinding is all but impossible as it is fairly obvious what is being eaten. Compliance to fixed diets may be an even larger problem. Imagine requiring that for several years coffee drinkers abstain from coffee or those who dislike coffee consume it regularly; or that meat lovers become vegetarian or vegetarians omnivores. However, such studies are feasible. For example, a 4-month trial using the DASH diet as a treatment for elevated blood pressure achieved excellent compliance [53]. The Women's Health Initiative set a much more ambitious target with the aim of persuading healthy women to make major changes in their diets and maintain them for 6 years [54]. For example, they aimed to reduce total fat intake to 20% of calories. However, the actual change was only about half of this. The PREDIMED study [22] was successfully carried out with a mean follow-up of approximately 5 years.

Top Down Approach

Tapsell et al. [6] pointed out that dietary guidelines are intended to promote healthy eating so as to avoid chronic disease. They expressed a need for statements about specific foods or food groups. Following a recommendation by Jacobs and Steffen [3], they carefully detailed investigations that use a "top down approach" of diet patterns, then individual foods, and then nutrients in order to understand mechanisms. On the one hand, membership of a food group within a diet pattern is a sort of endorsement of that food group as a part of the diet pattern. That level of endorsement might be sufficient advice to justify consumption or not of a food in question. However, it may be useful to make statements about individual food groups without much reference to the overall diet (that is, no matter what the rest of the diet is). Tapsell et al. [6] then asserted that statements about nutrients may be helpful in understanding the mechanics of diet and health, and working from the bottom up in making recommendations for what foods to consume. This scenario may also be applied in the case of Fardet and Rock's [8] 3 V's: "vegetal" (eat plant foods), "varie" (vary what you eat), and "vrai" (eat real food, in a form close to "as grown"). In making food choices, which "vegetal" foods should be preferred? Does eating a lot of brands or types of junk food satisfy "varie"? And is "vrai" violated if whole-grain food is ground into meal or flour?

These issues lead to a desire to go beyond diet patterns, and a suggestion to endorse nutrient-based guidelines. Tapsell et al. [6] focused on three examples where they consider that a nutrient is important in dietary guidelines. These are saturated fat, refined and added sugar, and salt. They noted that the food industry has capitalized on the fact that fat, sugar, and salt tend to make food more palatable. For saturated fat, they argued that a dietary guideline limitation is needed and effective because saturated fat is a strong indicator of demonized foods, such as cheese pizza (also high in refined grain and salt). But Choi et al. [55] showed that purely limiting saturated fat was not related to future CVD, even though it was related to lower low-density lipoprotein cholesterol, whereas a general plant-centered pattern was related to incident CHD and stroke, and to incident total CVD [36]. Furthermore, perhaps in order to further simplify the message, Fardet and Rock [56] asserted that

the matrix of real food is the single most important aspect of food. While we agree that the food matrix is an important consideration, we think that this assertion [56] dilutes the power of the food synergy argument. Thus, we acknowledge the need for greater depth of understanding of what to eat and support further research into the subtleties of the resulting arguments.

Conclusion

Food that emanates from a living organism is a mixture of constituents, but not a random mixture. Rather, the particular mixture has proven adequate through evolution for the life of the organism eaten. To the extent that the organism has been eaten for a long time, evolution has also tested the mixture of constituents as food for the eater.

There is still much to be gained from research that investigates individual nutrients and bioactive substances in food and then attempts to determine their role in health and disease. This is especially valuable in cases where problems of confounding are relatively small and it is therefore possible to investigate nutrients or other substances as single variables. An interesting example is vitamin D where sun exposure is important in addition to food.

In several cases research on single nutrient has lead to important measures that have improved public health. We see this with folate in relation to spina bifida, although there are reservations about whether the good findings for NTDs carry over to the whole population for protection from chronic diseases of adulthood. Other notable cases of single-nutrient solutions to health problems are iron supplementation for iron deficiency anemia and vitamin B_{12} supplementation for the elderly. However, these instances usually occur in situations of relative deficiency.

We must stay open to the possibility of more such cases appearing. It is entirely possible that some phytochemicals will be proven to have valuable health-enhancing actions. In such cases, they could have potential as drugs. Indeed, some evidence of this has already been documented: lutein is showing promise for improving eye health [57, 58] and soy isoflavones for improving bone health [59]. Whether these substances would be useful as supplements in the general population is an unanswered question; or, perhaps they should be thought of as drugs.

But, increasingly, we are seeing the limitations of this approach. There is a strong case for placing much more emphasis on food synergy and regarding findings for foods or dietary patterns as final answers to questions. This can include dietary patterns, such as the Mediterranean diet, or single foods, such as red meat. It is not clear whether food synergy reflects a true mathematical synergistic relationship (i.e., the whole risk or benefit is greater than the sum of the parts) or else is simply an additive effect. At a minimum, though, even in the absence of mathematical synergy, foods are complex mixtures, tested by evolution, which we would not come to by constituting them de novo from individual constituents.

We are sympathetic to attempts to properly understand the detailed causes of chronic diseases. However, we believe that the complexity of metabolism and pathology is such that nutrition research is a long way from being able to achieve this goal. Epidemiologic studies of nutrients are often misleading because they miss the context of the whole food and diet pattern. In other words, both epidemiologic study of nutrients and mechanistic research are inferior strategies for achieving valuable breakthroughs that lead to improvements in public health through improved diet. Despite that, mechanistic research attracts far more resources than food-based research. We conclude therefore that improved infrastructure for food-oriented research would be most valuable.

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Genomics and Gene-Based Personalized Nutrition

24

Ashwini Rajasekaran and Karen Davison

Key Points

- Nutrigenetics describes how genes determine the effects that nutrients have on the body; nutrigenomics describes how the foods change how genes are expressed.
- Gene-based personalized nutrition aims to integrate an individual's genetic, phenotypic, and health-related information to provide precise dietary guidance to improve or optimize health status.
- Although based on the scientific underpinnings of nutrigenetics and nutrigenomics, applications in practice vary and are largely unregulated.
- There is a continued need to consider the public health implications of gene-based personalized nutrition, including ethical, legal, and policy considerations.
- When guided by robust scientific evidence that considers multifactorial disease etiology, ethical principles, health policy, and health law, gene-based personalized nutrition could hold significant promise in positively impacting eating behaviors to help prevent and manage chronic diseases.

A. Rajasekaran
Department of Pharmacology-Physiology, Université de Sherbrooke, QC, Canada
e-mail: Ashwini.Rajasekaran@usherbrooke.ca

K. Davison (✉)
Health Science Program, Kwantlen Polytechnic University, Richmond, BC, Canada
e-mail: karen.davison@kpu.ca

Introduction: Nutrigenetics and Nutrigenomics

It is well established that nutrition status and genetic predisposition are major determinants of human health. Furthermore, tailoring one's diet based on an individual's genotype to optimize health is not new. Individuals with health conditions, such as phenylketonuria, galactosemia, and celiac disease [1–3], must adjust their food intake to bypass metabolic deficiency. In these instances, specific dietary recommendations have been defined, validated, and used in clinical practice. Gene-based personalized nutrition draws upon this knowledge to suggest that utilizing the results of nutrition-related gene tests in combination with phenotypic and health status information can provide individuals with precise dietary advice. This may motivate people to make dietary changes that can improve their health.

Gene-based personalized nutrition is based on the sciences of nutrigenetics and nutrigenomics. Nutrigenetics considers the effects of inter-individual differences of genetic variants on responses to nutrients and other food components in the context of health requirements. It contributes to knowledge about disease etiology [4].

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_24

Conversely, nutrigenomics considers the effect of nutrition-related DNA modifications and regulatory interactions of nutrients and bioactive food components with DNA and RNA elements [5, 6]. Both of these sciences demonstrate that there is individual diversity in the inherited genome which affects nutrient bioavailability and metabolism. Furthermore, dietary deficiencies or excesses can affect the expression of genes and/or increase genetic polymorphisms. This can cause abnormal gene dosage and gene expression leading to adverse phenotypes [7].

Gene-based personalized nutrition may be viewed as a component of personalized or precision nutrition. The goal is to tailor nutrition recommendations. It includes factors such as socioeconomics, gene-test results, blood biomarkers, protein abundance, metabolites, and the gut microbiome [8]. These practices may be considered as a part of precision or personalized medicine which focuses on the customization of healthcare, with medical decisions, treatments, practices, or products being tailored to individuals and subgroups [9]. Both personalized medicine and personalized nutrition aim to develop and implement interventions to prevent or treat chronic diseases based on a person's unique characteristics like DNA, race, gender, health history, and lifestyle habits. Genes are known to determine body function, and nutrition can modify how genes are expressed.

Gene–Diet Interactions

While humans are phenotypically diverse, genomes differ by, on average, less than 1% [10]. Genetic variation can occur in four instances [11] (1) as single base pair differences known as single nucleotide polymorphisms (SNPs), which is most common; (2) as insertions and deletions of short DNA fragments (INDELs); (3) as copy number variants (CNV), where a given gene is present in multiple copies; the number varies by individual; and (4) as structural variants (SVs), where larger genomic rearrangements exist due to translocation. Most research to date has focused on SNPs.

There are several components of the modern human diet that interact with different genetic variants to cause gene–diet interactions. These can impact the metabolism of certain nutrients [12]. As illustrated in Fig. 24.1, these interactions affect the expression of metabolism-associated genes, which impact levels of expression or activities of enzymes that synthesize or catabolize that nutrient [11]. This can alter levels of bioactive nutrient products and their metabolites as well as phenotypic outcomes, including human disease. These interactions can also be impacted by several other environmental and biological factors.

Gene–diet interactions can contribute to epigenetic alterations that influence key biological processes, including the metabolism of nutrients. The process of epigenetics occurs when the readability, or expression, of genes is modified by environmental influences without changing the DNA code itself [13]. The modulation and regulation of gene expression occur as a result of adding or removing epigenomic "marks" to the DNA or histone proteins. These marks either cause or remove tighter conformations of DNA which can result in up- or down-regulation of the genes that regulate the cellular processes. Through epigenetic marks, factors such as diet can make an imprint on genes that are passed from one generation to the next.

Both beneficial and harmful epigenetic changes can result from various dietary exposures [14]. For example, children who were exposed to famine conditions in utero during the Dutch famine in 1944 experienced epigenetic changes in multiple genes and alterations in lipid profiles later in life [15]. Epigenetic changes mean that what we eat is not just an input but can also change body system functions. Furthermore, our genetic variation can influence epigenetic modifications. Applications of gene-based personalized nutrition focus on aligning customized nutriomes (i.e., nutrient intake combinations) that are based on the integration of information, such as one's life stage, diet, anthropometrics, biomarkers, family history, dietary preferences, and current health status, with one's inherited

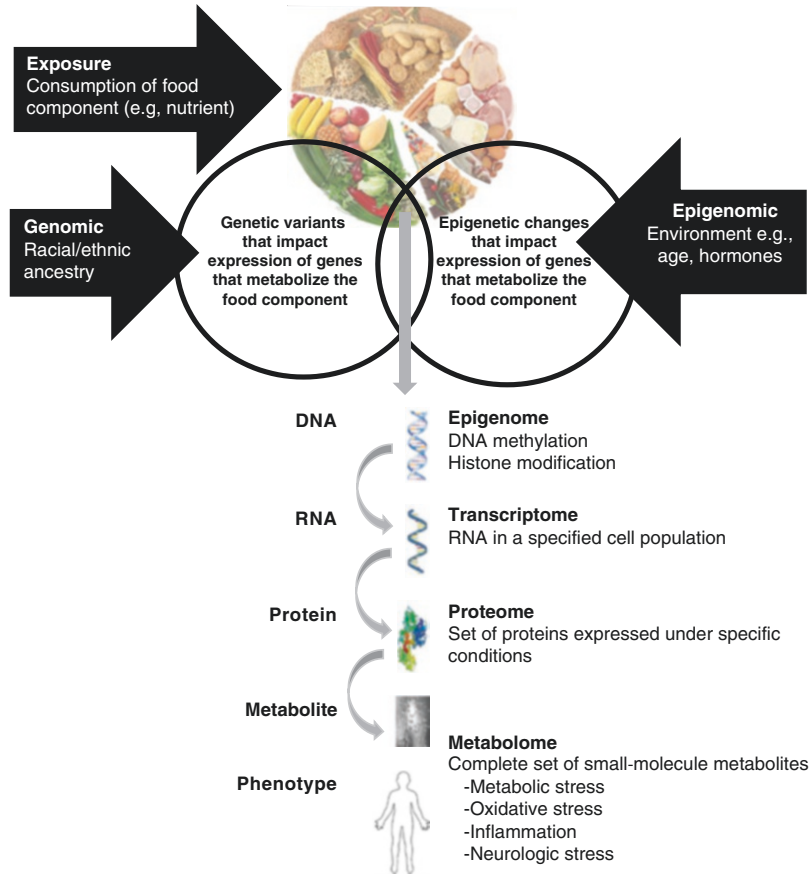

Fig. 24.1 Diet–gene interactions. Adapted from Mullins et al. (2020) [11]

genome. This is believed to preserve genome integrity and prevent disease [16].

Genome-wide association studies have uncovered how SNPs impact absorption, transportation, and metabolism of certain nutrients (e.g., lipids, folate) as well as the development of health conditions [17, 18]. Advances in the field are also being achieved by technological progress in investigations of the complete set of epigenetic modifications on the genetic material of cells (epigenomics) and the RNA transcripts (transcriptomics) [19]. Nutrigenetics and nutrigenomics provide the foundation for gene-based personalized nutrition where targeted nutritional advice is provided based on genetic test results that assess different SNPs. It is estimated that genetic predisposition accounts for up to 30% of health outcomes related to premature mortality [20]. Furthermore, a suboptimal diet is identified as a major modifiable risk factor that contributes to noncommunicable disease morbidity and mortality [21]. Thus, gene-based personalized nutrition may contribute to improved eating patterns and help reduce the burden of many common health problems, many of which include a genetic and dietary component, such as obesity, type 2 diabetes, cardiovascular disease, dementia, musculoskeletal problems, and some cancers [22].

Gene-Based Personalized Nutrition

Applications and Testing

Gene-based personalized nutrition encompasses a broad range of applications. Many laboratory techniques have been developed that are useful for gene-based personalized nutrition including

mass spectrometry, chromatography, electrophoresis, microarrays, and magnetic resonance spectroscopy [23]. These applications include omics technologies that provide for identification of disease risk, identification of appropriate transcriptome/biomarker assays that encompass proteomics, lipidomics, and metabolomics, as well as analyses of food bioactives and other compounds. Other considerations related to gene-based personalized nutrition include the development of functional foods, genetic products, applications in nutrition practice, commercialization, and the study of gene-related epidemiological underpinnings associated with population health outcomes.

Personalized gene-based nutrition prescriptions are based on an analysis of the interactions between health-related molecular mechanisms and body systems [24]. Uses of molecular biology technologies include detection of SNPs and identification of candidate genes and polymorphisms believed to be involved in gene–nutrient interactions; this information may lead to dietary recommendations based on genotype [25]. Genetic test panels have been developed that identify risk alleles; these facilitate a better understanding of metabolic diseases and their associated therapies. The genetic test results, combined with information, such as anthropometrics, nutrition-related biomarkers, and dietary intake, can enhance the ability of health professionals to recommend a personalized diet.

In vitro laboratory-developed tests are the most common applications that are used to provide information for gene-based personalized nutrition. Different types of direct-to-consumer (DTC) genetic tests have been designed by various companies and are available to consumers. The results they provide are intended to help consumers identify their predisposition to different health problems thus being a promising tool in disease prevention and management. Some examples of nutrition-related components drawn from DTC genetic tests are highlighted in Table 24.1.

Translating Genetic Test Results to Dietary Advice

Major concerns with the use of DTC genetic tests are the ease with which people can access them and the need to maintain the privacy and protection of their genetic data. Consumers can send cheek swab or saliva samples that contain their DNA to a company directly and then receive their results. Some companies offer services without the direct involvement of health professionals which can limit the consumer's interpretation and understanding of the results [26]. Computer-tailored nutrition education may help with individual motivation to make dietary changes [27], but from an ethical perspective the information disseminated must be in accordance with the ability of the individual to properly understand it and utilize it [28].

It is strongly advised that consumers work closely with a regulated health professional who has been trained in gene-based personalized nutrition. This will allow for a thorough consenting process, discussion about the nature and utility of the genetic test, scope of the results, possible risks, and information concerning confidentiality. A health professional should also conduct a full nutrition assessment of the individual, review the gene-test results, and work with that person to co-construct an appropriate individualized nutrition plan. For example, if an individual's test result indicates they have the CYP1A2 rs762551 C allele, they would be informed that they metabolize caffeine more slowly than those with the A variant [29]. They may be informed that those who metabolize caffeine at a slow rate may be at increased risk of heart disease [30] and then advised to limit caffeine intake to a maximum of 200 mg per day. To help them understand this, they may then be educated about foods and beverages that are significant sources of caffeine. The success of the uptake of gene-based personalized nutrition advice depends on an individual's motivation and on prospective benefits offered by such dietary changes [31].

Table 24.1 Select examples of genes tested to assess nutrition-related components

Nutrition-related component	Area of assessment related to genetic predisposition	Examples of genes tested
Macronutrients		
Carbohydrates	Process carbohydrates	*ABCC9, MC4R, PLIN1, PPARG, PPARGC1B*
Cholesterol—HDL	Regulate HDL cholesterol	*CEBPA, FADS1, LIPC, CETP, SCARB1*
Cholesterol—LDL	Regulate LDL cholesterol	*LPA, SLCO1B1, APOE, APOB, CELSR2*
Fat—Dietary	Metabolize dietary fats	*ADRB3, FABP2, APOA2, APOA5, FTO*
Fat—Stored	Utilize stored fats	*ADRB2, ADRB1, ADRB3*
Fat—Monounsaturated	Metabolize monounsaturated fats	*ADIPOQ, PPARG, APOB*
Fat—Saturated	Metabolize saturated fats	*APOE, APOA2*
Insulin	Regulate blood glucose	*CEBPA, PPARG, AGER, TCF7L2, LRP1*
Protein	Metabolize protein	*IGF1, PPARGC1A, TFAP2B*
Food tolerances		
Caffeine	Metabolize caffeine	*CYP1A2*
Gluten	Digest gluten	*HLA, RGS1, IL2*
Lactose	Digest lactose	*MCM6*
Salt	Process and regulate sodium	*AGT*
Vitamins		
Folate	Process folate for cell growth and healthy red blood cells	*PRICKLE2, MTHFR, MTHFD1*
Vitamin B12	Process vitamin B12 for healthy nerve and blood cells	*CUBN, TCN1, FUT2*
Vitamin C	Process vitamin C for growth and development	*SLC23A1, SLC23A2, MTHFR, HP1, HP2*
Vitamin D	Process vitamin D to support calcium absorption and cell growth	*CYP2R1, CYP27B1, DHCR7, GC, NADSYN1, VDR*
Minerals		
Calcium	Absorb calcium for bones, teeth, and muscles	*CASR, MCM6*
Iron	Regulate iron for red blood cells to carry oxygen	*G6PD, SLC17A1, HFE, TF, TMPRSS6*
Essential fatty acids		
Omega-3	Process omega-3 fatty acids for metabolism, brain health, and reducing disease	*NOS3, TNF, ACSL1*

There is a wide range of nutrigenetic information related to health topics that is being offered to consumers. Examples of topics covered include weight management, taste preferences, cardiovascular health, food intolerances, and nutrient metabolism. Information related to weight management may be based on fat storage, body size, weight regain, or weight loss responses related to consuming different quantities of macronutrients. As is the case with many areas of science and technology, there is great variation globally in the application of nutrigenomics.

Gene-Based Personalized Nutrition: Evidence and Progress

Various lines of evidence indicate the relationships that occur between specific human genetic polymorphisms and metabolism [32, 33]. Some SNPs directly affect metabolic pathways and

may therefore play a role in the development of diseases that are associated with diet and dietary requirements. Other SNPs related to the absorption, digestion, transportation, and excretion of nutrients and metabolites contribute to a greater understanding of the role of bioactive compounds [34]. Individual SNPs related to receptors or enzymes can alter the response to a given dietary intervention [34]. The impact of gene-based risk factors on health outcomes is based on statistical estimates from epidemiological studies [23].

Although nutrigenomics is a relatively young science, there is some evidence which suggests that gene-based personalized nutrition advice is better understood and more likely to be followed compared with general dietary advice [31, 35, 36]. The results of most studies show modest dietary improvements based on genetic testing, including increased fruit and vegetable consumption and decreased intake of red meat, salt, and saturated fat [37, 38]. It has also been reported that nutrigenomic applications may be beneficial in long-term weight control [39]. Clearly, more research is needed to fully evaluate the long-term effects of gene-based personalized nutrition approaches relative to conventional nutrition interventions.

Challenges of Gene-Based Personalized Nutrition

The challenges of gene-based personalized nutrition include limitations of the current science and research, barriers in practice, and integrating scientific and technological advancements [40].

Limitations of Current Science and Research

Most genetic testing is performed using DNA microarrays ("SNP chip") that can detect several thousand SNPs at a given time. Limitations of this type of testing include the potential for errors in SNP identification or imputation of an unobserved genotype, exclusion of rare variants, and the lack of account for other types of genetic alterations, such as insertions and deletions, across the genome. This results in an incomplete understanding of the functionality of identified genetic alterations and impacts the clinical utility of the genetic tests.

Nutrigenomics research, which is based on the investigation of specific genetic markers and dietary intakes and their associations with different health outcomes, has several limitations. Most nutrition-related diseases are complex, multifactorial, and multigenic. Studies that are based on commonly occurring individual SNPs cannot explain complex diseases, disorders, and phenotypes. Such studies do not account for gene–gene and gene–diet interactions; that information is needed to provide specific nutrigenetic recommendation algorithms [41]. Many of the SNP-based studies have used modest-sized samples which limits the generalizability of findings. These investigations also tend to have poor reproducibility across ethnic groups. Other nutrigenomics studies have used genetic risk scores, which combine multiple genetic variants into an algorithm to predict overall risk. However, these polygenic scores do not necessarily include variants known to impact the metabolism of specific dietary factors. Finally, the dietary intake measurement tools used in these studies may lack reliability in their reflection of long-term intakes. For these reasons, reported gene-nutrient associations may not be accurate. Future technologies which analyze the whole genome, build genetic algorithms known to impact metabolism, and more accurately quantify dietary intakes are expected to improve our understanding of gene–diet interactions, the pathways that influence nutritional metabolism, and their effects on nutrient requirements.

Although the use of genomic signatures to predict health outcomes has evolved substantially, the evidence which links them to reliable prognostic biomarkers remains limited [42]. Biomarkers, such as serum retinol, zinc, and ferritin, have been used in diagnostics [24, 43]. Indicators of dysregulated insulin secretion, elevated blood glucose, and branched-chain amino acids have been used as biomarkers for diabetes [44]. Blood profile proteins and circu-

lating levels of angiotensin-converting enzymes have also been used as tools to assess body weight management [45, 46]. Although epigenetics studies may help to identify epigenetic markers for the risk, diagnosis, and prognosis of diseases [47], the diversity of genetic variation presents significant challenges in ascertaining actual outcomes [48].

Barriers in Practice

The lack of policies and regulations to guide nutrigenomics and gene-based personalized nutrition presents risks for consumers. Some countries regulate the genetic testing industry; however, they are unable to control offshore companies that can access local markets via the Internet. As a result, there are potential problems related to privacy, the provision of genetic findings without appropriate medical oversight, variation in scientific validity, and appropriate informed consent. While health professionals may act as intermediaries between genetic testing companies and consumers, few are qualified to do so. Only a few health professional bodies recognize gene-based personalized nutrition, and, consequently, there is a lack of guidelines or educational resources for its implementation.

Another significant barrier in gene-based personalized nutrition practice is that there is a charge for the service. The high cost of more comprehensive gene tests that include genome and exome sequencing [49] limits the applications of nutrigenomics in health practice. This can further contribute to disparities in population health. Scientists and industries are making efforts to reduce the cost of genetic testing, technologies, and products so that they are more affordable. However, it will also be necessary to reduce the cost of advisory services for interpretation of such tests [50].

It is apparent that the evidence which underlies nutrigenetic-based advice needs to be as robust as that used for conventional nutritional guidelines, such as the *Dietary Reference Intakes*. However, conventional guidelines differ between countries as they are based on expert committees that make interpretations of what is perceived to be the best evidence available. Gene-based personalized nutrition practice is challenged by the limited information available about dietary exposures that induce a detrimental gene–diet interaction across diverse populations. Recently, different frameworks to assess evidence related to gene–diet interactions have been developed which are based on factors that include study quality, nature of the interaction (direct, intermediate, or indirect relation to phenotype), nature of the genetic variant (e.g., causal link vs association), biological plausibility, and scientific validity [51]. In addition, nutrigenomics care maps have been developed to guide professional practice [8]. It is recommended that experts in gene-based personalized nutrition apply these frameworks in order to develop guidelines to define science-based, consistent, and ethical practice.

Currently, gene-based personalized nutrition is not part of routine health care. For this to happen it needs to be supported by health professionals who possess the expertise and are able to maintain close relations with individuals to ensure appropriate follow-up [52]. In addition, the consumer needs to be assured that their genetic test results will not impact their insurance coverage. In most jurisdictions, federal law prohibits health insurers from using genetic information to make decisions about whether to sell health insurance or how much to charge. But these rules may not apply to long-term care, life, or disability insurance. Finally, the effectiveness of personalized health approaches largely depends on shared decision-making. But this is problematic at present as many health professionals report that they are not qualified to incorporate nutrigenomics into their practice [27] while others have no interest [53].

Consumers must be able to trust the practice of gene-based personalized nutrition. Before this can be achieved appropriate evidence-based services based on the ethical principles of autonomy, beneficence, no misconduct, and justice must be provided [54, 55].

The application of gene-based personalized nutrition depends on multidisciplinary teams,

such as physicians, geneticists, and dietitians, who can analyze genetic profiles, integrate all data from omics analyses, and translate knowledge acquired into dietary recommendations and nutritional education. The evidence must also be used to guide public health policy interventions and strategies that are of benefit to personalized medicine for different health issues [56], including obesity which is the most prevalent metabolic disease [57].

Integrating Scientific and Technological Advancements

Nutrigenetics and nutrigenomics have been the favored tools for gene-based personalized nutrition. However, for these tools to be truly meaningful to individual and population health, a better understanding of and integration with metagenomics is needed [58]. This includes incorporating knowledge about human physiology and metabolism, including the human gut microbiota and genome, and the interactions between these genomes. The human intestinal microbiome can be altered transiently by environmental factors, such as diet and medications. In addition, the malleable and metabolically active gut microbial ecosystem can influence what is extracted from the diet which can lead to alterations in gene expression and protein synthesis, and the production of metabolites [59]. Thus, the results from intestinal microbial genome investigations could help improve diagnostics and interventions in gene-based personalized nutrition [60, 61].

Nutrigenomic understanding draws upon insights from lipidomics, proteomics, and metabolomics, all of which are sciences that are continuing to evolve. Therefore, limits in the ability to encode the paths of metabolism and to generate and apply biomarkers that are relevant to the development of dietary interventions [62] persist. The "exposome" research paradigm, which encompasses all accumulative environmental exposures in association with genetic factors, is being increasingly recognized as a comprehensive and valid way in which to determine the risk of disease [63]. Evidently, there is a need to advance scientific disciplines and research paradigms that can provide comprehensive and integrated evaluation of genotype and environment, characterize nutritional status and risk of disease, and customize appropriate diets [47, 64].

Conclusion

Research evidence has demonstrated that there are notable individual variations in nutrient requirements and metabolism. Nutrigenomics, including all omics technologies, may help health professionals offer more customized nutrition plans and further both clinical practice and population health. However, the science and application of gene-based personalized nutrition are still evolving and challenges remain. There are limitations in the current science that point to the need for improved understanding in areas such as metagenomics as well as applications of research paradigms that better capture the complexity of gene–environment interactions in relation to disease etiology. Improvements in technologies, data interpretation tools, and practice resources are also needed to ensure accurate results based on robust evidence and defined standards are delivered to individuals by trained and regulated health professionals. Health policy and health law can play important roles in the development of ethical and legal regulations that are needed to ensure consistent, safe, and universal applications.

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25 Nutrition and the Gut Microbiome: Insights into New Dietary Strategies for Health

Zhenhua Liu, Sarah Gonzalez-Nahm, Guodong Zhang, Achsah Dorsey, and David A. Sela

Abbreviations

BCAA	Branched-chain amino acids
CRC	Colorectal cancer
CVD	Cardiovascular diseases
FAA	Free amino acids
GI	Gastrointestinal (tract)
IBD	Inflammatory bowel disease
MSD	Mediterranean-style diet
PUFA	Polyunsaturated fatty acids
SCFA	Short-chain fatty acid
T2DM	Type 2 diabetes mellitus
FMT	Fecal microbiota transplantation
WSD	Western-style diet

Z. Liu (✉)
Department of Nutrition, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA, USA

UMass Cancer Center, University of Massachusetts Chan Medical School, Worcester, MA, USA
e-mail: zliu@nutrition.umass.edu

S. Gonzalez-Nahm
Department of Nutrition, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA, USA
e-mail: snahm@umass.edu

G. Zhang
Department of Food Science and Technology, National University of Singapore, Singapore, Singapore
e-mail: zhanggd@nus.edu.sg

A. Dorsey
Department of Anthropology, University of Massachusetts, Amherst, MA, USA
e-mail: adorsey@umass.edu

D. A. Sela
Department of Food Science, University of Massachusetts, Amherst, MA, USA
e-mail: davidsela@umass.edu

Key Points

- We coexist with our gut microbiota.
- They perform multiple important functions, including biosynthesis of certain vitamins and amino acids, metabolism of host-indigestible foods, and immune and endocrine regulatory influences.
- The gut microbiota play an important role in both the maintenance of host homeostasis and the pathogenesis of a variety of diseases, especially gastrointestinal health.
- The gut microbiota could be shaped by diet and influence host metabolism.
- Targeting the gut microbiota through dietary regimens offers an effective and applicable approach to improving human health and reducing the risk of various diseases.
- The gut microbiota should be considered as a key aspect of nutrition and health, and the medical community should consider the application of nutritional modulation of microbiome for health.

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_25

Introduction

The human microbiome (Table 25.1) represents the collective genetic material contained in all cells of the microorganisms (microbiota) that live on and within human beings, especially those in the human gut [1]. The understanding of the microbiome field has progressed dramatically in the past two decades. This is primarily driven by technological advances and reduced costs of analysis [2, 3]. Significant insights have been made regarding understanding the nature of microbial communities in the gastrointestinal (GI) tract. Accumulating evidence shows that the gut microbiota dynamically interact with host tissue and have a significant impact on host health, establishing the microbiome as a new target for the development of interventional strategies that can be used to improve human health and even the treatment of disease.

Table 25.1 Glossary of key terms

Term	Definition
Microbiota	The community of microorganisms in a particular environment
Gut microbiome	The collective genetic materials contained in all microbial cells of all the microorganisms harbored in the human gut
Richness and diversity	Richness refers to the number of different species found in a community or ecosystem. Diversity is more complex and takes into account both the number of different species in a community (richness) and the evenness of each species (abundance or distribution)
Dysbiosis	A disruption to the gut microbiota homeostasis caused by an imbalance in the microbiota, including changes in their metabolic activities and functions
Fecal microbiota transplantation	Fecal microbiota transplantation (FMT) is a procedure of transferring fecal microorganisms from a healthy individual into a sick patient to reintroduce or boost the helpful microbes and confer a health benefit
Metagenomics	Metagenomics is the study of a collection of genetic material (genomics) from a mixed community of organisms. It refers to the study of the microbiome when we cannot separate one microbe from another in a microbial community

The human gut microbiome encodes for more than three million genes, which is approximately 150 times greater than the number of genes found in the human genome [4, 5]. The intestinal microbiota produce thousands of metabolites, which have many functions and interact with almost all cells in the host [6, 7]. The gut microbiota can be considered as an essential "organ" that plays an integral role in maintaining health [8]. The microbiota that colonize our body are comprised of microbes that could be considered beneficial, many of them neutral, and some potentially harmful in certain contexts. When the microbes coexist peacefully, the symbiotic microbes are beneficial to health and the potentially pathogenic microorganisms have minimal impact. However, if there is a disturbance in the balance, called "dysbiosis," the interactions between microbes and the host are disrupted and, as a result, the host may become more susceptible to disease. Dysbiosis has not only been associated with diseases limited to localized gastrointestinal complications, but also with many disease conditions [9, 10] including metabolic syndrome, type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), hepatic illness, cancers not limited to those in GI tract, and neurologic diseases (Fig. 25.1).

Many factors can induce gut dysbiosis, including unbalanced diets, alcohol consumption, environmental factors, sedentary behavior, age, medication/drug use, psychological stress/anxiety, and conditions that affect the immune system [11, 12]. Among these factors, attention has been particularly given to understanding the impact of dietary factors on the gut microbiota, including nutrients, bioactive ingredients, food additives, and chemical contaminants. Evidence indicates that most of these factors trigger downstream effects in the host, mainly through interactions with gut microbiota [13, 14], and thus the gut microbiota act as a critical mediator by which our diet affects our health. This chapter focuses on diet-gut microbiome-health/dis-

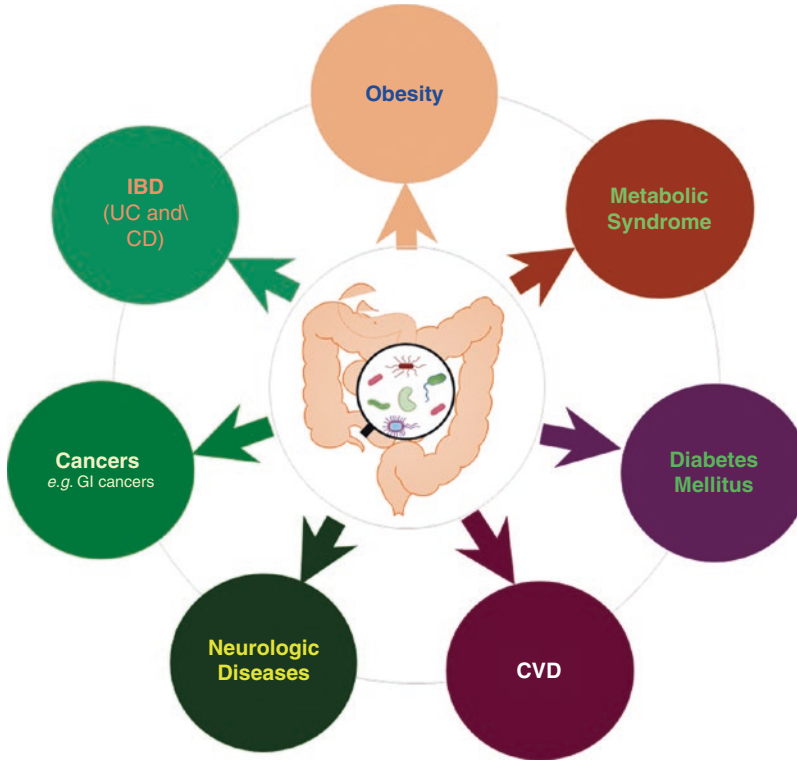

Fig. 25.1 Gut microbial dysbiosis is associated with a number of diseases in different systems in the human body. Only some common gut microbiome associated diseases are listed. *IBD* inflammatory bowel disease; *UC* ulcerative colitis; *CD* crohn's disease; *GI* gastrointestinal (tract); *CVD* cardiovascular disease

ease interactions, aiming to provide insights into new dietary strategies to improve health and prevent or even treat diseases by targeting the gut microbiome.

Gut Microbiome

The Ecosystem of the Gut Microbiota

The human gut microbiota is the entire collection of microorganisms in the human gut, which includes bacteria, archaea, eukaryotic fungi, protozoa, and viruses [15]. Each person harbors 10^{13}–10^{14} symbiotic microbial cells in the gut, which outnumber human cells by ~10 times [1, 16]. The major families of bacteria found in human intestines include *Prevotella*, *Ruminococcus*, *Bacteroides*, and *Firmicutes*. In the low-oxygen environment of the colon, the anaerobic bacteria *Bifidobacterium*, *Clostridium*, *Lactobacillus*, and *Peptostreptococcus* can also be present and important [17]. Although the major families of bacteria across individuals are similar, each person has a unique profile of microbiota. The distinctive pattern of microorganisms that reside within an individual's gut is influenced by mode of birth, infant feeding patterns, diet, lifestyle, environmental exposure in later life, and the genetics of the host.

The General Biological Functions of the Gut Microbiota

The anthropocentric concept of life has often neglected the functions of the microorganisms inside us. The importance of the gut microbiome on health was not recognized until the late 1990s. An integrated metagenome study based on data

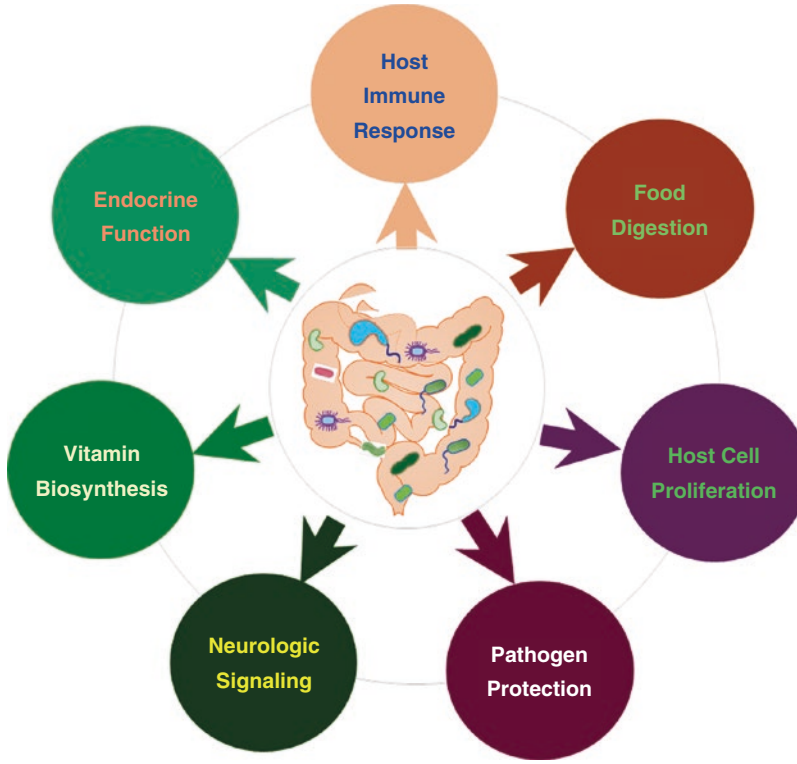

Fig. 25.2 Selected key functions of the gut microbiota contributing to the health of human beings, including immune and endocrine regulatory influences, biosynthesis of nutrients, and metabolism of foods and other endogenous or exogenous compounds

from 1200 people in the United States, Europe, and China identified an aggregate ~10 million microbial genes across their fecal microbiomes [18], highlighting the multifunctional nature of the gut microbiota [19]. These intestinal microbes are not invaders but beneficial colonizers. The benefits these microbes include, but are not limited to, (1) stimulating immune response; (2) influencing host cell proliferation; (3) regulating intestinal endocrine functions; (4) contributing to the nutrition needs of the host; (5) assisting food digestion; (6) breaking down potentially toxic compounds; and (7) providing neurologic signaling (Fig. 25.2). Three major functions related to diet and nutrition are briefly discussed below.

Nutrient Biosynthesis

The gut microbiota play a critical role in contributing to the nutritional needs of the host. These microbes synthesize certain essential nutrients, including several B vitamins (e.g., thiamine, riboflavin, biotin, folate, cobalamin), vitamin C, and vitamin K [20, 21]. It has been known for nearly a century that ruminants do not have dietary requirements for water-soluble vitamins as the dense microbial populations in the rumen are capable of synthesizing them. Germ-free laboratory animals require dietary supplements of vitamins that are not needed by their conventionally reared counterparts [22]. It has been estimated that up to half of the daily vitamin K requirement in humans is provided by gut bacteria [22]. In fact, several epithelial transporters in the large intestine participate specifically in the absorption of vitamins derived from gut bacteria, suggesting that these microorganisms play a role in regulating the normal body homeostasis of these vitamins, especially the vitamin level in the local colonocytes [23].

Microbial Metabolism in Host Nutrition

Compared to the biosynthesis of several different essential nutrients, gut microbiota play an even more significant role in catabolic and anabolic functions. Gut microbiota harbor hundreds of metabolic pathways and represent a gigantic reservoir for the production of a significant number of molecules (metabolites) [24]. These chemicals are not only needed for microbial growth and survival but also affect host metabolic functions. An overwhelming amount of data generated from both human and animal studies suggest that these chemicals are significantly involved in host metabolism including energy homeostasis, body adiposity, glucose tolerance, and insulin sensitivity [10].

The gut microbiota significantly contribute to the digestion and metabolism of foods. Complex carbohydrates, such as starch and fibers, are not as easily digested and absorbed as simple carbohydrates by the host. A significant portion of these unabsorbed nutrients travels to the large intestine where the gut microbiota break them down using their digestive enzymes and produce short-chain fatty acids (SCFAs) which are used by the host as a nutrient source for enterocytes, and also play an important role in stimulating immune cell activity [25]. Branched-chain amino acids (BCAA) also play a critical role in maintaining homeostasis in mammals by regulating protein synthesis, glucose and lipid metabolism, insulin resistance, hepatocyte proliferation, and immunity [26]. The gut microbiome is a critical modulator of BCAA level as it can both produce and use BCAAs. *Prevotella copri* and *Bacteroides vulgatus* are potent producers of BCAAs, and their amounts correlate positively with BCAA levels in humans.

Diet, Microbiome, and Immunity

One of the most important regulatory functions of gut microbiota is their role in the development and maintenance of the host immune system [27]. First, the microbiome plays a critical role in the development of major components of the host's innate and adaptive immune system. The colonization of microbiota on the gut mucosal surfaces in early life plays an instrumental role in the development and education of the host's immune system [28]. Later, microbiota and the host immune system engage in an extensive bidirectional communication to maintain homeostasis for defense. Recent studies have unraveled the linkage between dietary modulation and host immunity. For example, the Western-Style Diet (WSD) has been shown to have a profound influence on the gut microbiome configuration and host immunity [29]. A diet rich in saturated fat increases the levels of taurocholic acid, which in turn fosters the expansion of *Bilophila wadsworthia*. This pathobiont promotes T helper type 1(Th1) type immune responses and increases susceptibility to colitis in IL10$^{-/-}$ mice [30]. Another example is *Turicibacter*, whose abundance is associated with dietary fat and fiber. This bacterium stimulates the production of serotonin, the biological function of which is complex and multifaceted, including not only the regulation of gut motility and immunity but also the stabilization of mood, feelings of well-being, and happiness [31].

Gut Microbiota in Human Health and Disease

As described above and in Fig. 25.2, the gut microbiota fulfill many critical roles in essential host functions including the biosynthesis and metabolism of nutrients. It is also involved in the metabolism of endogenous and exogenous chemicals, including toxins, and the development, maintenance, and regulation of various immune functions. Because of these various functions, the gut microbiota play an important role in maintaining human health and preventing disease. The key microbial features associated with some of the common chronic diseases (Table 25.2) are important to consider.

Gastrointestinal Health

Gastrointestinal (GI) health, or gut health, is a term increasingly used in the medical literature and by the food industry. Although definitions of

Table 25.2 Some microbial taxonomic characteristics associated with common chronic diseases[a]

Health Conditions	Increased Taxa	Decreased Taxa
Inflammatory bowel disease	• *Firmicutes* • *Actinobacteria* • *Proteobacteria (CD)*	• *Bacteroidetes (CD)* • *Proteobacteria (UC)*
Colorectal cancer	• *Streptococcus gallolyticus* • *Fusobacterium nucleatum* • *Escherichia coli* • *Bacteroides fragilis* • *Enterococcus faecali.*	• *Roseburia.* • *Clostridium.* • *Faecalibacterium* • *Bifidobacterium*
Obesity	• *Dorea longicatena* • *Eubacterium ventriosum* • *Roseburia intestinalis* • *Ruminococcus gnavus*	• *Bacteroidetes* to *Firmicutes* ratio • *Bacteroides thetaiotaomicron* • *Clostridium histolyticum* • *Faecalibacterium prausnitzii*
Type 2 diabetes	• *Ruminococcus* • *Fusobacterium* • *Blautia*	• *Bifidobacterium* • *Bacteroides* • *Faecalibacterium* • *Akkermansia* • *Roseburia*
Cardiovascular disease	• *Enterobacter aerogenes* • *Escherichia coli* • *Klebsiella* spp	• *Faecalibacterium prausnitzii* • *Bacteroides* spp

[a]A summary of selected key gut microbial profiles associated with common health conditions and chronic diseases. The list is not comprehensive but represents some common patterns observed across studies. It is noteworthy that results reported from different studies may be inconsistent. This could be due to the lack of standardization across microbiome techniques or a reflection of heterogeneity associated with individual disease conditions [10, 33, 36, 43, 45]. CD, Crohn's disease; UC, ulcerative colitis

gut health vary, it generally refers to the physical state and physiological function of many parts of the GI tract, such as effective digestion and absorption of food, stable intestinal microbiota composition, effective immune status, and a state of well-being. It is central to our overall health. GI diseases, or digestive diseases, are all illnesses of the digestive organs along the GI tract, which include functional and structural diseases. Functional GI diseases are those in which the GI tract appears normal when examined but does not behave properly. Constipation, irritable bowel syndrome, nausea, food poisoning, gas, bloating, gastroesophageal reflux disease, and diarrhea are common examples. Structural GI diseases are those where the bowel looks abnormal upon examination and does not function properly. Common examples of structural GI diseases include strictures, stenosis, hemorrhoids, diverticular disease, colon polyps, colorectal cancer (CRC), irritable bowel syndrome, and inflammatory bowel disease (IBD). The majority of the aforementioned GI complications are directly associated with gut dysbiosis, and, as examples, the imbalances of microbiota associated with IBD and CRC are discussed.

Inflammatory Bowel Disease

IBD is an umbrella term that describes chronic inflammatory conditions of the GI tract, the two most common ones of which are Crohn's disease and ulcerative colitis. IBD affects ~three million people in the United States [32]. Although the pathogenesis of IBD is poorly understood, a key aspect is the dysregulation of a correctly assembled microbiota. A large number of microorganisms residing in the intestine have coevolved with the host in a symbiotic relationship. In normal gut homeostasis, the host mucosal immune system preserves the ability to mount an immune response against an invading pathogen while avoiding harmful inflammatory responses to commensals. However, in persons with IBD, the symbiotic relationship between the host and gut microbiota is altered. Inappropriate microorganisms accumulate near the epithelial surface of the intestine; this triggers the activation of a harm-

ful inflammatory response and leads to chronic inflammation in the gut. Though there is a large degree of variability across studies, with many reporting contradictory findings, accumulating evidence indicates that persons with IBD display different structures and compositions of microbial profiles compared to individuals without IBD. Studies have demonstrated that patients with IBD display a substantial imbalance across four major bacterial phyla including *Firmicutes*, *Bacteroidetes*, *Proteobacteria,* and *Actinobacteria*, which together constitute > 98% of the gut microbiota [33].

Colorectal Cancer

CRC is the third most commonly diagnosed cancer and the third leading cause of cancer-related deaths in the United States, with ~146,000 new cases and ~52,000 deaths per year [34]. Increasing evidence has demonstrated that the gut microbiota play an important role in the development of CRC. Dysbiosis promotes CRC initiation and progression by modulating multiple mechanisms, such as inflammation and DNA damage, and by producing metabolites involved in tumorigenic pathways. Since the seminal discovery of the association of *Fusobacterium nucleatum* with CRC [35], metagenomic studies have revealed the links between a number of microbial species and functional activities with CRC [36]. Although the gut microbiome signatures of CRC in association studies are not always consistent across different cohort studies and populations, it is a current scientific priority to establish a microbial link to CRC across different cohorts and populations. A recent meta-analysis of eight geographically and technically diverse metagenomic studies of CRC identified a core set of 29 species significantly enriched in CRC metagenomes and established a generalizable and predictive taxonomic and functional microbiome CRC signature as a basis for future diagnostics [37].

Obesity

The prevalence of obesity, which is defined as a body mass index (BMI) ≥ 30, has increased dramatically in recent decades [38]. Worldwide, more than 1.9 illion adults aged 18 years and older carry excess weight (BMI >25), accounting for 39% of the population, and of these over 650 million were obese, accounting for 13% of the population [38]. In the United States in 2017–2018, according to the National Health and Nutrition Examination Survey data, the age-adjusted prevalence of obesity among adults aged 20 and over was 42.4%.

Growing evidence suggests that the gut microbiota are involved in obesity pathogenesis. In 2006, a seminal study [39] revealed that obesity is associated with changes in the relative abundance of the two dominant bacterial divisions, the *Bacteroidetes* and the *Firmicutes*. These findings were based on a comparison of the gut microbiota of genetically obese mice and their lean littermates as well as those of obese and lean humans. Changes to those bacteria affect the metabolic potential. These obesity-associated microbiota promote host energy harvest from the diet. Moreover, the study further demonstrated that the obesity-related microbiota is transmissible: colonization of germ-free mice with an "obese microbiota" results in a significantly greater increase in total body fat than colonization with a "lean microbiota." Subsequently, some specific obesity- or lean-related bacteria have been identified. At the species level, some SCFA producers, such as *Eubacterium ventriosum* and *Roseburia intestinalis,* have been associated with obesity [40], whereas butyrate producers, such as *Oscillospira spp.,* may be associated with leanness [41]. *Bacteroides thetaiotaomicron*, a glutamate decarboxylation-related bacteria, was shown to be markedly decreased in individuals with obesity, and mice colonized with this bacterium were protected against adiposity [42].

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is often confounded with obesity. Its incidence and prevalence are increasing rapidly; the disease now affects between 5% and 15% of the adult popula-

tion, making it the most common endocrine complication [10]. The non-modifiable and modifiable factors linked to the etiology of T2DM are largely shared with those for obesity, including microbial composition. The intestinal microbiome in individuals with overt T2DM and prediabetes is typically depleted in bacterial butyrate producers and exhibits an increase in species with a pro-inflammatory functional potential [10]. A recent review reported that the genera of *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, *Akkermansia,* and *Roseburia* were negatively associated with T2DM, while the genera of *Ruminococcus*, *Fusobacterium*, and *Blautia* were positively associated with T2DM [43].

Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of mortality in Western countries [44]. People who suffer from arteriosclerosis, the main underlying cause of CVD, frequently have prior metabolic complications which make it challenging to tease apart genuine CVD signatures in the gut microbiota from profiles of other metabolic complications. A metagenome-wide association study reported that the gut microbiome of patients with CVD displayed an enriched abundance of *Enterobacteriaceae* including *Escherichia coli*, *Klebsiella* spp., and *Enterobacter aerogenes*, and decreased abundance of *Bacteroides* spp. and *Faecalibacterium prausnitzii* without adjustments for pre- or comorbidities [45].

Nutritional Regulation of the Gut Microbiome

Recent epidemiological and experimental studies have demonstrated the considerable impact on human health and diseases that may be mediated or modified by microbial communities [19]. Nutrition is believed to be one of the major determinants of intestinal microbial composition. Nutrition has an important impact on the gastrointestinal function of the host and thereby on health, mainly by influencing the composition and activity of the gut microbiota. The impact of several common dietary compounds and dietary patterns on common microbial taxonomic features and functional implications is summarized in Fig. 25.3 and described below.

Carbohydrates: Dietary Fiber and Sugar

Carbohydrates are the main source of energy for the human body. Generally, there are two types of carbohydrates in food: digestible and non-digestible. Although non-digestible carbohydrates cannot be utilized by the host directly, they can be broken down by the microbes in the gut, and thus are called as microbiome-accessible carbohydrates. They are the main energy source for microbes and also provide energy for host enterocytes [46]. These non-digestible carbohydrates have a huge impact on the gut microbiome; dietary fiber is one of them and has been intensively studied. State-of-the-art sequencing technology has advanced our understanding of the function of dietary fiber, demonstrating that it plays an important role in reshaping the gut microbial ecosystem. Studies have revealed that populations consuming a diet high in dietary fiber exhibit an abundance of *Prevotella* but low amounts of *Faecalibacterium*, *Bacteroides*, and *Blautia* [47–49]. The major function of dietary fiber is the production of SCFAs via microbial metabolism. SCFAs, including acetic acid (C2), propionic acid (C3), and butyric acid (C4), possess key roles in regulating the immune system, host metabolism, and cell proliferation [50].

Compared to dietary fiber, research on the effects of sugar (mono- and disaccharides) on the gut microbiome is limited. There is evidence that the Western-style diet (WSD), which generally contains a high level of sugar, causes a shift in the gut microbiota composition, but it is difficult to identify the specific effects of sugar from other features of the WSD, such as a high content of saturated fat. A handful of studies have investigated the effects of some simple sugars on the microbiome. A recent study reported that mice fed with glucose and fructose had a signifi-

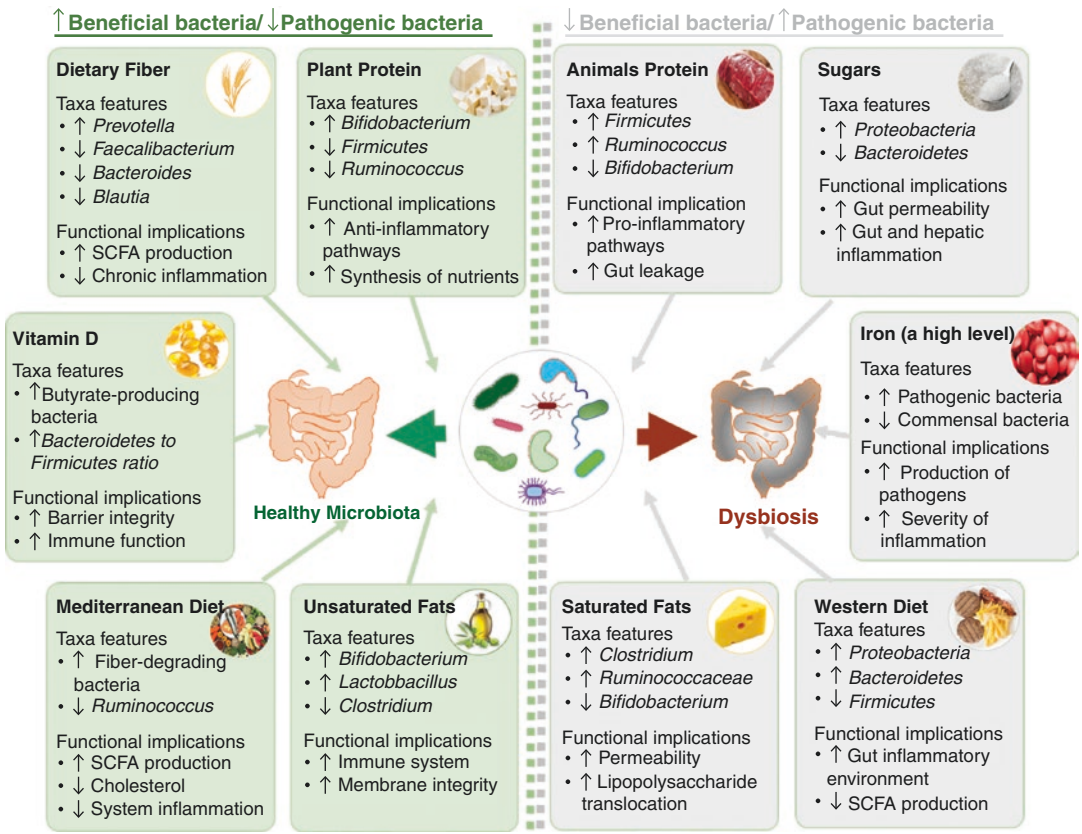

Fig. 25.3 Some common intestinal microbial taxonomic features and functional implications of dietary compounds. An outline of some reported key gut microbial features and its related functional implications [49, 51, 58, 60, 75]. The list is not comprehensive but represents some common patterns observed across studies. It is noted that the results of bacterial species and functional features in metabolic diseases differ between studies. SCFA, short-chain fatty acid. ↑, higher levels of bacterial abundance or functions when compared with control. ↓, lower level of bacterial abundance or functions when compared with control

cantly lower relative abundance of *Bacteroidetes* and a significantly increased abundance of *Proteobacteria*. These mice displayed increased gut permeability, as well as gut and hepatic inflammation [51]. As sugar is generally absorbed in the small intestine, only a limited amount is passed to the colon. Therefore, sugar is more likely to have an indirect effect on the gut microbiota (e.g., by causing weight gain).

Protein: Plant-Based Protein vs Animal-Based Protein

Dietary protein is primarily digested by proteases into peptides and free amino acids (FAA) and absorbed in the upper GI tract. However, some dietary proteins, peptides, and FAAs may escape digestion and absorption in the small intestine and enter the large intestine. The quantity of colonic dietary protein is further increased during the consumption of high-protein diets that are often used for weight loss [52]. Excessive protein in the large intestine promotes the growth of pathogenic microorganisms. Several human studies have shown that high-protein diets induce a shift of gut microbiota towards protein fermentation with a decrease in presumed beneficial butyrate-producing bacteria [53, 54]. Proteins, peptides, and FAAs that reach the large intestine will be fermented by gut microbiota via either deamination or decarboxylation reactions, which

generate SCFAs or amines, respectively. These metabolites elicit a wide range of biological functions and influence human health and diseases [55]. Some of the metabolites are detrimental, such as hydrogen sulfide, p-cresol, and ammonia [56], whereas others, such as indolic compounds, contribute to the maintenance of the epithelial barrier function [54, 57].

Different sources of dietary protein have significantly different impacts on microbiota composition, bacterial metabolite production, and consequences for human health. This is mainly due to the quality of the protein and the compounds associated with dietary proteins from different types of food. Several studies have unraveled the different impacts on the gut microbiota of animal-based and plant-based protein sources. Animal-based protein is associated with a higher abundance of the phylum *Firmicutes*, family *Erysipelotrichaceae*, and species *Ruminococcus* and *Streptococcus*, but a negative association has been found for plant-based protein. The latter is consistently linked to a higher *Bifidobacterium* abundance, while an animal-based protein diet is associated with a lower abundance [58].

Fats: Saturated Fats vs Unsaturated Fats

Fat is mainly digested and absorbed in the small intestine, where it is hydrolyzed into glycerol and fatty acids by pancreatic lipases, with the assistance of bile acids, for host energy needs. High-fat diets are associated with a reduction in gut bacterial richness and diversity, disruption of membrane integrity, increased permeability and lipopolysaccharide translocation, and alterations to the immune system. These changes often result in low intensity of chronic inflammation. Mouse experiments have demonstrated that a high-fat diet causes a significant increase in intestinal deoxycholic acid. This may in turn lead to microbial disorders by promoting the growth of *Firmicutes* at the expense of *Bacteroidetes* [59]. A high-fat diet also promotes the growth of *Bacteriodetes wadsworthia*, which produces H_2S, a compound thought to inflame intestinal tissue, resulting in inflammatory bowel disease [30].

Similar to carbohydrates and proteins, the quantity, sources, and composition of dietary fat have significant influences on the gut microbiota. Many studies of high-fat diets and gut microbiota have focused on saturated fats from animal-based diets and have frequently shown an increase in the abundance of *Firmicutes* and other detrimental bacteria [60]. Generally, diets rich in total fat and saturated fatty acids exert unfavorable effects on gut microbiota and are associated with an unhealthy metabolic state. More specifically, diets rich in monounsaturated fatty acids may also negatively affect gut microbiota, whereas polyunsaturated fatty acids (PUFA) generally promote an increase in beneficial microorganisms in the gut and are associated with healthy outcomes. Evidence from a number of human and animal studies shows a beneficial shift in the gut microbiota after ω-3 PUFA supplementation; it is associated with a decrease in *Faecalibacterium*, but an increase in the *Bacteroidetes* and *butyrate-producing bacteria* [61]. Coincidentally, studies showed that ω-3 PUFA can exert a positive action by reversing dysbiosis in patients with IBD and increase the production of anti-inflammatory compounds [62].

Micronutrients: Vitamins and Minerals

Micronutrients, namely minerals and vitamins, are necessary for maintaining development, growth, and health. It is well known that a WSD influences nearly all Western diseases by encouraging gut dysbiosis. Because the WSD is generally deficient in micronutrients relative to a traditional diet, the process of dysbiosis appears to be promoted, at least in part, by micronutrient deficiency. Numerous studies have demonstrated that the gut microbiome plays a critical role in the biosynthesis of the vitamins described earlier. There is also some evidence indicating direct regulation of the gut microbiome by vitamins and minerals.

Vitamins

Vitamins are cofactors for a myriad of enzymes, and some of them have direct and indirect influence on immune function. Studies in animals and humans report that microbes can synthesize multiple vitamins including vitamins C, K, and B vitamins [20, 21]. A large portion of vitamins may also be used by some gut microbes, and thus these vitamins may have a gut microbiota-modulating role. Several recent studies demonstrated that microbiome dysbiosis and vitamin deficiency are interrelated and that this relationship may directly impact host health [63]. Therefore, modulation of the gut microbiome via vitamin administration may provide a potential avenue to improve health and prevent disease. A recent study [64] investigated the effects of colon-delivered vitamins A, B_2, C, D, and E on the gut microbiota using a human clinical study and batch fermentation experiments. The findings demonstrated that vitamins B2, C, and D modulate the human gut microbiome in terms of metabolic activity and bacterial composition. Vitamin D has been recognized as having anti-inflammatory effects on various immune cells. A recent study showed that gut microbiome diversity is closely associated with the active form of vitamin D [65]. This research noted that 12 types of bacteria appeared more often in the gut microbiomes of men with high active vitamin D, and most of them are butyrate-producing bacteria, which are generally considered as being beneficial. In addition to bacteria, multiple epidemiological studies in adults and children have demonstrated that sufficient vitamin D is associated with reduced risk and severity of virus infection, particularly of the respiratory tract [66]. A number of studies have suggested that high vitamin D levels may protect against Covid-19 [67–69].

Minerals

Minerals have many important functions in the human body. Many studies have explored microbiota–mineral interactions and have mainly focused on the impact of the gut microbiome on the metabolism of minerals, largely of iron and calcium. Iron is a component of hemoglobin, which is responsible for the transport of oxygen, and myoglobin. Additionally, iron is a cofactor for many enzymes, such as catalase and peroxidase. Iron is absorbed in the duodenum and the small intestine in the form of Fe^{2+}. It significantly affects the intestinal microbiota as it is responsible for the energy acquisition of intestinal bacteria [70]. A high level of iron may cause a decrease in the amount of commensal bacteria and promote the development of pathogenic flora [71].

Calcium is an important bone component. It also activates various enzymes, participates in the conduction of bioelectric impulses and muscle contraction, and plays an important role in blood coagulation, inflammation, and hormonal secretion. Calcium is absorbed in the small intestine in the presence of the active form of vitamin D. A study on obese animals demonstrated that calcium conferred a prebiotic-like effect on the gut microbiota leading to lower plasmatic endotoxin levels and lower hepatic lipid content [72].

Dietary Pattern: Western-Style Diet vs Mediterranean-Style Diet

The Western-style diet (WSD) is a major contributor to the current obesity epidemic [73]. A landmark study in 2013 showed that mice fed a diet high in saturated fat and low in fruit and vegetables, two characteristics of the WSD, lowered gut bacterial taxa associated with leanness [74]. In this twin study, the effects of fecal microbiota transplantation (FMT) from adult twin pairs discordant for obesity were examined in germ-free mice fed with diets representing different levels of saturated fat and fruit and vegetables. When mice were fed on the lower tertile of saturated fat and the upper tertile of fruit and vegetables, the gut microbiota were transmissible from the mice receiving the “lean” microbiota to the mice transplanted with the “obese” microbiota from the twins. However, when the mice were fed on the upper tertile of saturated fat and the low tertile of fruit and vegetables, the gut microbiota associated with leanness was not transferrable between the two types of recipient mice of the twins when they were co-housed [74]. These findings reveal a

clear modifiable effect of the WSD on the gut microbiome [75].

A Mediterranean-style diet (MSD), which is based on the food habits of people living in the Mediterranean region, has been recognized as one of the healthiest and sustainable dietary patterns in the world. It primarily includes vegetables, fresh fruit, and legumes, and the principal source of fat comes from olive oil. The diet also includes moderate consumption of fish, dairy products, and poultry, a very low intake of red meat, and a moderate consumption of red wine. The traditional MSD has far more refined carbohydrates (white bread) than whole grain, whereas the recommendation for the modern MSD is to eat whole grains and avoid sugar. Many studies have reported that MSD promotes the growth of beneficial gut microbiota, which has a positive impact on multiple host metabolic pathways and immune functions. A study explored the effects of an isocaloric MSD intervention on the gut microbiome and metabolic health in subjects with lifestyle risk factors for metabolic disease. The findings revealed that switching subjects to the MSD while maintaining their energy intake induced multiple changes in their microbiome and metabolic parameters; these changes were in the direction of improving their metabolic health [76]. It is now well accepted that specific dietary patterns are associated with microbiome alterations, and that healthy diets can contribute to host-gut microbiome interactions in a positive manner towards improving host health.

Dietary Supplements, Prebiotics and Probiotics

Manipulation of the gut microbiota has become a promising approach for improving host health and preventing diseases. Diet, prebiotics, probiotics, antimicrobial agents, and fecal transplantation are current avenues with great potential to regulate the gut microbiota for health. It has been shown that dietary supplements can effectively shape the gut microbiota [77]. Among the dietary supplements for the modulation of gut microbiota, dietary fibers are important as they cannot be digested or absorbed in the upper part of the GI tract, but they can be fermented by the gut microbiota in the large colon. Prebiotics generally refer to as a subgroup of dietary fibers with resistance to gastric acidity and digestive enzymes, and which confer a variety of health benefits [78]. The main characteristic of prebiotics is their selective promotion/inhibition of the growth and/or activity of intestinal bacteria associated with health and well-being. In addition to dietary fibers, our understanding continuously increases in terms of the modulatory roles of many other dietary components on the gut microbiota. A variety of dietary components which have regulatory capability on shaping gut microbiota have been discovered and can potentially be used as dietary supplements to manipulate gut microbiota [79].

Probiotics are live microorganisms that are promoted to maintain normal intestinal function and confer health benefits to the host when consumed in an adequate amount. They can be found in yogurt and some other fermented foods. Probiotics may help the body maintain a healthy community of microbiota, produce substances that may have beneficial effects, and influence the host's immune response. A variety of health benefits has been reported from the use of probiotics. A number of studies have reported a positive response of probiotics supplementation on the amelioration of overweight and obesity [80, 81]. However, despite potential beneficial indications, probiotic supplements may pose risks to certain people. Several cases have reported serious adverse events, especially among immune-compromised individuals [82]. Poor-quality probiotic supplements raise additional safety concerns. Therefore, further research is needed to evaluate the efficacy and safety before recommending the use of probiotics for health [83, 84].

Conclusion

The gut microbiota consists of approximately 100 trillion microorganisms, most of which are bacteria living symbiotically within the human

body. Prior to the development of enabling sequencing technology, the gut microbiota were neglected, but it is now regarded as a vital organ system. The gut microbiome refers to the collective genomes of the microorganisms in the human intestinal tract. It plays important roles in both the maintenance of health and the pathogenesis of many diseases. The bacteria in the gut stimulate the host immune system thereby protecting against pathogenic organisms that enter our body. They also produce several essential nutrients and help digest foods, particularly complex host-indigestible dietary fiber.

The bacteria living in the human gut are neither invaders, nor are they passive bystanders, but instead they are beneficial colonizers. These gut microorganisms play an integral role in maintaining health and preventing disease. Imbalance of gut microbiota has been linked to gastrointestinal conditions, as well as wider systemic manifestations of disease including T2DM, CVD, cancer, and neurological diseases.

Changes in the microbiome could significantly affect the overall health of the host. Manipulating the gut microbiota may offer a novel alternative to improving health and preventing disease. The gut microecosystem is a living dynamic environment where species richness and relative abundance fluctuate depending on diet, medications, exercise, and other environmental exposures. Of these, diet is one of the easiest to modify and thus presents the simplest route for intervention. Specific foods and dietary patterns can all influence the richness, abundance, and functions of the bacteria in the gut, which in turn affect host health.

Over recent decades, our knowledge of the gut microbiome has been significantly expanded. We have entered an era where we could modify our health through diets and measure the effects through our gut microbiome and their metabolites. Scientists continue to work on understanding the microbiome's broad role in health and exploring dietary strategies to manipulate individual gut microbiota for health.

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Food Insecurity, Nutrition, and the COVID-19 Pandemic

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Jason M. Nagata, Omar M. Sajjad, and Sheri D. Weiser

Key Points

- The Coronavirus disease 2019 (COVID-19) pandemic has impacted food systems, food insecurity, and nutrition in complex ways.
- Food insecurity is defined as the limited or uncertain availability of nutritionally adequate, safe foods, or the inability to acquire personally acceptable foods in socially acceptable ways.
- Food insecurity increased during the COVID-19 pandemic and disproportionately affects racial and ethnic minorities, women, and the elderly.
- The pandemic disrupted the international delivery of food and agricultural products, creating gaps in the continuous supply of food to markets.
- Consumption of food shifted from communal settings to household settings, placing stress on grocery stores and food aid programs, such as food banks and school lunches.
- Food insecurity and poor nutritional status can increase susceptibility to COVID-19 infection and severity.

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic has impacted food systems, food insecurity, and nutrition in complex ways. Food insecurity is defined as the limited or uncertain availability of nutritionally adequate, safe foods, or the inability to acquire personally acceptable foods in socially acceptable ways. Prior to the COVID-19 pandemic, food insecurity was estimated to affect 37 million Americans with approximately one in nine American households in 2018 experiencing food insecurity [1, 2]. The financial burden associated with food insecurity totaled more than $165 billion each year [3]. It is estimated that the number of food-insecure Americans increased by 17 million in 2020 [4]. In this chapter, we first review the structural context of food insecurity and nutrition during the pandemic, including disparities, food systems, and international perspectives. We then assess the downstream impacts of the pandemic on food insecurity and nutrition. We also examine how food insecurity and poor nutrition can affect susceptibility to COVID-19 disease risk through

J. M. Nagata (✉)
Department of Pediatrics, University of California, San Francisco, San Francisco, CA, USA
e-mail: jason.nagata@ucsf.edu

O. M. Sajjad
Geisel School of Medicine at Dartmouth, Hanover, NH, USA
e-mail: omar.m.sajjad.med@dartmouth.edu

S. D. Weiser
Division of HIV, Infectious Diseases and Global Medicine, School of Medicine, University of California, San Francisco, San Francisco, CA, USA
e-mail: sheri.weiser@ucsf.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_26

immune system suppression and higher chronic disease risk. Finally, we review clinical and policy implications of the pandemic on food insecurity and nutrition, as well as directions for future research.

Structural Context

Previous studies have found that food insecurity disproportionately affects ethnic minorities, women, and the elderly [1]. Lower income households, Black and Hispanic households, households with children under 6 years old, female-led households, adults with disabilities, and adults living by themselves are particularly susceptible to food insecurity [5]. These populations were also faced with a higher prevalence and more severe forms of food insecurity as a result of the COVID-19 pandemic and the ensuing economic fallout [6].

The disparity in the prevalence of food insecurity between White individuals and people of color has been well documented [3]. Between 2001 and 2016, one study found that food insecurity rates for Hispanic and Black households were at least two times higher than that of non-Hispanic white households [3], and another analysis including American Indian/Alaska Native (AI/AN) households yielded similar results [7].

Racial discrimination can affect people of color in two primary ways: disparate treatment and disparate impact [3]. Disparate racial treatment can restrict access to job and educational opportunities, creating economic and social consequences that are often conducive to food insecurity [8]. Disparate racial impact, on the other hand, refers to treatment that is not explicitly tied to race but, nonetheless, disadvantages a racial group [3]. For instance, incarceration rates for African Americans in state prisons are five times higher than that of Whites [3]. Consequently, restrictive hiring practices against the formerly incarcerated, while not explicitly discriminatory by race, still disadvantage people of color and potentially lead to food insecurity.

Impact of the Pandemic on Food Systems

The COVID-19 pandemic and its subsequent consequences led to a major disruption of food systems and a subsequent worsening of incidence and severity of food insecurity. As a result of lockdowns and social distancing requirements, the closure of restaurants, workplaces, and schools disrupted not only access to regular provisions of food but also the food supply system of grocery stores, food banks, and food pantries, thus creating an increased demand for food at home [5]. The resulting drop in consumer dependency on external sources of food caused the spoilage and/or waste of huge amounts of fruits, vegetables, and dairy products intended for consumption outside the home [5].

Food Systems in the USA

In addition to traditional food services, COVID-19 has placed an increased strain on food aid programs such as pantries, food banks, school lunches, and food stamps. The nationwide demand for soup kitchens, food banks, and food pantries rose by 61% among US adults in 2020, and the number of applicants for food stamps via the Supplemental Nutrition Assistance Program (SNAP) almost doubled in Los Angeles County [5, 9]. School closures in particular have had notable implications, especially for low-income families, as more than 30 million children in the USA depend on meals from the National School Lunch Program and School Breakfast Program [10]. School meals and snacks comprise as much as two-thirds of a child's daily nutritional needs, and thus, with the closure of schools and the discontinuation of school meals, low-income families have faced the financial burden of providing additional meals to their children [10].

The American food system is organized around two different avenues of food consumption: one oriented towards consumption in communal settings (e.g., businesses, schools, restaurants, etc.) and one oriented towards con-

sumption within the household (e.g., food banks, grocery stores, supermarkets, etc.) [11]. The closure of locations that support communal consumption and the subsequent increase in household consumption has impacted food aid services. Grocery stores, which are the primary source of donations to food pantries and banks, were found to be less able to donate food during the pandemic as they faced panic buying and an increasing number of people choosing to eat at home versus in communal settings [5]. Consequently, some food banks have had to purchase more food, raise costs, and/or distribute less food to each household, further limiting low-income households' access to food [5].

International Food Systems

Unlike foodborne pathogens, such as *Listeria* and *E. coli*, the SARS-CoV-2 virus does not directly impact food safety since it does not spread through agricultural products or livestock. However, the pandemic heavily limited the international transportation of goods and labor. In France, for example, food distribution via trucks declined by 60% after government restrictions were put in place [12]. Similarly, due to labor shortages, the United Kingdom launched a campaign to find 70,000 people to perform agricultural labor [13]. Farms and agricultural firms have experienced an overall shortage of workers due to social distancing measures and illnesses that have resulted from the pandemic [13].

The delivery of food and agricultural products has slowed down, creating gaps in the continuous supply of food to markets [13]. As consumers have transitioned to increased household consumption, food retailers have faced shortages while the food service industry (deemed nonessential) has struggled to adapt to increased demand [11]. In March 2020, the revenue of the food service industry decreased by 28%, a noted departure from the trend of the previous 20 years [11]. The closure of venues such as restaurants, bars, and stadiums has also led to job and income losses, and, in turn, to greater food insecurity [11].

Despite these issues, the food supply chain has shown resilience throughout the pandemic. Multiple steps were taken by food retailers and processors to adapt: increasing factory hours and hiring more employees, reducing the variety of products in favor of the most popular kinds, and identifying backup sources of supply in the face of disruptions [14].

Downstream Impact of the Pandemic on Food Insecurity and Nutrition

Preliminary studies indicate that food insecurity increased during the COVID-19 pandemic. Food insufficiency, which is the most severe form of food insecurity, was estimated to increase from 8.1 to 10.0% in the USA from March to June 2020 [6]. Factors contributing to the rise in food insecurity included job loss and economic hardship, as well as increased grocery costs due to the pandemic's impact on supply and demand. Low-wage positions, such as food services and retail, may be the most vulnerable to job loss and subsequent food insecurity, leaving vulnerable populations to be particularly susceptible both to the COVID-19 disease and to food insecurity. Additionally, the elderly may fear going to grocery stores and food banks due to the possible risk of exposure to COVID-19. People with comorbidities, such as hypertension, diabetes, and obesity, have a higher risk of mortality, severe disease, and hospitalization from COVID-19 infection, and thus may also be more reluctant to go to public spaces to procure food [15]. Lastly, people with COVID-19 may accrue heavy healthcare costs for treatment and testing that can reduce available funds for buying food.

Changes at the individual and household levels during the COVID-19 pandemic can also impact nutrition. During the prolonged periods of social isolation through lockdowns and quarantines, there were increased reports of weight gain and excessive snacking. In one study from the Netherlands, 20–32% of respondents reported overeating, particularly via snacking [16]. Social isolation also led to a rise in uncon-

trolled and emotional eating, especially among women [17]. Eating disorders and disordered eating behaviors increased during the pandemic, likely linked to isolation, loss of daily routines, and increased anxiety symptoms. At the same time, opportunities for physical activity decreased with the closing of gyms and postponement of sports seasons, leading to more sedentary behavior. For example, a study of Canadian college students reported increased sedentary activities, increased alcohol intake, and reduced physical activity during the pandemic [16], which are predictive factors of malnutrition in normal non-pandemic conditions.

Negative mental health outcomes have been another downstream effect of COVID-19 on food insecurity. Food insecurity and poor mental health are related, both having risen during the pandemic [6, 18]. Furthermore, pandemic-related food insecurity is associated with an over 250% higher risk of both anxiety and depression among low-income Americans [19]. Losing one's job during the pandemic is also associated with a 27% increased risk of depression and a 32% increased risk of anxiety [20]. Overall, individuals who are food insecure are almost three times more likely to have adverse mental health outcomes than those who lost their job during the pandemic [19]. In addition to the risk of mental health consequences, food insufficiency was associated with a threefold higher risk of an unmet mental health need for counseling or therapy as well as higher psychotropic medication use during the pandemic [21]. Nationally representative studies from the US Census Household Pulse Surveys during the pandemic have found that the association between food insufficiency and poor mental health was attenuated among people who received food assistance in the form of free groceries and meals [6], although these programs were not universally available.

Additionally, the pandemic has led to increases in intimate partner violence (IPV) when stay-at-home guidelines were implemented in March 2020. American police departments reported as much as a 27% rise in domestic violence calls [22]. Pre-pandemic studies have established a strong positive association between reporting food insecurity and IPV, and also indicated that unmarried women had a higher probability of IPV at levels of food insecurity [23]. African American women experienced higher rates of food insecurity and were more likely to report severe IPV than White women [23].

Nutrition and COVID-19 Disease

Increased food insecurity potentially leads to micronutrient and macronutrient deficiencies, which worsen overall health, weaken defense mechanisms, and thus can lead to immunologic decline [24]. Moreover, the stressors and anxiety associated with food insecurity can impair immune function [25]. Food insecurity has been associated with elevated inflammation among women living with HIV (WWH) in the USA and is also associated with persistent immune activation and senescence in WWH on antiretroviral therapy [26, 27]. Both of these findings were observed regardless of HIV control status [26, 27]. This evidence strongly suggests that food insecurity and poor nutritional status can lead to a weakened immune system and thence increase susceptibility to COVID-19 infection and severity [10].

Adding to these problems food insecurity can lead to the consumption of cheaper and less nutritious food, which can increase susceptibility to chronic medical conditions, such as diabetes, cardiovascular disease, obstructive pulmonary disease, and obesity, all of which put a person at higher risk for severe complications of COVID-19 [25, 28, 29]. Obesity and other comorbidities are also linked to physiological changes that may cause higher susceptibility to the transmission, pathogenicity, and infection of SARS-CoV-2 [15]. Food insecurity has also been linked to poorer medication adherence [30] which could exacerbate preexisting chronic diseases and comorbidities.

Lastly, food insecurity is also associated with greater smoking and use of alcohol and other substances [31]. Smoking, in particular, is a significant risk factor for severe COVID-19 complications, admission to an intensive care unit, need for mechanical ventilation, and death from COVID-19.

COVID-19 and Vitamin D

The possible role of vitamin D in relation to COVID-19 has attracted much attention. Persons with food insecurity may lack access to foods rich in vitamin D as well as vitamin D supplements. A cross-sectional analysis of US children observed that those who are food insecure face a higher risk of inadequate vitamin D intake [32]. With regards to COVID-19 infection, the potential role of vitamin D status is inconclusive. A 2020 systematic review found that vitamin D deficient individuals were at a greater risk for COVID-19 infection than those with sufficient levels [33]. Additionally, vitamin D levels higher than what is traditionally deemed sufficient (30–40 ng/mL) may reduce the risk of COVID-19 infection [34]. This was especially observed among Black individuals, as those within the traditionally sufficient range were at a 2.6 times higher risk of a positive test than those with a level above 40 ng/ul [34]. Conversely, a genome-wide association analysis (GWA) in the United Kingdom found no evidence of a causal relationship between vitamin D levels and COVID-19 infection and severity among individuals with European ancestry [35]. The findings corroborated existing UK guidelines which state that vitamin D supplementation should not be considered protective against SARS-CoV-2 [35]. Overall, uncertainty remains as to whether blood vitamin D levels can help determine one's risk of COVID-19 infection, severity, and mortality [36].

Clinical and Policy Implications

Healthcare providers can help address food insecurity during the pandemic by screening for possible cases and offering referrals. Several medical organizations, including the American Academy of Family Physicians, the American Academy of Pediatrics, and the American College of Obstetrics and Gynecology, recommend screening for food insecurity at least annually [37]. A short screening tool (2 questions) has been developed for clinical practice (Table 26.1) [38]:

Table 26.1 Two-item screen to identify families at risk for food insecurity [38]

"Within the past 12 months we worried whether our food would run out before we got money to buy more." Reponses: Never true, sometimes true, often true
"Within the past 12 months the food we bought just didn't last, and we didn't have the money to get more." Reponses: Never true, sometimes true, often true
A response of "sometimes" or "often" true to either question should trigger a clinical response

Healthcare providers can offer referrals to food assistance programs or help enroll patients in other resources including the Supplemental Nutrition Assistance Program (SNAP), the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), the National School Lunch Program, the National School Breakfast Program, and community food pantries. Clinicians can prescribe medically tailored meals for people with food insecurity and chronic medical conditions [10]. People with COVID-19 who must isolate could also benefit from home deliveries of groceries or meals.

National policies early in the pandemic, such as the Families First Coronavirus Response Act (H.R. 6201) [39] and the Coronavirus Aid, Relief, and Economic Security Act (H.R. 748), allocated funding for households newly eligible for SNAP and suspended time limits for SNAP enrollment [40]. The American Rescue Plan Act of 2021 provided $12 billion in funding for food assistance programs, such as SNAP and WIC, including a 15% increase in SNAP benefits through September 2021 [21]. Despite such actions, however, the long-term consequences of the COVID-19 pandemic on food insecurity and nutritional insufficiency remain largely unknown.

Conclusion

The COVID-19 pandemic has impacted food insecurity and nutrition in complex ways, from structural to individual levels. The pandemic has exacerbated structural disparities and food systems that serve as social determinants of food insecurity and nutrition. As a result, the overall

level of food insecurity has worsened during the pandemic, leading to poorer nutritional status, weight gain, and eating disorders. Health consequences of food insecurity, such as chronic disease and obesity, serve as significant risk factors for severe COVID-19 illness.

Healthcare providers should screen for food insecurity and provide resources to those affected, both during and in the aftermath of the pandemic. Clinicians should also consider the specific nutritional needs of people with COVID-19. Further research on nutritional support for people with the disease could optimize medical treatments and therapies. Multisectoral interventions to address food insecurity at multiple levels, including households, communities, and food systems, are needed. Future research should examine the long-term impact of COVID-19 on food insecurity and nutritional health at the individual, community, and systematic levels.

Lessons Learned

Several lessons from the COVID-19 pandemic thus far could be applied to future pandemics. Response to pandemics requires cross-disciplinary, multisector approaches that extend beyond medicine and public health. Disciplines, including agriculture, business, education, nutrition, and several others, are required to address food insecurity during pandemics. Interventions need to address both short-term and long-term food shortages at the international, national, and local levels. Supply and demand chains may be disrupted, requiring flexibility and adaptability. Finally, social and economic protections for vulnerable populations can help to mitigate food insecurity during pandemics.

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Towards Sustainable Diets and Food Systems

27

Andrew Berardy and Joan Sabaté

Key Points

- Modern food systems provide nutrition to meet the societal demands of a growing global population.
- Food systems impact both human and planetary health by providing nutrition but also emitting pollution and using natural resources.
- The global food system, including agriculture, storage, transportation, processing, packaging, retail, and consumption, has a very large impact on global warming and biodiversity loss.
- Diets become both healthier and more sustainable as they emphasize plant-based, whole, and seasonal foods, and reduce food waste.
- Actions for improved sustainability include advising a healthy whole food plant-centric diet and calling for an end to subsidies of foods that are damaging to health and the environment.

Introduction

Sustainability, Nutrition, and Health

There are environmental challenges that humanity must grapple with, ranging from local to global scales. One of the most significant of these is unprecedented global warming, which is unequivocally due to human activities and is causing extreme weather that is likely to get worse, especially if too little is done to mitigate it [1]. Of the anthropogenic greenhouse gasses (GHGs) contributing to global warming between 21% and 37% can be attributed to the global food system [2]. About 40% of Earth's land is occupied by agricultural production and about 70% of freshwater withdrawals are used for agricultural production [3]. At the same time, dietary choices can lead to cardiovascular disease, type 2 diabetes, and cancer, among other negative health outcomes [4, 5].

Sustainability efforts are an attempt to counter such negative consequences for humanity through mitigation and adaptation efforts while also addressing other relevant issues. Mitigation efforts are those that reduce the drivers of environmental change, while adaptation efforts are those that attempt to adjust to the reality of such changes. Unfortunately, the GHGs previously emitted are already a sufficient amount to ensure that global warming will likely continue until at least 2060 even under the most optimistic sce-

A. Berardy (✉) · J. Sabaté
Loma Linda University School of Public Health, Loma Linda, CA, USA
e-mail: AndrewBerardy@llu.edu; JSabate@llu.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_27

nario, and will likely worsen under more pessimistic scenarios [1]. Drastic measures to combat climate change such as geoengineering could be more effective but also come with high uncertainty and potential risks [6]. A less drastic, but still powerful option for mitigation is to change the patterns of production and consumption of food thereby reducing the food system's contribution to climate change. For example, it is possible for dietary changes to make a large difference in both promoting health and reducing environmental impacts. One hypothetical option, substituting the calories and protein from beef with beans across the US would reduce cropland use by 42% and reduce GHG emissions by 335 million metric tons [7]. Of course, this would require significant changes in the average diet and a shift away from raising cattle, but maintaining the current food system is unsustainable. Alternatively, a more realistic and less disruptive option would be switching only 10% of daily calories from beef and processed meat to fruits, vegetables, nuts, legumes, and some seafood, which would reduce carbon footprint by a third while also increasing life expectancy and not requiring drastic dietary or agricultural changes [8].

More than just addressing climate change, sustainability is an attempt to indefinitely prolong humanity's existence while retaining similar capacities across generations by living within the natural limits of Earth. At its core, sustainability requires balancing social, economic, and environmental concerns in a way that essential systems are not irreversibly damaged and that allows future generations similar opportunities and resources to what the current generation has [9, 10]. This is similar to the ecological concept of carrying capacity, which is an expression of how many organisms an ecosystem can support without causing environmental degradation [11]. Operationalized for humanity within the global ecosystem, the "safe operating space" has been surpassed in multiple different ways that exceed tolerable biodiversity loss, disruptions to the nitrogen cycle, and climate change [12].

Food choice is the clearest connection between sustainability, nutrition, and health because it has an impact on all three. A sustainable diet can therefore improve environmental, nutrition, and health outcomes simultaneously. The Food and Agriculture Organization of the United Nations definition states:

> *Sustainable diets are those diets with low environmental impacts which contribute to food and nutrition security and to healthy life for present and future generations. Sustainable diets are protective and respectful of biodiversity and ecosystems, culturally acceptable, accessible, economically fair and affordable; nutritionally adequate, safe and healthy; while optimizing natural and human resources* [13].

The Diet—Health—Environment Trilemma

The so-called trilemma between diet, health, and the environment is an excellent example of the widespread impact of the food system on humans and the world (Fig. 27.1) [14, 15].

The food system, mediated by dietary patterns, has a significant impact on both human health and planetary health, creating a trilemma. Dietary patterns have a clear impact on both planetary and human health as the produc-

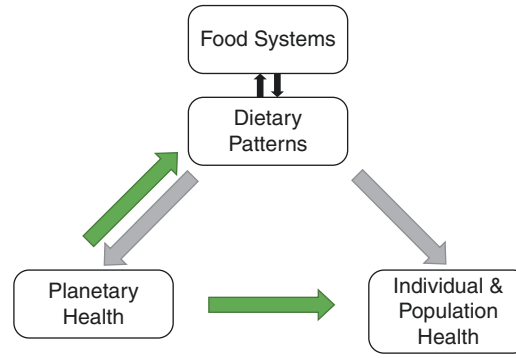

Fig. 27.1 Food systems and dietary patterns are interconnected (black arrows) and influence (grey arrows) both planetary health and individual and population health. In addition, planetary health influences (green arrows) food systems and individual and population health

tion of food has associated environmental impacts, and different dietary choices lead to different health outcomes. An unfortunate reality is that the global food system simultaneously leads to both widespread obesity and hunger, while also depleting natural resources through intensive monoculture farming and degrading the environment in ways that threaten biodiversity and exacerbate climate change [16]. Feedback within the trilemma dynamic means that the negative effects on planetary health then cause problems with meeting dietary needs, worsening human health. Planetary health issues can also directly negatively impact human health. For example, extreme weather events such as cold and heat waves and flooding can worsen respiratory conditions and vascular issues. In addition, climate change worsens extreme weather events such as flooding, heatwaves, and cold waves, which then cause injuries, mortalities, and disruptions to health and social care systems through infrastructure and property damage as well as spikes in demand for services [17].

To better address the challenges posed by the food system to human and planetary health, it is necessary to understand its components and drivers, which is the focus of environmental nutrition [18].

The Environmental Nutrition Model

The Environmental Nutrition Model is a conceptual framework to better understand the food system and the connections between its components. A full, detailed explanation of environmental nutrition is available in a textbook of the same name [19]. The most basic explanation of the food system is that resource inputs are used to produce the foods that reflect societal demand, and are accompanied by the undesired output of waste emissions (Fig. 27.2).

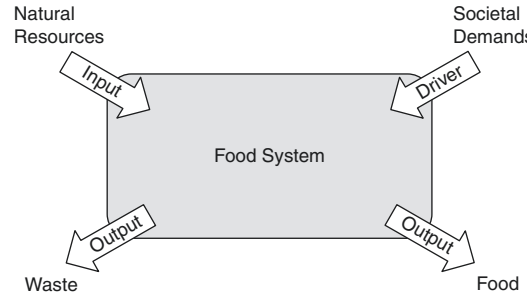

Fig. 27.2 The basic elements of the food system. Inputs of resources and societal demands drive outputs of food and undesired waste emissions [19]

The environmental nutrition model expands on this basic idea by exploring these core components in more detail and identifying interconnections between different domains of the food system (Fig. 27.3) [20].

The resource inputs necessary for the food system to operate include sunlight, water, and land, and industrial food systems also require chemical inputs and energy from fossil fuels. These inputs support agriculture including the growth of crops, raising livestock, and operating fisheries. To reach the end consumer as final products, agricultural commodities must be processed, packaged, distributed, and sold. The specific foods that are produced are driven by consumer demand, which is influenced by marketing and social dynamics, available technology, and policy decisions. All food production systems generate pollution in the form of emissions and waste, although this varies widely between types of foods and across agricultural practices. The desired output—food—then feeds into consumption patterns that vary widely across populations, ranging from the undernourished to the overfed. The type of food and overall consumption patterns can exacerbate or alleviate food-related health outcomes, including obesity, chronic diseases, malnutrition, and deficiency diseases [20].

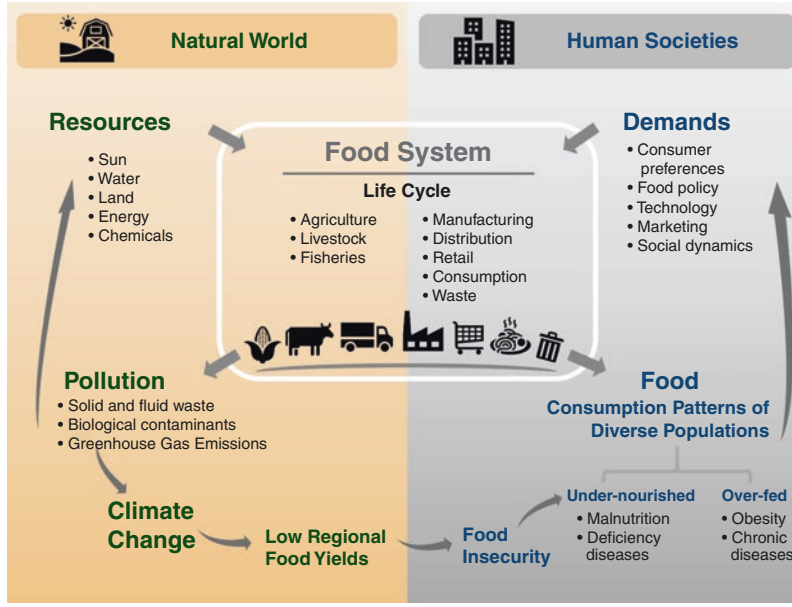

Fig. 27.3 The Environmental Nutrition Model. Expanding on the basic food system model, this includes the interconnected nature of pollution and the food system, as illustrated by the interactions of climate change [20]

Challenges to Sustainable Food Systems

Natural Resource Constraints

The Earth has a finite amount of natural resources that can be used in meeting our material needs including food. As the global population has increased and prosperity has grown, these demands have grown alongside them, but the quantity of natural resources has not. Thomas Malthus originally predicted that these two converging trends would eventually become a serious problem for feeding the world, stating that "Population, when unchecked, increases in a geometric ratio, subsistence increases only in an arithmetic ratio" [21]. Modern society may fall into the same cycle that ancient societies did as their growth and development are followed by decline and collapse when their size is no longer supported by their available resources [21]. Climate change may exacerbate resource constraints by reducing expected crop yields and introducing shocks to agricultural systems that can lead to cascading failures [22].

Societal Demands on Food System

Most Western food systems are now dominated by fast food and eating away from home as consumers demand food that is cheap, tasty, and convenient above all other considerations. Highly processed foods in the form of pre-prepared meals are also exceedingly common. These factors as well as other consumer demands create the modern Western diet which is high in red meat and processed foods but lacking in produce and whole grains. Consumers also expect to have a wide range of foods regardless of the time of year, causing many out-of-season foods to be shipped globally to meet this demand. Finally, portion sizes have grown over time to be excessively large, which has the dual negative impact of contributing to both overconsumption and food waste [23]. Societal food preferences can change based on consumer sentiment as well as external factors. Nationwide lockdowns during the COVID-19 pandemic led to an overall shift towards a more traditional Mediterranean diet including more fruits and vegetables, legumes, cereals, and olive oil, but also an increase in consumption of snacks and sweets [24].

Adverse Health and Nutritional Outcomes

Diets can have protective or harmful effects depending on the foods consumed. The Dietary Guidelines for Americans recommend a healthy eating pattern including a variety of vegetables, fruits, grains, low-fat dairy, protein foods, and oils while limiting saturated and trans fats, added sugars, and sodium [25]. Observational studies have demonstrated favorable risk profiles among vegetarians for multiple chronic diseases including obesity, type 2 diabetes mellitus, cardiovascular disease, and cancer, though some of this may be due to vegetarians practicing healthier lifestyle habits [26]. More specifically, intake of fruits, vegetables, whole grains, and nuts is inversely associated with risk of cardiovascular disease (including coronary artery disease and stroke), total cancer, and all-cause mortality [27]. In fact, all-cause mortality can be reduced by 56% through optimal consumption of certain foods, including more whole grains, vegetables, fruits, nuts, and fish, or reduced by 52% by not consuming red meat, processed meat, eggs, and sugar sweetened beverages [28].

Unfortunately, most consumers choose unhealthy foods or are unable to procure healthy foods for a variety of factors including lack of resources and/or access. Resulting unhealthy diets can then lead to malnutrition, obesity, and connected diseases. A vicious cycle is created in which marketing encourages unhealthy food choices, which drives consumer spending and consumption, and then, in turn, leads to more production and profit, enabling additional marketing. Healthier foods typically do not receive the same marketing as processed junk foods as they tend to be whole foods that are more difficult to differentiate by brand to make marketing clearly profitable. Food deserts are areas with limited food access, often distant from grocery stores, and often with a history of uneven development and racial bias [29]. However, simply providing a new grocery store may be insufficient to change the food environment and provide better access to healthy foods [30]. Areas with a high density of fast and junk food compared to healthier options, known as food swamps, pose an obstacle to healthy eating and in fact are an even stronger predictor of obesity than food deserts [31].

Environmental Degradation from Food Production

Food production is a major driver of many important environmental problems, including biodiversity loss, deforestation, climate change, and eutrophication. Agricultural activities shape and disrupt natural ecosystems, typically with negative effects, and also use resources with their own upstream impact. Farming in turn has downstream pollution emissions, and agricultural products are typically transported and processed further before distribution, consumption, and final disposal. Every step in this process contributes more to the environmental impact associated with the food system. Agricultural activities are a major emitter of GHG emissions, especially when considering livestock due to their feeding requirements and the enteric fermentation of ruminants that causes methane emissions [32]. Eutrophication leading to algal blooms and subsequent hypoxia is another example of damage to the environment directly tied to agriculture as it is caused by fertilizer runoff from farms as well as other sources such as lawns, parks, and golf courses. It is no coincidence that one of the largest such examples is in the Gulf of Mexico at the mouth of the Mississippi River [32]. In addition, agriculture also disrupts soil nutrient cycles through the use of fertilizer; it also employs pesticides and herbicides to protect crops, which themselves are vulnerable due to monoculture practices, all of which reduce the richness of life and biodiversity in the process of farming land [32].

Sustainability Metrics and Assessment

To address the challenges to sustainable diets, it is necessary to understand how sustainable different choices are. Therefore, tools are necessary to quantitatively measure the environmental impact associated with different foods and diets in a way that allows comparison between alternatives.

Life Cycle Assessment

Life cycle assessment (LCA) is a methodology in which the inputs and outputs associated with a given product are quantified and translated into the estimated impact (Fig. 27.4). LCA quantifies the environmental impact relative to a functional unit, which is meant to represent the purpose of the product. That functional unit is based on the "obligatory properties" that are necessary for the product to be considered an option (e.g., a container for a beverage must not leak) [33].

By performing multiple LCAs for different products fulfilling similar functions, it is possible to determine which product meets the desired functionality with the lowest environmental burden. It is important to note that while LCA is a useful methodology, it is not a complete sustainability assessment as there are other aspects of sustainability that are not captured, especially those that are more qualitative in nature, as outlined in sect. 4.3, *Other Methodologies* [34].

Types of Environmental Impact in LCA

The LCA methodology facilitates the quantification of many different types of impact by first gathering data regarding inputs and outputs and then applying characterization factors to translate those into impacts of concern. While there are different impact assessment methodologies, with different approaches to characterization, LCAs of food most frequently assess global warming potential, while land use and water consumption are also common but less ubiquitous [35–38].

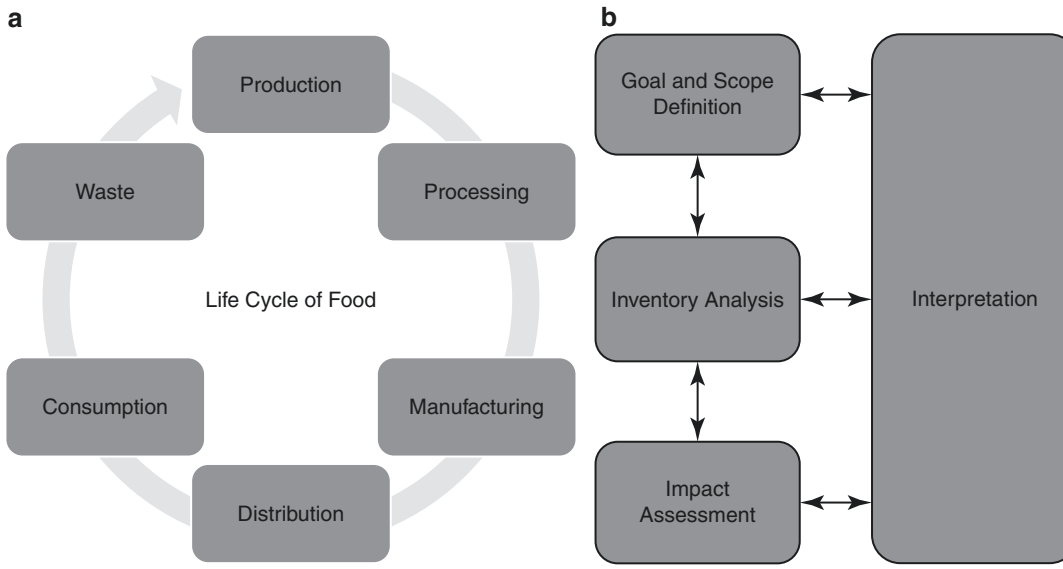

Fig. 27.4 Panel (**a**) displays the steps in the life cycle of food, including production (farming), processing (harvest), manufacturing, distribution, consumption, and waste (disposal). Panel (**b**) displays the steps in performing a life cycle assessment, and shows that it is an iterative process, with each step informing the others

Assessment methodologies can characterize both "midpoint" and "endpoint" environmental impact indicators, which are proximal and distal effects of the inventory data. For example, the ReCiPe 2016 methodology has 17 midpoint indicators (e.g., particulate matter, global warming, water use, freshwater eutrophication, and land use/transformation) that are linked via various damage pathways to three endpoint indicators (damage to human health, ecosystems, and resource availability) [39].

Other Methodologies

While LCA is useful for estimating the environmental impact associated with specific foods, and facilitating comparisons between alternatives on a quantitative basis, sustainability assessment requires a more holistic approach to also capture the qualitative dimensions of sustainability. Other methods that can complement LCA include food systems assessments, backcasting, and scenario building [34].

Food systems assessments examine multiple dimensions of food systems operations using quantitative and qualitative data from a systems perspective [40, 41]. Tools utilized in food systems assessments include foodshed assessments, land inventory food assessments, community food security assessments, food desert assessments, and local food economy assessments [42].

Backcasting and scenario building is the process of envisioning a desired future, then thinking backward from that to determine the steps necessary to realize that future [43]. Combining LCA with these and other sustainability assessment approaches can provide greater insight into the sustainability of food and food systems and identify opportunities for improvement that might not be clear with any one single approach.

One example of merging disciplines for a better assessment is nutritional LCA, which integrates nutrition research with LCA. For example, considering a measure of protein digestibility, the digestible indispensable amino acid score (DIAAS), together with LCA results from commonly consumed protein foods, resulted in a shift in the ranking of the best and worst foods to consume for protein. Among common sources of protein, on a weight basis, beef, shrimp, and cheddar cheese have the highest global warming potential (GWP), while potatoes, peanuts, and whey have the lowest GWP, but when also considering protein quality and serving size, the highest GWP is from beef, white rice, and bread, while the lowest GWP is from peanuts, whey, and soy protein isolate [36].

Sustainable Food Systems and Diets

Approaches for Sustainable Food Systems

Three major avenues towards sustainable food systems exist, and the primary differences have to do with how producers and consumers interact and may or may not be required to change. First, the simplest solution from a consumer perspective is the improvement of food production technology, but keeping the same amount and types of foods in the market, so that the existing diet pattern can be maintained by consumers but with a lower environmental impact. This approach places the burden for change on the producers. A second proposed solution is a drastic reduction in food losses and food waste. The ability to drive this change is with both producers and consumers. Since it is estimated that globally one-third of food produced is lost or wasted [44], using food more efficiently will ultimately reduce the food required to be produced thereby substantially reducing the overall environmental impact of the food system. Another approach that also requires effort from both producers and consumers is behavioral change with shifts in food choices and dietary patterns towards more sustainable options and the resulting concomitant market changes in the types of foods being produced. This solution has the potential advantage that the dietary shift can benefit human health in addition to planetary health [45, 46]. Such an approach is ambitious as dietary change is the most difficult health behavior change to accomplish, and producers have to be responsive to con-

sumer demands, potentially resulting in socioeconomic restructuring. These three approaches are not mutually exclusive and can be combined for the maximum effect, but they also face similar challenges, including population growth driving increased demand for food, which will offset the advances made.

Food Determinants of Sustainable and Healthy Diets

There is substantial overlap in many cases between food choices that are health-promoting and those with a lower environmental impact. These can be summarized along four axes between two extremes for some common characteristics of food.

To pursue a more sustainable diet, consumer choices should tend towards the right side of the spectrum displayed in Fig. 27.5. It is not an all-or-nothing scenario in which any deviation makes a diet unsustainable, but rather a continuum in which the higher the proportion of plant-based, whole, seasonal, and efficiently produced and consumed foods in a diet is, compared to the alternatives, the better [47].

Animal-Based vs. Plant-based Foods

Eating meat requires livestock, which itself requires food to live and grow. Knowing this makes it intuitive that animal-based foods have a higher environmental impact than plant-based foods. In fact, this concept is captured in ecology, by the idea of trophic levels. Typically, only about 10% of the energy stored as biomass in a trophic level is passed from one level to the next [48]. Some of the lowest environmental impact foods include fruits, grains, and vegetables, while meats have some of the highest environmental impact [35]. In general, plant-based foods have a lower impact on the environment than animal-based foods [48]. Participants in the EPIC-Oxford and AHS-2 studies both showed the lowest GHG emissions among vegetarians and vegans compared to nonvegetarians and omnivores [49]. Even just shifting some meals from animal- to plant-based would have a positive impact on sustainability and health [8].

Processed vs. Whole Foods

Processed foods inherently have a higher environmental impact than the ingredients from which they were derived, which is reflected in comparisons where ultra-processed foods have the highest global warming potential, while minimally processed foods have the lowest land use [35]. The degree to which a food is processed may influence the energy required to process it. In this regard, we need to consider primary and secondary processing methods. Primary processing is required to make food safe for consumption and only minimally alters the food (e.g., washing, milling, and packaging), while secondary processing alters foods into other products (e.g., juicing, canning, baking) [50]. All of these

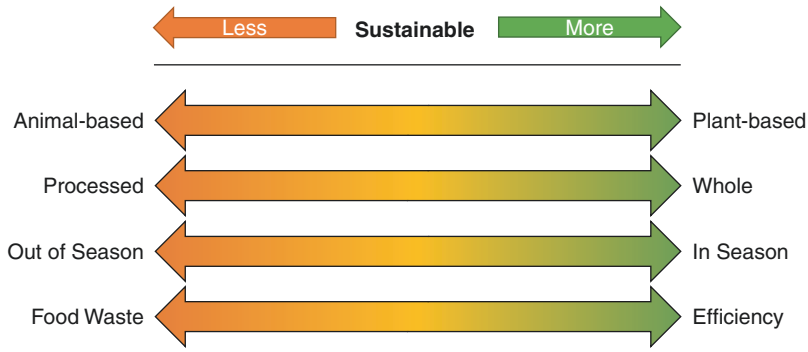

Fig. 27.5 Four food-related determinants of sustainable diets

processing steps require additional energy beyond what was required at the agricultural stage, and the result is a higher environmental impact.

Imported vs. Seasonal Foods

Modern consumers expect to have year-round access to a wide variety of fresh foods, which would be impossible to provide without the global infrastructure supporting the import and export of foods. In order to meet this expectation the United States is actually a net importer of produce, which many will find surprising in view of the country's agricultural productivity [47]. Local seasonal foods are a more efficient choice than foods that were produced in a similar manner but imported or stored prior to purchase or consumption. In the case of transportation, different modes have different levels of additional impact. Ships and trains are the most efficient, followed by trucks, while airplanes are the least efficient. Seasonal foods that are grown and procured locally require less transportation than those imported from overseas, and less storage than those that were harvested earlier in the year. However, this distinction is less clear when considering tradeoffs in the efficiency with which food can be produced across different regions of the world. Choosing local seasonal foods will typically mean they are fresher, and will likely increase the variety of foods consumed.

Food Waste vs. Efficiency

There is widespread agreement that food waste is a serious problem facing modern food systems, as is food loss. The distinction between food waste and food loss is where in the life cycle of food they occur. Prior to the consumer, spoiled or otherwise unusable food is considered food loss, whereas at the consumer phase, procured food that is disposed of is considered food waste. Food waste therefore has the added consequence of the upstream life cycle impact up to the point of disposal, making it a more damaging outcome than food loss earlier in the same product's supply chain. Intervention at the consumer level can have some benefit in the reduction of food waste, while also potentially improving nutritional outcomes [51]. However, reducing both food loss and food waste are potential avenues to a more sustainable food system. Reducing food waste may also increase opportunities for healthy eating, especially as produce is a common category of wasted food. Despite the obvious benefit of reducing food waste, and public sentiment that it is an undesirable outcome and serious problem, it remains very common, with roughly one-third of food produced globally being wasted.

In addition to reducing food waste, improving the efficiency of the food system can also support sustainability goals. This is an ongoing process. One of the most notable advances in efficiency was the widespread use of synthetic fertilizers, pesticides, and herbicides in the Green Revolution in the second half of the twentieth century [52]. There are drawbacks however as more chemical resources are required, which increases cost and dependency for farmers. Consumers are also concerned about potential health implications of certain production techniques, and monocultures lead to more brittle rather than resilient food systems. In addition, there is the potential for a rebound effect (i.e., Jevons' paradox, the idea that energy efficiency improvements will increase rather than decrease energy consumption by reducing cost and thereby increasing access and usage) wherein more efficient production leads to lower prices, which increase consumption and actually makes the entire system less sustainable [53]. Modern approaches to efficiency must balance such efforts with resilience concerns.

Food Policy Options

A more sustainable food system requires changes that are unlikely to happen without the support of policymakers, who are in turn beholden to their constituents. While individual behavior changes can influence production decisions to some degree, certain foods are subsidized to an extent that they are unlikely to slow production even during a significant drop in demand. The range of possible interventions is outlined in the Nuffield intervention ladder, which is a simple metaphor to explain the range of efforts that can be made to

change behavior [54]. The lowest level is to do nothing and simply monitor the situation, but above that is providing information and enabling consumer choices. The next steps up include guiding choices through changing defaults (nudging) or through providing incentives. The most extreme measures are then to provide disincentives, restrict choice, and finally eliminate choice entirely. Small changes, such as changing serving utensils at a salad bar, have proven to be effective in changing behavior, such as reducing the amount of food taken [55]. At the other extreme, certain foods or food components can be effectively banned. The FDA removed trans fats from the "Generally Recognized as Safe" list starting in 2015, meaning that in the majority of cases, partially hydrogenated oils would no longer be allowed in manufactured foods by 2020 [56]. A range of policy options exists to move towards a more sustainable food system. Subtle approaches to shifting consumer choice include nudges, clear and informative labeling to guide decisions, educational materials, and advertising that promotes better options [57]. At the government level, removing subsidies from foods with a high environmental impact, removing taxes on healthy foods, and spending public funds on procurement of nutritious, but sustainably grown, foods would advance the goal of a sustainable food system [57]. Finally, research and development to overcome barriers to sustainable diets, and banning foods that are deemed intolerable can help address any remaining issues [57].

Conclusion

There are significant challenges facing the sustainability of the food system that threaten both human and planetary health, but they are not insurmountable. There are actionable recommendations that can support a more sustainable food system in the future. Following the food determinants of sustainable diets, consumers should drastically reduce or eliminate meat consumption, eat more seasonal, whole plant foods, and reduce their food waste. If there is any ambiguity regarding what is the more sustainable food choice between alternatives, researchers should use life cycle assessment and complementary methodologies to evaluate them. Price is a major deciding factor for many consumers when choosing food, so eliminating subsidies for unhealthy and unsustainable foods and shifting that to supporting better options would help reduce demand and therefore production of such foods.

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Part VI

Areas of Controversy

28

Technological Approaches to Improve Food Quality for Human Health

Yu Hasegawa and Bradley W. Bolling

Key Points

- Nutrients and non-nutrients are highly variable, and, in some cases, unstable in food.
- Health-promoting components of food can be enhanced and preserved using pre- or postharvest/slaughter technologies.
- Modification of animal feeds and plant cultivars through traditional breeding or using bioengineering to produce genetically modified organisms (GMOs) can improve their nutritional profiles.
- Fortification of nutrients to specific foods is applied to reduce nutrient deficiencies.
- Fortification of non-nutrient health-promoting compounds, or "bioactives," can lead to increased consumption of health-promoting compounds.
- Fermentation alters food composition and can be used to create unique molecules for improving human health.
- There have been many developments in the production of various modified foods including lactose-free milk, gluten-free foods, and substitutes for meat.

Introduction

Food science is the application of technology and scientific principles to improve the quality and production of food. It is also a multidisciplinary pursuit which involves chemistry, microbiology, engineering, physics, biology, horticulture, nutrition, toxicology, and many other fields of science. Food scientists have the challenge and opportunity to apply discoveries from these fields to the production of food.

Y. Hasegawa · B. W. Bolling (✉)
Department of Food Science, University of Wisconsin-Madison, Madison, WI, USA
e-mail: yhasegawa2@wisc.edu; bwbolling@wisc.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_28

Food production occurs at many different scales and contexts, from microscale to mass production. The production of food often requires the transformation of raw and inedible materials into edible food. The goal of food processing is to ensure safety, increase quality, and reduce food waste. The initial priority of food scientists is to ensure that foods are microbiologically and chemically safe to eat. Food scientists also pursue the challenge of producing foods with desirable taste, price, and healthfulness. The environmental sustainability of food production must also be considered.

Foods need to meet basic nutrient needs but can also provide extra-nutritional benefits upon consumption. Foods that provide non-nutritional health benefits have also been called "functional foods" in the fields of food science and nutritional sciences. The evidence for the benefits of functional foods varies considerably. However, governmental regulatory agencies such as the United States Food and Drug Administration (US FDA), the European Food Safety Authority, and the Ministry of Health, Labor and Welfare of Japan have issued claims where well-documented evidence is available. These claims include increased consumption of fruits and vegetables to reduce cancer risk; plant sterols and stanols to reduce the risk of coronary heart disease; and cocoa polyphenols to improve vascular function [1, 2].

The goal of this chapter is to present a variety of technological approaches used to improve food quality for human health. This requires consideration of basic nutritional quality and the non-nutrient components that may improve health (also called "food bioactives"). The approaches applied can be classified as "*preharvest*" (occurring prior to the harvest/collection of the material) or "*postharvest*" (technology applied after harvest/slaughter including fermentation of raw materials). While this chapter is not intended as an exhaustive review of the topic, we intend to present an overview of different ways that food science has been applied with the goal of improving nutritive value or health benefits of foods (Fig. 28.1).

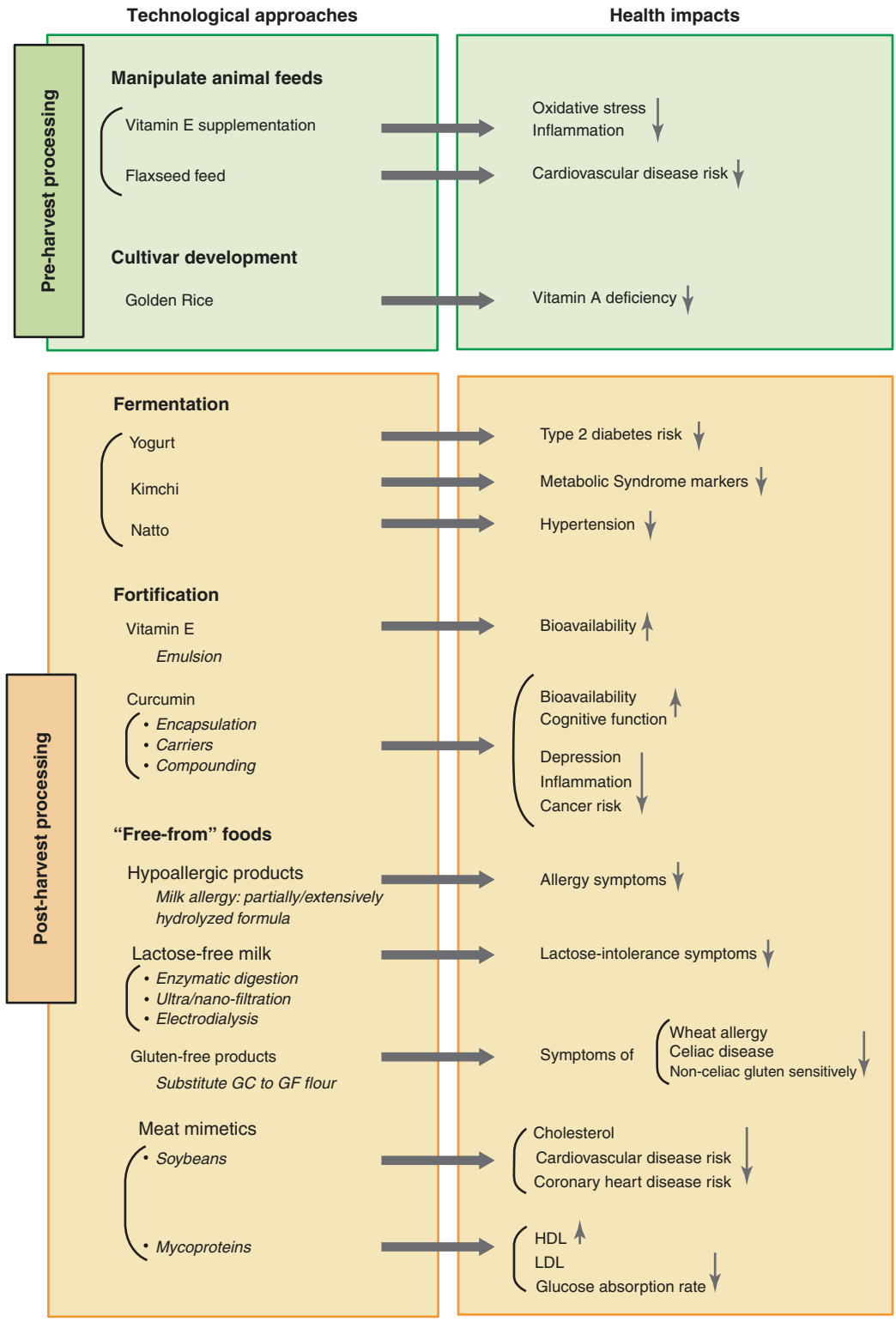

Fig. 28.1 Examples of technologies deployed to improve food quality for reducing risk of chronic disease. Abbreviations: *GC* gluten-containing; *GF* gluten-free; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein

Preharvest Technologies

The fields of agronomy, horticulture, and animal and dairy sciences have led to insights in the production of food for improved health. It is well known that the manipulation of animal feeds can alter the nutritional quality of animal products. For example, constituents of meat and meat products, such as lipids, proteins, pigments, and vitamins, are susceptible to oxidation processes, leading to deterioration of the product quality in color, texture, rancidity development, as well as nutritional value [3]. Vitamin E supplementation of the feed of steers leads to higher levels of α-tocopherol and reduced markers of lipid oxidation in the ground muscle meat [4]. Reducing the potential oxidative end products of meat is highly desirable, as consumption of lipid peroxidation end products may be detrimental to health by increasing oxidative stress and inducing inflammatory responses [5, 6].

Another example of manipulating feed is in the production of eggs enriched with omega-3 polyunsaturated fatty acids (PUFA). Feed enriched in flaxseed increase α-linolenic acid, while fish oil supplementation increases the long-chain omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in chicken eggs [7]. Increased dietary intake of omega-3 is desirable to reduce risk of cardiovascular diseases [8]. Intake of long-chain PUFA, especially DHA, in pregnant women and children may contribute to brain and vision development in early childhood [8]. These foods seem to have a role in improving nutrient status in healthy adults as intake of 3 servings/week for 6 months of omega-3 enriched chicken meat and eggs increased red blood cell omega-3 index in healthy adults relative to non-enriched chicken and egg intake [9]. Although participants were normotensive, diastolic blood pressure was significantly reduced by 3.1 mmHg, suggesting a potential cardiovascular benefit [9]. Similar approaches have been taken to alter the lipid profile of cow's milk. As such, grassmilk, or milk from grass-fed cows, is produced and marketed for improved nutrient and bioactive content. The health-promoting benefits of these strategies need to be placed in the context of the dietary patterns of consumers. For example, those consuming sufficient omega-3 PUFA from foods such as fish or walnuts may have limited benefit from further consuming PUFA-enriched foods for the red blood cell omega-3 index.

Sufficient intake of omega-3 PUFA is recommended by American Heart Association to reduce the risk of cardiovascular disease [10]. Salmon is a particularly good source as it contains higher levels of EPA and DHA compared to most other fish species and all terrestrial livestock [11]. As the productivity of aquaculture continues to grow, farming systems that are sustainable and environmentally friendly are required. Although farmed salmon were traditionally fed a diet composed of marine ingredients (fish oil, fishmeal), in response to pressure on wild fish stock, plant sources (oilseed) are now used in salmon feeds [11]. An analysis of the changes in the composition of farmed Scottish salmon feeds illustrated changes over time in fish flesh lipid profiles, having increased omega-6 but lower in omega-3 PUFA [11]. Despite these changes, Scottish-farmed salmon delivered more EPA and DHA than wild samples [11]. Supplementation of astaxanthin in farmed salmon feed is necessary for flesh color and is also a putative bioactive for improving health, although more evidence is needed to determine its effects on oxidative stress, inflammation, and cardiovascular disease risk in humans. Feed optimization is expected to increase in importance as aquaculture operations expand and evidence is developed supporting recommendations for bioactive intake.

In plant-based foods, the selection of cultivars with favorable nutrient or bioactive profiles may be used as a starting point to improve food quality. Traditional breeding programs or bioengineering can be used to enhance nutrient and bioactive profiles of plants. Also, genetic modification technology has been utilized. Golden Rice is one of the examples of genetically modified organisms (GMOs) developed as a way to help prevent vitamin A deficiency. That deficiency leads to blindness and affects more than 250 million children worldwide—a serious health problem in half of the world's countries [12]. Golden

Rice was engineered to express the genes necessary to synthesize β-carotene which is metabolized to vitamin A upon consumption. The challenges of government regulatory approval and consumer resistance have limited the widespread adoption of this crop. Golden Rice was approved for production by the Philippines in 2021 [13]. However, efforts are still ongoing to scale up Golden Rice production as well as introduce other bio-fortified rice cultivars that address deficiencies of zinc, folate, and amino acids [14].

Another molecular tool to improve agricultural production is clustered regularly interspaced short palindromic repeats (CRISPRs) and the CRISPR-associated enzyme (Cas) [15]. It allows a precise insertion and modification of the target DNA. While many consumers have shown a negative reaction towards GMOs, products made with CRISPR/Cas9 technology are more accepted, where familiarity and perceptions of safety contribute. Also, while traditional GMOs are generated by inserting a foreign DNA fragment into the target species, CRISPR/Cas9 technology can produce non-GMO products as well by introducing changes to DNA and its expression intrinsic to the target species/cultivar [16].

Potatoes have also been bioengineered with the goal of reducing acrylamide formation during production of chips and French fries. Acrylamide is a suspected carcinogen that is a process-induced contaminant that is a product of the reaction between the amino acid asparagine and reducing sugars such as glucose and fructose. The reaction occurs at temperatures greater than 120 °C during the roasting, baking, or frying of potatoes. Although acrylamide intake is monitored by the FDA and mitigation strategies are available, target levels are yet to be established [17]. In the National Fry Processing Trial, a US research consortium screened a large number of potato breeding lines to identify potatoes with favorable compositions that can result in lower acrylamide levels [18]. Bioengineering potatoes by silencing the vacuolar invertase gene lowers reducing sugars in potatoes and reduces acrylamide formation as effectively as silencing asparagine synthetase genes [19]. The bioengineered Snowden Z6 and Innate W8 Russet Burbank potatoes are now approved by the USDA and produced by the J.R. Simplot Company [20]. Thus, food scientists can utilize plants with engineered traits to complement other mitigation strategies with the goal of reducing potential toxicants in potato products. Despite these benefits, there is resistance to adoption of GMO foods. McDonald's USA, which uses conventional J.R. Simplot potatoes, refuses to use the new potatoes for their fries [21].

Cultivar selection can also impact the bioavailability of dietary bioactives in plants. For example, the *Tangerine* tomato has a variation in carotenoid biosynthetic genes that leads it to accumulate non-crystalline tetra-*cis*-lycopene, in contrast to the crystalline *trans*-lycopene pigment produced by red tomatoes [22]. In adults consuming 10 mg of lycopene from tomato juice, lycopene bioavailability was increased from 5% in red tomato juice to 48% in *Tangerine* tomato juice [22]. Other cultivars of tomatoes have been bred or bioengineered to be rich in anthocyanin pigments. This is potentially of value as bioengineered anthocyanin-rich tomatoes extend the lifespan of rodents compared to red tomatoes [23]. However, these anthocyanin-rich tomatoes are not yet commercially available.

These advancements point to a future where technology is deployed in advance of food production; this strategy will extend the shelf life and improve the nutritional and bioactive profiles of plant and animal products and reduce potentially harmful components of cooked and processed foods. The utility of these advancements will be tied to advancing the knowledge of how specific components of food improve or harm human health.

Postharvest Technologies

Preservation Processes

The harvest of plants or slaughter of animals initiates biochemical, chemical, physical, and microbial changes to these materials. Strategies to limit or control these changes constitute the basis of producing safe, edible, and nutritious

foods and limiting food waste. Preservation processes enable health-promoting foods to be consumed out of season. These processes include refrigerated and frozen storage, thermal processing, drying, irradiation, and high-pressure processing. It is well known that these processes impact the nutritional and bioactive quality of foods, and these must be optimized to produce high-quality food.

During food storage, oxidation and other chemical reactions may reduce food quality. Certain nutrients and bioactives are sensitive to heat, light, oxygen, and pH, so packaging and formulation of mixed foods must also be optimized to ensure food quality throughout storage. Thus, the precise profile of nutrients and bioactives in foods are highly dynamic and depend on pre- and postharvest processes. The ultimate impact of these processes on health relate to the amount of nutrients, bioactives, and toxicants throughout the shelf life of the product and the potential changes to the food matrix that may impact nutrient absorption and gut microbiota.

Fermentation Processes

Fermented foods or beverages are produced by the action of microbial activities which carry out enzymatic and/or chemical reactions on the raw food materials [24]. Fermented foods were historically developed as a means of preservation of perishable foods. They have had an essential role in some cuisines due to their unique sensory attributes [24]. However, the increase in their popularity in recent years partly comes from their health-promoting properties.

Fermented foods have a number of potential health benefits. For example, several human studies have reported that yogurt consumption has a significant and inverse correlation with type 2 diabetes risk, while intake of total dairy consumption and non-fermented dairy products did not show a significant association [25, 26]. Kimchi, which is made in Korea, is a mixture of fermented vegetables, mainly produced by the action of lactic acid bacteria [27]. Consumption of kimchi for 8 weeks improved body composition and markers of dysmetabolism in participants with metabolic syndrome [28]. Of particular note, those who consumed fermented kimchi (10 days old) showed a greater reduction in blood pressure compared to those who consumed fresh kimchi (1 day old), suggesting that fermentates enhanced the antihypertensive effects of kimchi [28]. Other fermented foods also have antihypertensive effects, such as natto, a Japanese food produced by fermenting boiled soybeans with *Bacillus subtilis* subsp. *natto* [29]. The antihypertensive effect is due, in part, to the production of subtilisin (also called nattokinase) by *B. subtilis* which inhibits the activity of angiotensin-converting enzyme [29]. A similar effect has been reported with chongkukjang, a Korean fermented soybean product, that also has potential antidiabetic, anti-inflammatory, antimicrobial, antioxidant, and neuroprotective effects [27].

To enhance the health-promoting properties of fermented foods, certain strains of microorganisms, categorized as probiotics, may be supplemented in foods. Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" according to FAO/WHO. There is also supporting data from animal and human studies that suggest a role for probiotics in improving health [30]. They may exert health benefits to the host via production of metabolites (e.g., vitamins, bile acids, short-chain fatty acids) or competing for colonization on epithelial cells with pathogens [30]. For example, a common genera of bacteria used as probiotics is *Lactobacillus*; oral administration of *Lactobacillus* strains alleviated abdominal pain in patients with irritable bowel syndrome [31]. While persons with functional bowel diseases may develop comorbid anxiety and depression, administration of *L. rhamnosus* JB-1 reduced anxiety- and depression-related behaviors by altering GABAergic neurotransmission in a mouse model [32]. Furthermore, CRISPR/Cas9 gene editing technology has been utilized to engineer probiotic strains [33]. Such technologies may facilitate the development of therapeutic probiotics that deliver specific health-giving molecules or kill target pathogens. In addition to probiotics, non-

digestible dietary substrates, known as prebiotics, may be added to promote the growth and activity of microorganisms that exert health-promoting properties. Probiotics and prebiotics are known collectively as synbiotics [34].

Fortification

The fortification of certain foods with essential nutrients is aimed at reducing nutrient deficiency and disease risk. The most notable examples include enriching grains with folate, thiamin, riboflavin, niacin, and iron; fortifying milk and margarine with vitamins A and D; and iodized salt. The FDA prohibits the fortification of alcoholic beverages, meat, fresh products, and candy [35]. While fortification may be mandated by the standard of identification for certain products (e.g., "enriched" grain), most fortification is applied at the discretion of the food manufacturer. Many fortified products have been developed to increase the delivery of nutrients and bioactives in food. For example, a variety of orange juice products have been fortified with vitamins C and D, calcium, zinc, omega-3 fatty acids (DHA and EPA), or phytosterols. Producers may target fortification strategies to enhance the nutritional profile of foods that have a low content of specific nutrients, such as adding calcium and vitamins C and D to plant-based dairy replacement products. Other nutrients may be added to target specific health claims (e.g., soluble fiber or phytosterols for reducing risk of coronary heart disease).

Technological advancements have improved the stability and delivery of nutrients and bioactives in foods. Carrier agents, encapsulants, and emulsions have been employed to improve the dispersibility, stability, and bioavailability of nutrients and bioactives in foods. For example, the bioaccessibility of emulsified fat-soluble vitamin E is improved by formulation with long-chain fatty acids rather than medium-chain fatty acids [36]. There are many possible routes to manipulate the solubility and bioavailability of a bioactive. The bioactive curcumin, from turmeric, has been extensively studied in this regard. Approaches, such as emulsions, nano-emulsions, carriers (e.g., gamma-cyclodextrin), compounding, encapsulation, and reducing to tetra-hydrocurcumin, have been investigated as means to improve the bioavailability of this compound. The potential health benefits of curcumin are many, from preventing depression, improving cognitive function, reducing inflammation, and cancer prevention—but results from human intervention studies have been promising or mixed and require further study [37–39]. Lastly, since many bioactives are bitter, astringent, or have distinct flavors, the fortification method must be designed to ensure foods are still palatable.

Voluntary fortification of food with nonessential nutrients has been criticized as a strategy primarily utilized for marketing purposes, without delivering on promises to improve the health of consumers. While it is true that well-balanced diets can meet the nutritional needs of most individuals, fortified foods can be convenient, economical, and desirable for consumers. Voluntary fortification has a role in improving the nutritional status of consumers. For example, children consuming fortified, ready-to-eat cereals had increased intake of vitamins A and B_{12}, iron, and magnesium among other nutrients [40]. A systematic review and meta-analysis of randomized controlled trials suggests that consumption of phytosterol-fortified foods improves apolipoprotein profiles, but there is a high degree of heterogeneity between studies [41]. Homogeneous studies with fortified foods are needed to strengthen these conclusions [42].

Production of "Free from" Foods

Specialty foods that are free from particular ingredients and that target specific populations have emerged in the market [43]. This is partly because of the increase in awareness and diagnosis of food allergy [44]. The self-reported prevalence of food allergy in the USA is estimated at 2.9% for shellfish, 1.9% for milk, 1.8% for peanut, 1.2% for tree nut, and 0.9% for fin fish [43, 45 46]. In addition, in response to a growing interest in environmental sustainability and ani-

mal welfare, the demand for animal-free foods is increasing [43, 46]. Animal-free foods may also be relevant to reducing chronic disease risk as high levels of consumption of red and processed meats are associated with increased risk of cardiovascular disease [47], diabetes [48], colon and rectal cancers [49], and mortality [47]. In this section, technologies involved in producing allergen- or animal-free foods, along with the potential health benefits, are introduced.

Hypoallergenic and Lactose-Free Milk

Cow's milk is among the most common allergens for infants and young children [50]. Caseins as well as β-lactoglobulin and α-lactalbumin (whey proteins) are potential allergens as they are abundant in bovine milk [51]. In infants, milk allergens induce immunoglobulin E-associated allergy, possibly leading to abdominal pain, diarrhea, vomiting, and skin problems such as rashes and atopic eczema [52]. To avoid milk allergy, specialized formulas are available, such as partially hydrolyzed formula (phMF) and extensively hydrolyzed formula (ehMF) [52]. Although phMF products are not completely hypoallergenic, the whey proteins have been hydrolyzed to peptides that are smaller than 5 kDa so that they are more digestible than formulas with whole milk proteins. On the other hand, ehMF products go through more extensive hydrolysis, where milk peptides become less than 1.5 kDa in size. They are therefore appropriate for infants who are more sensitive to milk proteins. These technologies result in milk protein hydrolysates that are not only non-allergic but may also be beneficial by having immunomodulating properties and be protective against the development of allergic symptoms [52].

The presence of lactose in milk can also lead to digestive problems as 65–70% of people worldwide have a lactase non-persistent phenotype [53]. Lactose is the major carbohydrate in milk, and tolerance to lactose is genetically programmed to decline after weaning as a result of reduced levels of lactase [53]. Lack of sufficient lactase leads to incomplete digestion of lactose in the small intestine which then flows into the colon where it can be metabolized by the gut microorganisms to generate fatty acids and gas that cause flatulence and discomfort [54]. Lactose may also cause osmotic diarrhea.

Lactose-free milk is widely available in the market and sales are increasing [55]. These milk products are beneficial for people with lactose intolerance or malabsorption as consumers can still obtain the beneficial macro- and micronutrients provided by dairy products. Although the FDA has not adopted a standardized lactose content requirement to label foods as a lactose-free product, producers aim to reduce lactose content as low as possible [55]. Most lactose-free or low-lactose products in the market are generated by enzymatic digestion of lactose by β-galactosidase, typically derived from the dairy yeast *Kluyveromyces lactis*, *K. marxianus*, *K. fragilis,* or *Saccharomyces lactis* [55]. However, lactose hydrolysis results in elevated sweetness by producing glucose and galactose [56], which is not ideal for persons with hyperglycemia.

Alternatively, membrane technologies, such as ultrafiltration and nanofiltration, have been utilized to reduce lactose in milk [57]. Both methods use pressure-driven membrane processes to separate substances. Ultrafiltration can filter substances with molecular weights between 10^3–10^6 Da and nanofiltration is between 100–500 Da. However, membrane fouling can be a problem for ultrafiltration, and nanofiltration requires high pressure over multiple steps, resulting in high energy demand, and may therefore be costly [58]. Electrodialysis can also be used as an approach for the reduction of milk lactose. Unlike filtration that utilizes the difference in molecular size to separate, electrodialysis uses difference in charge of molecules [59]. Although electrodialysis equipment is expensive and is susceptible to blocking, it consumes less energy, does not cause membrane fouling, and is suitable for products that are heat sensitive [59]. Otherwise, methods that combine the aforementioned technologies together are being developed to better produce lactose-free milk [58].

Gluten-Free Products

Gluten is a protein complex found in grains such as wheat, rye, barley, and oats. Gluten-free (GF)

products are produced by replacing gluten-containing (GC) flour with flour that does not contain gluten (e.g., rice, corn) [60]. There are three health conditions that require a GF diet: wheat allergy, celiac disease, and non-celiac gluten sensitivity, where ingestion of GC foods may cause gastrointestinal symptoms (e.g., diarrhea, steatorrhea) and/or extraintestinal symptoms (e.g., anemia, osteoporosis, dermatitis herpetiformis) [61].

While a GF diet alleviates the symptoms, it needs to be introduced carefully. GF flours tend to be deficient or poor in some macro- or micronutrients compared to GC flours [60]. Also, in order to mimic the quality attributes of gluten, surface-active ingredients may be added, such as starches, fat-rich ingredients like dairy and egg, hydrocolloids, and/or gums. However, starch is hydrolyzed when mixed with water and heated during bread making. This increases the glycemic index and may elevate the risk for developing metabolic syndrome. Also, the fat and carbohydrate content tends to be higher in GF products than in GC products. More studies are therefore needed so as to develop therapeutic approaches that do not rely solely on a GF diet [61].

Meat Mimetics

Soy protein is the most common substitute for meat in alternative (meat mimetic) products [62]. Soybeans have a well-balanced content of amino acids and are rich in calcium and linoleic acid. Importantly, soy protein intake is associated with lowering of the blood cholesterol level, and, therefore, may lead to a lower risk for coronary heart disease [43, 62]. Soy protein isolate is prepared by defatting soy meal by aqueous or mild alkali extraction to collect proteins and soluble carbohydrates, followed by centrifugation to remove the insoluble residue, such as carbohydrates [63]. The protein is precipitated by bringing the pH of the solution to the isoelectric point. It is then collected by decanting, washing, and drying. To prepare meat substitutes, extracted soy protein goes through an extrusion process to make meat alternatives [62]. Although soy protein is by far the most common and cost-effective ingredient for use as a meat substitute, the texture typically remains fibrous due to disulfide bonding and the strong off-flavor may be a disadvantage [43, 62]. Given the consumer interest in meat mimetics, other isolated plant proteins have also been tested, including wheat, pea, and different types of beans, but these also present flavor and textural challenges in product formulation.

They have received attention for their potential health-promoting properties and utility for meat mimetics. *Quorn*® is a mycoprotein meat mimetic that is marketed in most US grocery stores. Mycoprotein is extracted from single-cell fungi that are rich in dietary fiber (chitin and glucan from cell walls of hyphae), polyunsaturated fatty acids (cell membranes), and proteins (cytoplasm) [43]. Mycoprotein may lower low-density lipoproteins and raise high-density lipoproteins [62], as well as slow the rate of glucose absorption, which is relevant to managing obesity and type 2 diabetes [64]. To produce mycoprotein commercially, *Fusarium venenatum* is cultured via continuous-flow fermentation on glucose substrate for approximately 6 weeks [43]. Unlike soy proteins, most mycoproteins are tasteless and colorless, and the product therefore has more flexibility to be used for the preparation of imitation fish, chicken, veal, or ham [62].

To overcome flavor challenges in the preparation of meat mimetics based on plant protein, soy leghemoglobin has been produced through bioengineered yeast and used as a flavor and color enhancer [65]. Other innovations, such as the use of cultured cells, are on the horizon. As these products are introduced and refined, it will be important to deliver nutrient-dense products that can reduce chronic disease risk.

Glyphosate-Free Foods

Glyphosate is an herbicide used to control weeds in the production of soy, corn, and other food crops. GMO soy and corn varieties that are resistant to glyphosate (e.g., Roundup Ready) are widely grown in the USA. While this approach may increase crop yield and food availability, there are concerns with the sustainability and human exposure to glyphosate from foods. Third-party certification of "glyphosate residue-free" food is available for branding purposes [66]. The

US Environmental Protection Agency (EPA) sets tolerances and evaluates safety of pesticides in the USA. The FDA has monitored glyphosate residue in soybeans, corn, milk, and eggs, and testing through 2016–2017 found that 60% of samples contained detectable glyphosate, but levels were well below tolerance levels established by the EPA [67].

Conclusion

The production of safe and nutritious food with the potential to reduce the risk of chronic disease requires multidisciplinary technological approaches. The challenges of producing high-quality foods include the inherent properties of nutrients and bioactives which have limited stability and potentially undesirable sensory properties. Strategies are deployed throughout the food production process, from agriculture, processing, and preservation methods (Fig. 28.1). Furthermore, the increased demand for clean-label and minimally processed foods will be an opportunity to deploy innovative technologies for formulating and processing foods and ingredients for health.

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Optimizing Nutrition for Exercise and Sports

29

Drew E. Gonzalez, Scarlett Lin Latt, Tricia Blalock, Brian Leutholtz, and Richard B. Kreider

Key Points

- Athletes should follow these rules in order to optimize their nutrition.
- Eat enough calories to offset energy expenditure (typically 50–80 kcal/kg/day).
- Consume the proper amount of carbohydrate (e.g., 5–8 g/kg/day during normal training and 8–10 g/kg/day during heavy training), protein (1.2–2.0 g/kg/day), and fat (0.5–1.5 g/kg/day).
- Ingest meals and snacks at appropriate time intervals prior to, during, and/or following exercise in order to provide energy as well as to promote recovery following exercise; include more liquid and quickly digestible type forms of nutrition within an hour of exercise; Ensure athletes are properly hydrated prior to exercise and competition.
- Incorporate rest and nutritional strategies to optimize recovery.
- Only consider using nutritional supplements that have been found to be an effective and safe means for improving performance capacity and/or enhancing recovery.

Introduction

Several primary factors such as an individual's genetic endowment, the quality of training, and effective coaching affect exercise performance capacity (Fig. 29.1). Nutrition subsequently

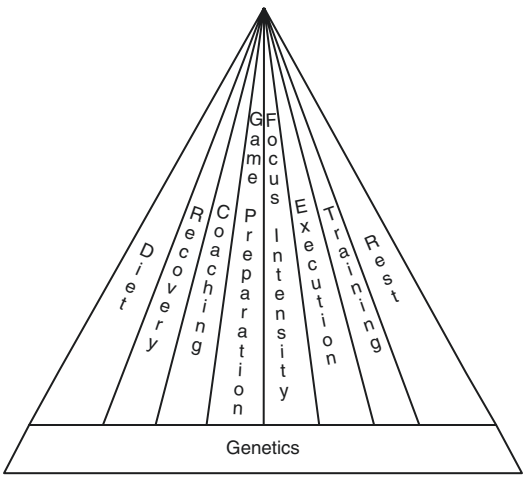

Fig. 29.1 Factors that affect performance. Reprinted with permission from Kreider et al. [1]

D. E. Gonzalez · R. B. Kreider (✉)
Exercise and Sport Nutrition Laboratory, Department of Kinesiology and Sport Management, Texas A&M University, College Station, TX, USA
e-mail: dg18@tamu.edu; rbkreider@tamu.edu

S. L. Latt · T. Blalock
Department of Health, Human Performance and Recreation, Baylor University, Waco, TX, USA
e-mail: scarlett_linlatt1@baylor.edu; Tricia_Blalock@baylor.edu

B. Leutholtz
Center for Exercise, Nutrition and Preventive Health Research, Department of Health, Human Performance and Recreation, Baylor University, Waco, TX, USA
e-mail: Brian_Leutholtz@baylor.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_29

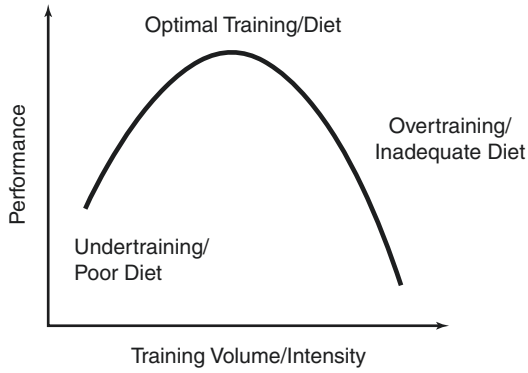

Fig. 29.2 Relationship of training volume/intensity to performance. Reprinted with permission from Kreider et al. [1]

plays a crucial role in optimizing performance capacity. Diet and training must be optimal for athletes to perform well. If athletes do not train enough or have an inadequate diet, their performance may be decreased [1]. However, if athletes train too much, in the absence of a diet sufficient in calories and nutrients, they may be susceptible to becoming overtrained (Fig. 29.2), which may decrease performance and increase risk of injury. Overtraining occurs when the stressor (from training) is too great and/or the recovery (and nutritional practices) do not adequately match training demands. The athlete will likely feel fatigued and underperform during training, practice, and games when suffering from overtraining. Therefore, care should be given to an athlete's training, diet, and recovery in order to optimize performance and reduce injury risk.

Members of a sports performance team (e.g., coaches, sports scientists, dietitians, and athletes) have searched for various ways to enhance exercise performance capacity through the use of *ergogenic aids*, since optimizing training and dietary practices are critical to peak performance. An *ergogenic aid* is any training technique, mechanical device, nutritional practice, pharmacological method, or psychological technique that can improve exercise performance capacity and/or enhance training adaptations [2]. Practices with aids to help prepare an individual for exercise, improve the efficiency of exercise, and/or enhance recovery from exercise may be categorized as an ergogenic aid. This chapter presents an overview of the role nutrition plays in optimizing sport performance; describes nutritional guidelines athletes should employ to optimize training adaptations; and evaluates the potential ergogenic value of various nutrients that have been proposed to improve exercise capacity and/or training adaptations. The guidelines discussed have been adapted from several previous publications [1, 3] and comprehevsive position stands coauthored with the International Society of Sports Nutrition (ISSN) [2, 4–15].

General Energy and Macronutrient Guidelines for Athletes

The provision and timing of adequate amounts of carbohydrate, fat, protein, and water are critical for athletes to meet performance demands and reduce the risk of injury. Table 29.1 outlines the general caloric intake and macronutrient guidelines, based on body mass, for individuals training at various levels of experience as well as those involved in serious training for strength/power and endurance athletes. The following sections discuss the ISSN's recent macronutrient guidelines [16] as well as provide insight on how to structure the diet in order to optimize performance [3].

Table 29.1 General caloric intake and macronutrient needs for active individuals

	Beginners (50–90 kg)	Intermediate (50–90 kg)	Advanced (50–100 kg)	Power athletes (60–120 kg)	Endurance athletes (50–80 kg)
Caloric intake (kcal/day)	1500–3150	1750–3600	2000–5000	2700–7200	2500–6400
Carbohydrate (%)	45–55%	45–55%	50–60%	40–50%	55–65%
(g/kg/day)	3–5	4–6	5–8	5–8	7–13
Protein (%)	11–14%	11–15%	10–16%	10–15%	10–12%
(g/kg/day)	0.8–1.2	1–1.5	1.2–2.0	1.7–2.2	1.5–2.0
Fat (%)	<30%	25–30%	22–30%	<30%	25–30%
(g/kg/day)	1.0–1.2	1–1.35	1–1.5	1.5–2.0	1.5–2.2

Adapted from Kreider [3]

Macronutrients and Micronutrients for Athletes

Carbohydrate

Carbohydrates are the primary fuel source for high-intensity, intermittent, or prolonged exercise. Carbohydrate is stored in the muscle (~15 g/kg) and liver (~80–100 g) [17]. During intense exercise, (around 75–85% of the aerobic capacity) muscle and liver glycogen stores are depleted, and dietary carbohydrate intake can replenish these stores. However, when significant amounts of carbohydrate are depleted, it may be difficult to fully replenish carbohydrate levels within 1 day. Consequently, when athletes train once or twice per day frequently (over a period of consecutive days), carbohydrate levels may gradually decline leading to fatigue, poor performance, and/or overtraining [17, 18].

Many athletes consume only about 3–5 g/kg/day of carbohydrate during training. While this may be sufficient for some, athletes involved in intense training (e.g., 2–3 h per day of intense exercise performed 5–6 times per week) will likely need to consume a diet consisting of 5–8 g/kg/day or 250–1200 g/day (for 50–150 kg athletes) of carbohydrate to maintain liver and muscle glycogen stores [19–21] and prevent decrements in performance. Research has indicated athletes involved in high-volume, intense training (e.g., 3–6 h per day of intense training in 1–2 daily workouts for 5–6 days per week) may need to consume 8–10 g/day of carbohydrate (i.e., 400–1500 g/day for 50–150 kg athletes) to maintain muscle glycogen levels [17, 18, 20, 22]. Athletes engaged in high-volume, intense training should eat frequently (e.g., 4–6 meals per day) and ingest high-calorie, carbohydrate foods and/or concentrated carbohydrate drinks. Preferably, the majority of dietary carbohydrate should come from whole grains, vegetables, and fruits, while quick gastric-emptying foods and possibly some high-glycemic index foods (e.g., refined sugars), some starches, and engineered sports nutrition products should be reserved for situations in which glycogen resynthesis needs to occur at accelerated rates [23]. In these situations, the absolute delivery of carbohydrate (>8 g of carbohydrate/kg/day or at least 1.2 g of carbohydrate/kg/h for the first 4 h into recovery) takes precedence over other nutritional and supplemental strategies such as those that may relate to timing or concomitant ingestion of other macronutrients (e.g., protein) or non-nutrients (e.g., caffeine) or carbohydrate type (e.g., glycemic index) [16, 20].

In terms of carbohydrate provision during exercise, the following key factors should be considered. Previous research has indicated athletes can oxidize carbohydrates at a rate of 1–1.1 g/min or about 60 g/h when undergoing prolonged bouts (2–3 h) of exercise training [24]. Several reviews advocate the ingestion of 0.7 g/kg/h of carbohydrate during exercise in a 6–8% solution (i.e., 6–8 g per 100 mL of fluid) [20, 24–26]. It is well established that various types of carbohydrates can be oxidized at different rates in skele-

tal muscle due to the involvement of different transporter proteins responsible for carbohydrate uptake [27–31]. Interestingly, combinations of glucose and sucrose, or maltodextrin and fructose, have been demonstrated to promote greater exogenous carbohydrate oxidation rates compared to single sources of carbohydrate (e.g., glucose only) [27–35]. These studies generally indicate a 1–1.2: 0.8–1.0 maltodextrin:fructose ratio, which seems to support the greatest rates of carbohydrate oxidation during exercise. Additional research on high molecular weight amylopectin indicates there may be a benefit to the lower osmolality of the starch, allowing for greater consumption (100 g/h) and possibly greater oxidation rates and performance improvement [36–39].

In addition to oxidation rates and carbohydrate types, fasting status and the exercise bout volume (i.e., the intensity and duration) are key variables for athletes and coaches to consider. In terms of exercise duration, reviews have documented bouts of moderate-to-intense exercise need to reach durations that extend well beyond 90 min of exercise before additional carbohydrate intake consistently yields an ergogenic outcome [24, 40, 41]. However, not all studies indicate shorter (60–75 min) bouts of higher intensity work may benefit from carbohydrate delivery. Currently, the mechanisms surrounding these findings are thought to be a replenishment of depleted carbohydrate stores during exercise bouts of longer duration of moderate intensities. On the other hand, for benefits seen during shorter, more intense bouts are thought to operate in a central fashion (i.e., central nervous system, neurocognition, perceived exertion). Additionally, these reviews have pointed to the impact of fasting status on documentation of ergogenic outcomes [24, 40, 41]. In this respect, when study protocols require participants to commence exercise in a fasted state, ergogenic outcomes are more consistently reported, yet other authors have questioned the ecological validity of this approach for competing athletes [42].

The need for optimal carbohydrates in the diet for athletes seeking maximal physical performance is unquestioned. Daily carbohydrate consumption is arguably the first and most important nutritional practice for any competitive athlete, and appropriate amounts of carbohydrate should be consumed to ensure readiness, recovery, and optimal performance. As exercise durations surpass the 2 h mark, the need to deliver carbohydrate increases, particularly when commencing exercise in a fasted state or when recovery is insufficient. Additional carbohydrate intake can help limit the likelihood of protein degradation for energy as well as maintain exercise intensity. Upon exercise cesassion, several dietary strategies should be considered to maximally replace muscle and liver glycogen stores, particularly when there is limited time to recovery. In these situations, the first priority is to rapidly replenish muscle and liver glycogen stores via carbohydrate consumption. Other strategies such as ingesting protein with lower carbohydrate amounts, carbohydrate and creatine co-ingestion, and/or certain forms of carbohydrate may help to facilitate rapid replacement of lost glycogen.

Protein

There is considerable debate regarding the amount of protein needed in an athlete's diet [43–47]. Initially, the recommendation for athletes did not need to exceed the RDA for protein (i.e., 0.8–1.0 g/kg/d for children, adolescents, and adults). However, research spanning the past 30 years has indicated athletes engaged in intense exercise training and sport may benefit from ingesting double the RDA amount (1.4–1.8 g/kg/d) to maintain positive protein balance [9, 43, 44, 46, 48–53] as well as promote muscle protein synthesis. Insufficient protein consumption can lead to a negative nitrogen balance, which indicates protein catabolism and may result in slow recovery. Over time, this can lead to muscle wasting, injuries, illness, and training intolerance [49, 50, 54].

The present body of literature indicates optimal protein intakes may fall within the range of 1.2–2.0 g/kg/day [9, 49, 52, 55]. Morton and investigators [56] conducted a meta-review and meta-regression including 49 studies and 1863

participants and concluded a protein intake of 1.62 g/kg/day may be an ideal target, as higher intakes likely will not provide further benefit (i.e., increases in fat-free mass). Athletes participating in moderate intensity exercise training should consume 1.2–2.0 g/kg/day of protein (60–300 g/day for a 50–150 kg athlete) while athletes involved in high-volume, intense exercise training are recommended to consume 1.7–2.2 g/kg/day of protein (85–330 g/day for a 50–150 kg athlete) [51, 57]. Smaller athletes likely consume an optimal amount of protein on a daily basis in their normal diet; however, larger athletes tend to struggle to consume an adequate amount of protein considering their requirements are increased with respect to body mass. Moreover, several athletic populations are susceptible to protein malnutrition (e.g., runners, cyclists, swimmers, triathletes, gymnasts, dancers, skaters, wrestlers, boxers) and, consequently, need additional education and counseling to reinforce the importance of meeting their daily protein needs. This is particularly true for athletes involved in sports that require periods of energy restriction to meet weight requirements as well as sports where esthetic appearances may encourage athletes to restrict energy intake. Provision and timing of protein intake and the quality of protein are important to athletic performance and recovery. Additionally, combining protein with carbohydrate is particularly important for maintaining lean body mass, training effects, and performance [58]. Protein timing may also play an essential role with slower release protein sources taken before beditime. For example, casein is typically digested and utilized over a period of 4 h or more, while whey, a faster protein source, is digested within 1–2 h after consumption. Thus, care should be given to ensure athletes consume sufficient amounts of protein in their diet to maintain positive nitrogen balance.

There are different strategies athletes can use to ensure they ingest sufficient amounts of protein, which include supplementing their diet with protein powders or other forms of protein supplements. This practice is not considered to be an absolute requirement for increased performance and adaptations, and it should not be encouraged to fully replace food protein sources with supplementation. Considering various nutritional, societal, emotional, and psychological reasons, it is preferable for the majority of daily protein consumed by athletes to occur as part of a food or meal. However, certain situations arise where efficiently delivering a high-quality source of protein takes precedence and might warrant supplementation. Jäger and colleagues [9] published an updated position statement of the ISSN regarding protein recommendations, which summarized by the following points:

1. An acute exercise stimulus, particularly resistance exercise and protein ingestion, both stimulate Muscle Protein Synthesis (MPS) and are synergistic when protein consumption occurs before or after resistance exercise.
2. For building and maintaining muscle mass, an overall daily protein intake of 1.4–2.0 g/kg/day is sufficient for most exercising individuals.
3. Higher protein intakes (2.3–3.1 g/kg fat-free mass/day) may be needed to maximize the retention of lean body weight in resistance-trained subjects during hypocaloric periods.
4. Higher protein intakes (>3.0 g/kg/day), when combined with resistance exercise, may have positive effects on body composition in resistance-trained individuals (i.e., promote loss of fat mass).
5. Optimal doses for athletes to maximize MPS are mixed and are dependent on age and recent resistance exercise stimuli. General recommendations are 0.25–0.55 g of a high-quality protein per kg of body weight, or an absolute dose of 20–40 g per serving with at least a 3 h separation between doses.
6. Acute protein doses should contain 700–3000 mg of leucine and/or a higher relative leucine content, in addition to a balanced array of the essential amino acids (EAAs).
7. Protein doses should ideally be evenly distributed, every 3–4 h, across the day.
8. The optimal time period during which to ingest protein is likely a matter of individual tolerance; however, the anabolic effect of

exercise is long-lasting (at least 24 h), but likely diminishes with increasing time postexercise.
9. Rapidly digested proteins that contain high proportions of EAAs and adequate leucine are most effective in stimulating MPS.
10. Different types and qualities of protein can affect amino acid bioavailability following protein supplementation; complete protein sources deliver all required EAAs.

Fat

The dietary recommendations for fat intake for athletes are similar to the dietary recommendations for nonathletes. Maintaining energy balance, replenishment of intramuscular triacylglycerol stores, and adequate consumption of essential fatty acids are important considerations for athletes, and it might be recommended to increase dietary fat intake to match the demands of their respective sport [59]. Depending upon the athlete's training status and goals, the recommended amount of dietary fat to be ingested may change. For example, better maintenance of circulating testosterone concentrations appears to result from high-fat diets compared to low-fat diets [60–62]. Additionally, higher fat intakes may provide valuable translational evidence to the documented testosterone suppression, which can occur during volume-type overtraining [63]. Generally, it is recommended athletes consume moderate amounts of fat (~30% of their daily caloric intake), and proportions up to 50% of daily energy intake from fat can be safely ingested and tolerated by athletes engaged in regular high-volume training [59]. During periods in which an athlete wishes to reduce his or her body fat, dietary fat intakes ranging from 0.5 to 1 g/kg/day (or 20% of total calories) are recommended [64]. Evidence from weight-loss studies involving nonathletic individuals support this range of dietary fat intake for reductions in body fat. It is plausible that individuals seeking to lose weight and/or maintain the weight loss might have success when reducing the amount of fat in their diet [65, 66] although this is not always the case [67]. Reducing dietary fat likely results in weight loss due to an induced caloric deficit. The 2017 ISSN position stand on diets and body composition has comprehensively outlined the literature regarding the effects of diet types (macronutrient composition) and the respective influences in regard to fat loss [68]. Importantly, the present body of literature highlights diet-induced weight loss (fat loss) is driven by a sustained caloric deficit [68]. Strategies to help athletes manage dietary fat intake include teaching them which foods contain various types of fat and how to recognize foods that contain "hidden fat" so that they can make better food choices and how to count fat grams [18, 64].

For years, high-fat diets have been used by athletes with the majority of the evidence showing no ergogenic benefit and consistent gastrointestinal challenges [69]. In recent years, significant debate has swirled regarding the impact of increasing dietary fat. One strategy, "train low, compete high," refers to an acute pattern of dietary periodization whereby an athlete first follows a high-fat, low-carbohydrate diet for 1–3 weeks while training before reintroducing carbohydrates back into the diet. While intramuscular adaptations result from that may theoretically impact performance [70, 71], no consistent, favorable impact on performance has been documented [69, 72]. Ketogenic diets are a variant of high-fat diets that have increased in popularity. While no exact prescription exists, nearly all ketogenic diet prescriptions derive at least 70–80% of their daily calories from dietary fat and prescribe a moderate amount of protein (20–25% total calories or 2.0–2.5 g/kg/day). This diet prescription is largely devoid of carbohydrate (10–40 g/day) which can limit the intensity of exercise. The diet leads to a greater reliance on ketones as a fuel source. Currently, there is limited and mixed evidence regarding the overall efficacy of a ketogenic diet for athletes. In favor, Cox et al. [73] demonstrated that ketogenic dieting can improve exercise endurance by shifting

fuel oxidation, while Burke and colleagues [72] failed to show an increase in performance in a cohort of Olympic-caliber race walkers. Additionally, Jabekk and colleagues [74] reported decreases in body fat with no change in lean mass in overweight women who followed a ketogenic diet for 10 weeks while carrying out resistance training. Nevertheless, dietary fat recommendations for athletes are generally at least 20% of daily energy intake and 0.5–1.5 g/kg/day.

Vitamins

The typical American diet may not provide all the necessary nutrients and there has been some concern from the medical community that the recommended daily intakes (RDI) are insufficient and need to be increased [75]. Athletes engaged in heavy training have also been found to be susceptible to vitamin deficiencies, particularly if they are training while maintaining a hypocaloric diet [16, 76, 77]. Vitamin deficiencies can reduce physical performance, usually by interfering with the energy process and/or increasing susceptibility to colds and infections. In general, vitamin supplements are not needed in healthy, well-nourished individuals (except for folic acid and iron during pregnancy) and in many elderly individuals (vitamin D) who are not exposed to sunlight or consuming adequate dairy products. However, it has been suggested that all Americans take a low-dose, one-a-day multivitamin to prevent deficiency of key nutrient needs [75]. Since athletes have been reported to have greater needs for certain vitamins and minerals, the International Society of Sports Nutrition recommends that athletes consume a low-dose multivitamin during intense training, particularly if they are maintaining an energy deficit or trying to lose weight to prevent deficiency and ensure nutrient needs are met [16]. Furthermore, a vitamin supplement analysis should be taken into account for athletes since overconsumption of some vitamin supplements that exceed the upper limit can be prevalent among athletes and cause health problems [78].

Nutritional Strategies

Table 29.2 summarizes nutrient timing strategies for athletes. It is critical that athletes maintain a high-carbohydrate, moderate-protein, and low-to-moderate-fat (~25–30% total energy intake) diet to ensure that macronutrient guidelines are met as shown in Table 29.1. Pretraining or precompetition meals should be ingested 3.5–4 h prior and become more liquid-based as the competition/training time approaches. Additionally, pre-exercise or pretraining carbohydrate, moderate-protein, low-fat snacks, and fluids (with electrolytes) should be provided to athletes as they arrive at practice or competition. It is critical to ensure the athlete(s) are well hydrated and provided some carbohydrate and protein prior to exercise in an effort to spare muscle glycogen stores and minimize exercise-induced muscle

Table 29.2 Recommended nutritional strategies for athletes

General diet
• Maintain high-carbohydrate, moderate-protein, low-fat diet that meets macronutrient intake goals.
• Taper training (30–50%) and carbohydrate load prior to competition.
Pretraining/competition meal (3.5–4 h before event)
• High-carbohydrate, moderate-protein, low-fat meal.
Pre-exercise (30–60 min before training/competition)
• 20–30 g carbohydrate
• 10–20 g protein
During exercise
• Water (<90 min).
• Sports drinks (>90 min and in hot/humid environments).
• Carbohydrate/Protein gels (intermissions).
After Exercise (within 30 min)
• 20–40 g of protein
• 60–120 g of carbohydrate
Post-exercise meal
• High-carbohydrate, moderate-protein, low-fat meal.
Pre-bed nutrient intake
• 30–40 g of carbohydrate
• 20–30 g of protein (primarily casein with some whey).

Adapted from Kreider [3]

catabolism. During practice or training bout, water and/or sports drinks should be readily available, as well as during competitive events or games. Athletic trainers and strength and conditioning coaches need to make sure plenty of water breaks are built into practices and/or athletes should have easy access to plenty of water or sports drinks. Preferably, athletes should consume fluids every 15–20 min during practice and/or competition, particularly if the athlete is training or competing in a hot and humid environment. Typically, if the duration of exercise is in the range 60–90 min, water can make up the bulk of the hydration; however, if training occurs under hot/humid conditions, it is important to factor in electrolyte replenishment. The use of sports gels containing carbohydrate (10–30 g) and protein (5–10 g with or without essential amino acids), or easily digestible energy bars, may also help to fuel energy needs. Following training or competition, it is important to provide carbohydrate and protein within the first 30 min to begin replenishing glycogen as well as provide amino acids for muscle protein synthesis and to reduce muscle catabolism. Typically, Ready-to-Drink drinks (RTD), energy bars, and fruit are consumed to meet these needs. Within 2 h of the exercise bout, the athlete should consume a high-carbohydrate meal with a quality, low-fat protein source. Finally, for athletes engaged in intense training and/or wanting to maximize muscle protein synthesis, it is recommended they consume a light meal and/or Meal Replacement Powder (MRP) or RTD that contains 30–40 g of carbohydrate with 20–30 g of protein (preferably casein) before they go to bed to further stimulates muscle protein synthesis and reduces fasting-related catabolism. This type of meal and nutrient timing should be planned prior to competition in order to optimize performance and recovery.

Promote Hydration

Promoting hydration is a key principle in optimizing the performance of athletes as well as preventing dehydration during exercise, which can compromise the performance and overall health of the athlete. Inadequate fluid replacement can lead to acute and/or chronic dehydration. A fluid loss of 2% of body weight (e.g., 3.6 lbs. [1.6 kg] for 180 lbs. [81.7 kg] individual) can reduce performance capacity and promote heat illness (i.e., cramping, heat syncope, and/or heat exhaustion). Fluid losses of 2–4% (proportion of body weight loss) or greater can lead to heat stroke and/or death. Consequently, athletes need to drink enough fluids (preferably cold or cooler fluids) prior to, during, and following training to maintain hydration. Hotter and more humid environments reduce the evaporation of sweat and increase the core temperature requiring a greater need for fluid replenishment and electrolytes. However, it should be noted that heat exhaustion and heat stroke can also occur in moderate conditions. Thirst is not a good indicator of hydration status. It is often that most people do not get thirsty until they have already become dehydrated. Consequently, it is important to plan fluid intake (6–8 oz) intervals 10–15 min during exercise. It is important to note the consumption of excess water can cause a dilution of sodium and other electrolytes in the blood resulting in a dangerous condition known as hyponatremia. It is also important to weigh athletes prior to and following exercise sessions when training or competing in hot and humid environments to account for the percent body weight lost. Every pound lost during exercise represents 3 cups of fluid the athlete should have ingested during exercise to offset fluid loss. While it is difficult to replenish all of the fluid lost during exercise, the goal should be to avoid more than 1–2% of weight loss during the workout session. If an athlete loses more than 2% of body weight during exercise, his or her performance will suffer and he or she is at greater risk of heat-related illness. Athletes should also try to ingest enough fluids to regain their lost weight before the next practice or workout. Beginning practice or competition fully hydrated and ensuring the ingestion of enough fluid to prevent dehydration is one of the most effective ways to optimize performance.

Promote Recovery

Optimizing recovery following intense exercise and during training has emerged recently as an area of focus in sport nutrition. Generally, nutritional support such as replenishing muscle and liver glycogen stores, stimulating muscle protein synthesis, promoting rehydration, and planning rest and recovery into an athletes' training program are practices used to lessen exercise-induced inflammation and immunosuppression. While many of the principles described above will assist in this process, a number of additional nutritional and supplemental strategies have been studied to determine potential benefits that might afford athletes a competitive edge. Studies have examined whether ingesting carbohydrate [79, 80], amino acids [81, 82], creatine [83, 84], L-carnitine tartrate [85–87], and fish oil [88] during heavy training periods promote recovery and/or improve an athlete's ability to maintain heavy training loads. The following outlines some of the supplements used to promote recovery. For a more comprehensive review of the literature the reader is directed to the ISSN position stand from 2018 [16].

Creatine.

While the ergogenic benefits of creatine are well-documented [6], it has also been purposed to aid an athlete's recovery from intense training. Green et al. [89] found 5 g of creatine with large amounts of glucose (95 g)-enhanced muscle creatine and carbohydrate stores. Creatine loading prior to exhaustive exercise bouts in addition to glycogen loading has been reported to promote greater glycogen restoration, which is an important factor in promoting recovery and preventing overtraining [90]. Additionally, Cooke et al. [84] reported noted greater isokinetic and isometric knee extension strength following an exercise-induced muscle damaging protocol, as well as significantly lower creatine kinase levels after 2, 3, 4, and 7 days of recovery in the group that supplemented with creatine versus control. Lastly, creatine supplementation has been reported to less inflammatory markers such as TNF- α and prostaglandin E2 [91] as well as inhibit the increase in c-reactive protein in response to intense exercise [92]. These findings suggest creatine supplementation may help an athlete enhance glycogen restoration, less inflammation following intense exercise bouts, and enhance recovery while preventing overtraining.

Essential Amino Acids

It is important for an athlete to maintain a positive protein balance by ingesting protein containing high amounts of essential amino acids (EAA) following intense exercise bouts. Researchers have demonstrated ingestion of protein or EAA following exercise (i.e., a resistance training bout) can substantially increase amino acids levels in blood and muscle, which results in maintenance of a positive protein balance [93, 94] and increases amino acid availability and muscle protein synthesis [95–98]. Moreover, the addition of carbohydrates appears to enhance the increase in muscle protein synthesis [99, 100]. Based on the current evidence, high-quality protein or EAA is an important nutritional strategy to promote recovery from an intense bout of exercise via stimulation of muscle protein synthesis.

Tart Cherry

Tart cherry juice supplementation has emerged as a potential aid to recovery following muscle-damaging exercise bouts due to potent antioxidant and inflammatory properties. Athletes who supplemented with tart cherry juice demonstrated improved recovery of maximal voluntary isometric contraction, countermovement jump, and agility, as well as attenuated delayed onset muscle soreness and reduced interleukin 6 concentrations [101]. In terms of resistance training, 8-day tart cherry supplementation resulted in attenuated strength loss and exercise-induced muscle pain compared to placebo [102]. We have also evaluated whether tart cherry supplementation (containing natural anti-inflammatories) reduces markers of inflammation associated with half-marathon performance and intense resistance exercise training [103, 104]. Short-term Montomorency powdered tart cherry supplementation appears to effectively attenuate muscle soreness, strength decrements during periods of recovery, and mark-

ers of catabolism following a single bout of resistance exercise among resistance-trained individuals [103]. With respect to aerobically trained individuals, Montmorency-powdered tart cherry supplementation attenuated muscle catabolism markers, reduced immune and inflammatory stress, and improved performance [104].

Fish Oils

Omega-3 fish oil supplementation has gained popularity for its potent anti-inflammatory effect and association with reduced coronary heart disease risk. Fish oils contain both eicosapentaenoic acid (EPA) and docosahexenoic acid (DHA), and a 2:1 ratio of EPA to DHA has been suggested to attenuate exercise-induced muscle damage when supplemented with chronically (i.e., 8-weeks duration) [105]. Several studies have demonstrated omega-3 fatty acid supplementation attenuates exercise-induced muscle damage [88, 106–108], which suggests that omega-3 fatty acids can aid an athlete to promote recovery following intense bouts of exercise.

While these strategies may not affect acute exercise performance in the traditional sense, they may allow athletes to recover faster, stay healthier, and/or maintain higher training volumes leading to greater gains over time. Thus, one of the principles in optimizing performance is to make sure that athletes incorporate enough rest and sleep into their training program as well as nutritional strategies that can help them recover, stay healthy, and tolerate the demands of training and competition. Recovery nutrition is a critical component to keeping an athlete healthy and ready for competition. Provisions and timing of nutrients are important for an athlete to consider to optimize performance.

Nutrient Timing

The final key principle in optimizing the diet of athletes is to properly time nutrient intake to augment physiological responses to exercise and promote recovery. Research has demonstrated that timing and composition of meals consumed may play an important role in optimizing performance, training adaptations, and preventing overtraining [17, 58, 64]. In this regard, it takes about 4 h for carbohydrate to be digested and assimilated into muscle and liver tissues as glycogen. Consequently, pre-exercise meals should be consumed about 4–6 h before exercise [17]. This means that if an athlete trains in the afternoon, breakfast can be viewed to have great importance to top off muscle and liver glycogen levels. Research has also indicated that ingesting a light-carbohydrate and protein snack 30–60 min prior to exercise (e.g., 50 g of carbohydrate and 5–10 g of protein) serves to increase carbohydrate availability toward the end of an intense exercise bout [109, 110]. This also serves to increase the availability of amino acids, decrease the exercise-induced catabolism of muscle protein, and minimize muscle damage [111–113]. Additionally, athletes who are going through periods of energy restriction to meet weight or esthetic demands of sports should be aware that protein intake, quality, and timing, as well as in combination with carbohydrate, are particularly important to maintain lean body mass, training effects, and performance [58]. When exercise lasts more than 1 h, and especially as duration extends beyond 90 min, athletes should ingest glucose/electrolyte solutions (GES) to maintain blood glucose levels, prevent dehydration, limit muscle protein breakdown for glucose (gluconeogenesis), and reduce the immunosuppressive effects of intense exercise [17, 114–119]. Notably, this strategy becomes even more important if the athlete is under-fueled or in a fasted state at the start of exercise [40, 41, 120]. Following intense exercise, athletes should consume carbohydrate and protein (e.g., 1 g/kg of carbohydrate and 0.5 g/kg of protein) within 30 min after exercise and consume a high-carbohydrate meal within 2 h following exercise [47, 64]. This nutritional strategy has been found to accelerate glycogen resynthesis as well as promote a more anabolic hormonal profile that may hasten recovery [111, 121, 122], but, as mentioned above, only when rapid glycogen restoration is needed or if the carbohydrate intake in the diet is inadequate (i.e., < 6 g/kg/day) [23, 123]. In other words, the total carbohydrate consumption

and its timing should be individualized to each athlete's needs according to the goals of the training cycle and bout [69]. Finally, for 2–3 days prior to competition, athletes should taper training by 30–50% and consume an additional 200–300 g of carbohydrate each day. This strategy has been shown to supersaturate carbohydrate stores prior to competition and improve endurance exercise capacity [17, 64]. Thus, the type of meal, amount of carbohydrate consumed, and timing of consuming meals and snacks are important factors to maximize glycogen storage and maintain carbohydrate availability during training while also potentially decreasing the incidence of overtraining [1, 124, 125].

Additionally, in the recent 2018 International Society of Sports Nutrition (ISSN) review [16], the ISSN adopted a position stand on nutrient timing in 2008 [11] that has been subsequently revised [12] and can be summarized with the points below.

1. Intramuscular and hepatic glycogen stores are best maximized by the consumption of a high-carbohydrate diet (8–12 g/kg/day). Strategies such as aggressive carbohydrate feedings (~1.2 g/kg/h) that favor high-glycemic (>70) carbohydrates, the addition of caffeine (3–8 mg/kg), and combining a moderate carbohydrate dose (0.8 g/kg/h) with protein (0.2–0.4 g/kg/h) have been shown to promote rapid restoration of glycogen stores.
2. High-intensity (>70% peak aerobic capacity) exercise bouts that extend beyond 90 min challenge fuel supply and fluid regulation. In these situations, it is advisable to consume carbohydrate at a rate of 30–60 g/h of carbohydrate in a 6–8% carbohydrate-electrolyte solution (6–12 fluid ounces) every 10–15 min throughout the entire exercise bout. The importance of this strategy is increased when poor feeding or recovery strategies were employed prior to exercise commencement. Consequently, when carbohydrate delivery is inadequate, adding protein may help increase performance, mitigate muscle use for glucose, promote euglycemia, and facilitate glycogen resynthesis.
3. Consuming a diet that delivers adequate energy (minimum of 27–30 kcal/kg) and protein (1.4–2.0 g/kg/day), preferably with evenly spaced (every 3–4 h) protein feedings (0.25–0.40 g/kg/dose) during the day, should be considered for all exercising individuals.
4. Ingesting efficacious doses (10–12 g) of EAAs, either in free form or as a protein bolus in 20–40 g doses (0.25–0.40 g/kg/dose), will maximally stimulate MPS.
5. Pre- and/or postexercise nutritional interventions (carbohydrate + protein or protein alone) can be an effective strategy to support improvements in strength and body composition. However, the size (0.25–0.40 g/kg/dose) and timing (0–4 h) of a pre-exercise meal may impact the benefit derived from the postexercise protein feeding.
6. Postexercise ingestion (immediately post to 2 h post) of high-quality protein sources stimulates robust increases in MPS. Similar increases in MPS have been found when high-quality proteins are ingested immediately before exercise.

Proposed Nutritional Ergogenic Aids

In addition to provisions and nutrient timing, a number of nutritional ergogenic aids have been shown to enhance performance and/or training adaptations. Table 29.3 summarizes dietary supplements that are effective/safe, possibly effective/safe, and noneffective based on the current literature. As outlined in Table 29.4 the Exercise and Sport Nutrition Laboratory (ESNL) and ISSN recommend strength/power and endurance athletes add various nutritional supplements to their training program, when appropriate, to optimize performance, recovery, and readiness. Creatine, β-alanine, sodium bicarbonate, and nitrates have been shown to improve high-intensity exercise performance [126–131]. Additionally, ingestion of caffeine or caffeine-containing supplements (i.e., pre-workouts) may also improve cognitive focus and the quality of a workout. For endurance athletes, optimizing gly-

Table 29.3 Summary of categorization of dietary supplements based on available literature

Category	Muscle building supplements	Weight-loss supplements	Performance enhancement
Effective/safe	Weight-gain powders Creatine Protein EAA Calcium HMB (untrained individuals initiating training and elderly)	Pre-packaged meals Dietary fiber Low-calorie foods, MRPs, and RTDs Ephedra, caffeine, and salicin-containing thermogenic supplements taken at recommended doses in appropriate populations Ephedra (with ephedrine alkaloids)[a] Green tea Guarana	Water and sports drinks Carbohydrate Creatine Sodium bicarbonate Sodium phosphate Caffeine β-Alanine Energy drinks and pre-workouts
Possibly effective/safe	Adenosine-5′-triphosphate Branched chain amino acids Calcium β-HMB (among trained Individuals)	Beta-D-glucans Chitosan Glucomannan Guar gum Gum arabic Inulin Pectin Psyllium Phaseolus vulgaris Betaine Calcium pyruvate (high dose) Conjugated linoleic acids Dichrostachys glomerata Garcinia cambogia Yohimbine Capsaicin Citrus aurantium	Postexercise carbohydrate and protein L-Alanyl-L-glutamine Arachidonic acid Citrulline Phosphatidic acid Glutathione Glycine-L-arginine-alpha-keotosiocaproic acid B-Hydroxy-β-methylbutyrate Nitrates Quercetin Taurine EAA BCAA HMB Glycerol
Noneffective	Admatine sulfate α- Glycerylphosphorylcholine α-Ketoglutarate α-Ketoisocaproate Arginine Conjugated linoleic acids D-aspartic acid Ecdysterones Fenugreek extract Gamma oryzanol GHRP and secretagogues Ornithine Smilax officinalis/sarsaparilla Isoflavones Glutamine Smilax Sulfo-polysaccharides (myostatin inhibitors) Boron Chromium CLA Gamma oryzanol Prohormones Tribulus terrestris Vanadyl sulfate (vanadium) Yohimbine Zinc/magnesium aspartate	Glycomarcopeptides Gymnema Sylvestre Hoodia gordonii Verbena officialis Lithospermum officinale, Taraxacum officinale [dandelion] Equiestum arvense Arctostaphylos uva-ursi Arctium lappa Silene saxifrage Phyllanthus sellowianus Muell. African mango extract Calcium pyruvate (at marketed doses) L-carnitine Chromium 7-keto DHEA Phosphatidyl choline Phosphatidylserine Sesamin Tetradecylthioacetic acid St. John's wort Kava Ginkgo biloba Ginseng	Glutamine Ribose Inosine Arginine Carnitine Gamma Aminobutyric acid Hydroxyisoleucine Medium-chain triglycerides Theanine

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[a] Banned by the FDA for sale in dietary supplements

Table 29.4 Dietary supplements shown to enhance performance and/or training adaptations in strength/power athletes, endurance athletes, and promote recovery

Strength/power athletes	Endurance athletes	Recovery nutrition
• Moderate-to-high CHO/PRO diet	• High CHO diet	• Rehydrate.
• Water/sports drinks	• Carbohydrate loading (HMW CHO)	• Carbohydrate.
• Postexercise PRO/EAA	• Water/sports drinks/gels	• Postexercise PRO/EAA.
• Creatine	• Caffeine	• Creatine.
• β-Alanine	• Sodium phosphate	• Tart cherry.
• Sodium bicarbonate	• Nitrates (beetroot juice)	• Omega-3 fatty acids.
• Nitrates (beetroot juice)	• Creatine	

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cogen stores via carbohydrate loading remains a primary emphasis. The ESNL recommends using high molecular weight (HMW) carbohydrate supplements, such as Vitargo, to optimize glycogen resynthesis, particularly when training and/or competing with only 1–2 days of recovery. Additionally, creatine and anti-inflammatory supplements, such as tart cherry and omega-3 fatty acids, may help athletes to tolerate heavy training periods. Finally, since intense exercise often suppresses the immune system, it is important to ingest nutrients that support a healthy immune system.

Summary

Nutritional and supplemental practices of athletes can significantly affect exercise performance, recovery, readiness, and overall health. In order to optimize performance, athletes should: (1) consume a diet sufficient in calories to offset energy expenditure (typically 50–80 kcal/kg/day); (2) consume adequate amounts of carbohydrates (5–10 g/kg/day), proteins (1.4–2.0 g/kg/day), and fats (0.5–1.5 g/kg/day); (3) ingest meals and snacks at appropriate time intervals before, during, and/or after exercise in order to replenish energy stores as well as promote recovery following exercise; and (4) only consider using nutritional supplements that have been found to be an effective and safe means to improve performance capacity.

Table 29.3 presents the ISSN's recommendation regarding nutrients that have been shown to be: effective; possibly effective; and apparently ineffective or potentially dangerous [2]. The foundation for good performance begins with a good diet and intelligent training. For strength/power athletes, research has indicated water, carbohydrate, post- and pre-exercise carbohydrate/protein intake, and creatine monohydrate may have the greatest impact on optimizing performance and training adaptations. Additionally, sodium phosphate and sodium bicarbonate are among other potentially beneficial strategies to impact performance. For endurance athletes, research suggests carbohydrate loading, water/GES sports drinks, caffeine, sodium phosphate loading, and possibly the use of glycerol in an attempt to hyper-hydrate prior to exercise may offer some ergogenic value. Sports drinks, carbohydrate, postexercise carbohydrate with protein or EAA, creatine, and beta-hydroxy beta-methylbutyric acid (HMB) have been reported to help athletes tolerate exercise and training. In addition, post and pre-exercise carbohydrate, protein, EAA, and glutamine, as well as vitamin C and zinc, help athletes maintain a healthy immune system during training. The use of these strategies can help optimize performance and/or help athletes tolerate intense periods of training.

Acknowledgments This chapter is a representation of updates to a number of articles and book chapters researchers in the ESNL have developed over the recent decade. This chapter incorporates guidelines developed as position stands by a number of colleagues for the International Society of Sports Nutrition. While we could not acknowledge everyone's contributions to this work, the authors would like to thank the students, colleagues, and research participants who have contributed to the research and exercise and sport nutrition guidelines presented in this chapter.

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Influence of the Food Industry: The Food Environment and Nutrition Policy

Julia McCarthy

Key Points

- Unhealthy foods and beverages are ubiquitous and unavoidable.
- They shape social norms, food preferences, and, ultimately, health.
- Through payments, relationships, and research, food and beverage manufacturers can strongly influence the food environment and national nutrition policy in their favor.
- Supermarkets are one of the most important places where Americans acquire food.
- In this setting, food and beverage manufacturers exert influence through trade promotion fees; direct store delivery (DSD) and category management; and, more recently, personalized data.
- Various actions in the political arena also help to ensure that food industry interests hold sway.
- These include spending on political campaigns, lobbying, and sponsorships; relationships developed through the revolving door; and the publication of self-serving research.
- Recent policy actions, like sugary drink taxes and dollar store restrictions, could help to ensure that, ultimately, public health interests prevail over special interests.

Introduction

On your daily commute, you may forgo the glazed donut at Dunkin' only to discover your caffeinated mocha has even more calories than the donut. Opening a new browser on your computer, you may find an advertisement suggesting that you reorder the chips purchased for a past party. After work, waiting to fill your prescription at the drug store, you resist rows of Reese's Pieces and Red Hots at the checkout. Watching television later that night you are subject to a barrage of commercials for candy and cola.

Trying to eat healthily in modern, industrialized nations can feel like swimming upstream. The food environment undermines our best intentions, exposing us to unhealthy food and beverages in schools, airports, and sports arenas; by way of sponsor billboards at concerts, community events, and outdoor festivals; and through advertisements on the radio, in print, on websites, and through our mobile devices. Exposure to unhealthy products is ubiquitous and unavoidable. It shapes our social norms, determines our food preferences, and, ultimately, predicts our future health [1].

Federal, state, and local governments are charged with protecting the public from harm. But supporting dietary health is difficult when industry exerts tremendous influence over the places where people purchase and consume food, as well as the public institutions responsible for protecting

J. McCarthy (✉)
New York Health Foundation, New York, NY, USA
e-mail: mccarthy@nyhealthfoundation.org

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_30

health. This chapter explores how, through payments, relationships, and research, food and beverage manufacturers shape both the food environment and national nutrition policy in their favor.

This chapter examines the problem of corporate influence in four parts. The first provides a brief background on why unhealthy food and beverages are so prevalent. The second part helps make the case for policy by focusing on industry's influence over the main source of people's food and beverages—the supermarket. Specifically, this section discusses how food and beverage manufacturers pay trade promotion fees, cozy up to retailers through such practices as direct store delivery and category management, and use personalized data to undermine healthy eating. The third section explains the various tactics that industry uses to undercut national nutrition policy—how payments to political powerbrokers, questionably close relationships with regulators, and industry-sponsored research stymy the timely development of effective policy. The fourth and final section explores policy actions at the federal, state, and local levels that could start to turn the tide toward healthy eating.

Swimming Upstream: The Ubiquity of Unhealthy Food and Beverages

In the United States, the number of calories available for each person each day is now almost double what is needed [2]. Foods that were scarce for most of human history—those high in salt, sugar, and fat—are now bountiful, and that bounty threatens health [3].

US farm subsidies are partially responsible for this bounty as they favor the production of commodities like corn, used to make high-fructose corn syrup, over "specialty crops" such as berries and broccoli. Commodities are attractive to companies, not only because subsidies make them cheaper but also because they are more easily processed, which may increase palatability, marketability, and consumption. Processing enables food and beverage manufacturers to increase profits, which is their primary goal in a free-market society, ironically a goal which subsidies erode. As one researcher explained: "The food industry has made a fortune because we retain Stone Age bodies that crave sugar, but live in a Space Age world in which sugar is cheap and plentiful." [4] In fact, a 2021 study of ultra-processed foods—packaged foods typically high in salt, sugar, and fat—found that food and beverage manufacturers peddle products with portion sizes that are up to five times larger than when they were first introduced [5].

In recent years, national lawmakers have passed landmark policies to protect consumers' health and improve the food environment. Some policies have improved product transparency, requiring added sugars to be disclosed on the back of products or securing calorie labeling on menus in restaurants. Others have gone further, removing *trans* fats from the food supply and updating the nutrition standards for meals served in schools and childcare settings. Still, officials have yet to successfully tackle the place where Americans acquire the largest proportion of their food: supermarkets.

Industry Influence at the Point of Purchase: The Supermarket

From both an industry and a public health perspective, supermarkets are a pinnacle of influence. Americans purchase more than 60% of their calories from these stores [6]. Though supermarkets sell a wide variety of healthy products, the majority of the consumable items these stores sell is unhealthy. They also contribute the majority of the unhealthy foods and beverages found in consumers' diets. Approximately 70% of the sugary beverages that children drink are purchased in food stores [7]. Supermarkets are also adults' greatest source of sugar-sweetened beverages and unhealthy snack foods [8].

One study that assessed in-store placement and promotion found that, on average, sugary drinks appear in 25 and unhealthy food in 40 different places across the store [9]. Another

study of a national chain that instituted a store-wide nutrition profiling system, Guiding Stars, awarding zero (low), one, two, or three stars to indicate products' healthfulness found that only 23% of items qualified for even a single star [10]. A single star is not a high bar; some potato chips even received one star [11]. Examining food and beverage companies' actions—the fees they pay, the relationships they cultivate, and the data they wield—helps to explain why in supermarkets, it is processed products, not the foods public health practitioners promote, that are prominent, prevalent, and priced to move.

Paying to Play: Trade Promotion Fees

Trade promotion fees are the primary means through which food and beverage manufacturers influence purchasing habits in the retail environment. These companies pay retailers more than $50 billion a year in trade fees and discounts to promote their packaged goods to consumers [12]. Trade promotion fees are the second largest expense for manufacturers, behind the cost of creating the product itself [13]. These fees skew the supermarket in favor of large manufacturers, those that typically produce highly processed food and beverages.

To illustrate this point, think about picking out the ingredients to make your own salsa to have with chips. If you forget to pick up the tomatoes or green peppers, you will not see them again once you leave the produce section. But if you choose to avoid the chip aisle, you will still see chips several times. End-of-aisle displays, free-standing cardboard crates, and the checkout will work to remind you to put those chips in your cart. The checkout area is typically the most expensive real estate in a store because every shopper must pass through it. A manufacturer can expect to pay several million dollars in trade promotion fees to place a single product on the shelf at the checkout [14]. These exorbitant marketing fees and their mark-up by the middleman are some of the reasons that healthier foods, such as fruits and vegetables, rarely appear outside of the produce section or in the most trafficked store areas. Produce companies and farmers who cannot afford these fees are not the only ones to lose out: consumers are exposed to fewer healthy options.

Trade promotion fees not only influence store layout; they also influence prices. Two-for-one deals, half-off sales, coupons—these are all methods that manufacturers make available to the retailer to ultimately entice customers to buy more and establish their product as part of a consumer's regular habits. Again, farmers are not paying these fees, so it is the chips, not the tomatoes, that are discounted. For people who must pay careful attention to food prices, this form of marketing is particularly powerful [15].

Cultivating Close Relationships with Retailers

Close relationships between manufacturers of shelf-stable, highly processed foods and retailers also help to explain why stores are saturated with salty, sugary, tempting foods. For example, by offering retailers direct store delivery (DSD), food and beverage manufacturers have gained greater influence over stocking and shelf space. Supermarkets operate on razor-thin margins, making between 1–2% profit. So when brands like Frito Lay offer to deliver, unpack, and arrange products directly onto store shelves, they reduce retailer labor costs. It is no surprise that retailers generally accept. It is also no surprise that so many Frito Lay products appear across the store.

Category management is another way manufacturers have been able to tie stores' sales so closely to their own [14]. With category management, the dominant manufacturer in a product category competes for the opportunity to track products' performance and to propose a shelf plan to the retailer. The category manager purchases data from companies like Nielsen that aggregate weekly pricing, volume, and store environment information across grocery chains. The category manager then analyzes industry-wide trends for the retailer to identify new prod-

ucts and determine pricing for a particular food category.

In theory, the category manager makes impartial recommendations not only about where their products should be placed on the shelves, but also about where their competitors' products are placed, and sometimes how those products are priced. In practice, companies like Coca-Cola get to decide not only how many slots their traditional sodas will get and where those slots will be, but also if competitors' healthier products will even appear in the beverage aisle.

Category management arguably saves the retailer significant sums: supermarkets gain access to expensive market data and outsource much of their planning. But it also can give the dominant manufacturer of a product undue control over a supermarket aisle. So close is the relationship that the manufacturer's staff assigned to a grocery chain typically works from that retailer's office. Both the American Antitrust Institute and the US Federal Trade Commission (FTC) have warned that category management creates a conflict of interest. A category manager can potentially exclude other manufacturers or facilitate collusion among competing industry actors, ultimately harming consumers [16].

Manipulation of prices is not the only way that category management can potentially harm consumers; it also undermines their health. The producers of shelf-stable products are tasked with "growing the category," that is increasing sales and expanding the space the category takes up in stores. It is no coincidence that in the time since this practice took off, it is the center of the store devoted to shelf-stable goods, not the produce section, that has grown in size as a proportion of the supermarket footprint.

Using Data to Advance Food Industry Interests

Data collection and analysis are the basis for the strong relationships that category managers develop with retailers, relationships that have granted manufacturers great influence over brick-and-mortar stores. More recently, manufacturers have begun collecting and analyzing personalized data to shape digital food platforms. Early studies of online grocery platforms suggest that digital practices, which make such data collection and management even easier, are also likely to favor the largest food and beverage manufacturers [17]. Marketers can now tag a consumer with unique identifiers, track that individual, analyze their behavior patterns, and develop a personal profile. For example, consumers opting to use a store's app or its free wireless Internet may also inadvertently opt to share their location, enabling marketers to send them advertisements when they are near the store.

Armed with this information from personal profiles, food and beverage companies have more leverage to promote the products they know people are likely to buy. They can make an individual's one-time purchase an ongoing promotion, for example, by pushing pop-up ads for Oreos on social media for an individual who once purchased the cookies for a celebration. Companies may also use personal data to cross-promote products in real time. For example, Hershey's is working with retailers to offer consumers an opportunity to "round-out a recipe," meaning an individual who adds eggs and flour to their online cart may be served a pop-up advertisement nudging them to also buy chocolate chips [18].

Online grocery shopping was made possible for the nation's 40 million Supplemental Nutrition Assistance Program (SNAP) participants during the COVID-19 crisis. Public health practitioners posited that this could help make the retail food environment more equitable [19]. But the use of personalized data could actually do the very opposite [20]. Emerging evidence suggests that targeted personalized data may reproduce patterns of discrimination already apparent in the physical retail environment by promoting unhealthy foods and beverages to low-income African American and Hispanic customers online.

Industry Influence on National Nutrition Policy

Protective regulatory policies could disrupt food and beverage manufacturers' practices in the numerous settings, such as supermarkets, where industry pays fees, leverages relationships, and wields data to have influence. Instead of asking consumers to repeatedly say "no" to unhealthy food in all the places they eat, policies could make it easier for everyone to say "yes" to eating healthfully. But, with food and beverage manufacturers using the same playbook to influence policy as they do to influence the food environment, the establishment of timely and effective policies proves difficult.

One reason why implementing effective nutrition policies in the United States can be so challenging is because efforts to reduce diet-related diseases are fragmented [21]. Twenty-one agencies oversee approximately 200 different efforts that fall into four categories: research, education and clinical services, food assistance and access, and regulatory action.

Of the 21 agencies, the United States Department of Agriculture (USDA) and Health and Human Services (HHS) are the two that are most relevant. Every 5 years, the USDA, along with HHS, publishes the *Dietary Guidelines for Americans*, forming the basis for all federal nutrition policy and programs. The USDA also regulates and funds many food access and benefits programs, including SNAP and the National School Lunch Program.

Within HHS, the Food and Drug Administration (FDA) regulates calorie labeling on menus, the Nutrition Facts label and health claims on food packages, and fortification of foods with vitamins and minerals. The Centers for Disease Control and Prevention (CDC) funds national nonprofits, state governments, and community groups to reduce obesity and improve community nutrition. For example, the CDC implements diet-related disease prevention strategies in early childcare facilities.

The Federal Trade Commission (FTC) also plays an important role, but one that is often underappreciated. The FTC regulates advertising. This authority empowers it to bring enforcement actions against companies for deceptive or unfair marketing. The agency also has subpoena power, meaning it can compel companies to provide information on their business practices.

To influence the nutrition policies that these agencies formulate and enforce, the food and beverage industry relies on its tried-and-tested methods: it provides hefty payments to influential actors; develops close, often questionable relationships with decision makers; and uses data to further its own narrow financial interests.

Paying for Political Influence: Campaign Contributions, Lobbying Fees, and Sponsorships

Payments to politically powerful institutions, including campaigns, lobbying firms, and well-connected community organizations, are among the most direct ways that the food industry works to shape nutrition policy in its favor. Just as trade promotion fees grant food and beverage manufacturers influence over the grocery environment, payments in the political arena give manufacturers influence over policies.

The food and beverage industry, like other industries, donates money to campaigns and pays lobbyists to ensure politicians are sympathetic to their interests. This money helps to guarantee companies access to officials who can influence the writing, enforcement, and retraction of laws and regulations. Between 2017 and 2020, the top 20 national food industry trade groups gave $33.7 million in campaign contributions and spent more than $303 million lobbying federal politicians. Members of the Senate and House leadership, as well as the agricultural committees, were among the biggest beneficiaries [22].

Temporary changes to the SNAP retailer stocking standards are a recent example of how lobbying dollars work to protect industry interests over public health. In 2017 and 2018, representatives of the National Association of Convenience Stores lobbied to block SNAP retailer requirements included in the 2014 Farm

Bill. Designed to increase participants' access to healthy food, the strengthened stocking standards required authorized SNAP stores to sell a greater number and diversity of healthy foods. The effects of the new requirements would have made it harder for stores that primarily sell sugary beverages, snack foods, and liquor to participate in the program. But, as a result of this lobbying, corporate interests prevailed 2 years running, and Congress cut all funding to the USDA for implementation of the stronger standards [20].

The following year, lobbyists put pressure on the executive branch to propose a new rule that would have further undermined SNAP retailer requirements. The SNAP authorizing statute makes it clear that retailers must provide "a meaningful variety of products for home preparation and consumption." [23] But with the 2019 proposed changes, a retailer could have stocked olives, limes, lemons, maraschino cherries, juice, Craisins, and trail mix—all items commonly found in a liquor store—and fulfilled the proposed fruit and vegetable requirements. When leadership at the USDA changed a year later, priorities changed, and the agency dropped this proposal.

Recognizing that citizens hold great sway over elected officials, food and beverage manufacturers also spend money sponsoring "community organizations." Some of these are legitimate, while others are front groups. The latter give the appearance of independence but are actually designed to bolster industry interests. One example of a front group is Americans Against Food Taxes (AAFT), the lead group that opposed a national effort to pass a tax on sugary drinks. On its Facebook page, AAFT claimed to be "a coalition of concerned citizens—responsible individuals, financially strapped families, small and large businesses in communities across the country—opposed to the government tax hikes on food and beverages." But further analysis reveals otherwise. Of the 500 member groups, 73% were affiliated with the food and beverage industry, while only 7% were community organizations. Of the community organizations for which there were available data 93% were sponsored by industry, and 83% were sponsored by Coca-Cola [24].

Political leaders listen to community members, so industry-sponsored front groups undermine the democratic process. As one journalist explained, AAFT smelled "like Astroturf, or corporate lobbyists posing as a grass-roots organization. It is entirely suitable for interested parties to participate in public debate; it is not suitable to conceal who's doing the debating." [25]

Sponsoring community organizations can create pressure to participate in front groups; it can also cause those organizations to disengage from the officials responsible for creating and implementing policy. The experience of New York City Department of Health officials in 2015 provides a salient example. That year, Coca-Cola, Dr. Pepper, and PepsiCo launched a self-regulatory program, the Balance Calorie Initiative to "help" reduce the number of calories that Americans consume from beverages by 20% by 2025. With the Balance Calorie Initiative, the manufacturers were essentially playing offense as a form of defense, committing to promote lower calorie and smaller portion beverages rather than full-calorie, full-size sodas in pilot neighborhoods like the Bronx [26].

That same year the Coca-Cola Foundation gave more than $1 million to community groups working in New York, including a $125,000 grant to the Bronx Overall Economic Development Corporation to "promote health, wellness, and physical activity in the community" and a $25,000 grant to a nutrition education group working with Bronx elementary students [27]. Around the same time, Bronx-based Department of Health officials found themselves uninvited from meetings and community events. Longstanding partners explained that it would be "uncomfortable" to have both a representative from the Balance Calorie Initiative and the Department of Health present. As to the question of whether this voluntary industry initiative succeeded in improving the local food environment, early evaluation from other pilot neighborhoods suggests not [9].

Building Relationships for Influence through the Revolving Door

Political spending is not the only way food and beverage manufacturers access decision makers; another means through which these companies guarantee a voice in the policymaking process is through the "revolving door." Industry leaders gain employment in the very government agencies that regulate them and vice versa. (This practice has been described many times over the last several decades in the context of the Pentagon and the defense industry.)

In theory, the flow of employees between the private and public sectors can facilitate the flow of knowledge and experience useful to both parties. But the "revolving door" can also undermine public trust in agencies. Former food company executives that join the government can stymy policies that could impact industry's bottom line, and officials entering industry can use their connections to influence regulatory actions in industry's favor. There are many examples of lawmakers leaving the government for companies they previously regulated. Filings from the American Beverage Association show that more than 70% of the lobbyists they hired in 2021 previously worked as Congressional staff or government regulators, including as the former deputy chief of staff at USDA [28]. A high-profile example that also occurred in 2021 can be found in Dr. Robert Johansson. Formerly the Chief Economist for the USDA, Johansson accepted a position with the American Sugar Alliance after leaving the agency [29].

Officials who take roles with food and beverage manufacturing companies can be problematic, but industry movement into government likely presents the greater conflict of interest. For example, in 2017 the USDA Secretary Perdue appointed Kailee Tkacz, a former lobbyist for the Corn Refiners Association, as a policy advisor. Though Tkacz had no training in science, public health, or nutrition, White House counsel issued a waiver allowing her to work on the federal *Dietary Guidelines* update, a process she had lobbied on only the year before [30].

Documents obtained by the Project on Government Oversight show that organizations representing food and beverage manufacturers were not shy about leveraging their relationship with Tkacz, who had also held roles at the Snack Food Association and the National Grocers Association. She received numerous emails from her former employers. Among those emails was one proposing names for potential members of a federal advisory committee and another suggesting talking points for the USDA Secretary at the National Grocers Association annual show [31]. News coverage suggests these points were incorporated: Secretary Perdue discussed "the negative impacts of burdensome regulation" at the industry show [32]. The emails between this agency official and her former industry associates demonstrate the subtle, often underappreciated ways that relationships established through the revolving door can influence policymaking.

Sponsoring Research: More about Marketing than Science

A third strategy in the industry influence playbook is producing and promulgating self-serving research. As in physical environments, industry's use of data in political spheres can undermine healthy eating. Sponsored studies sow consumer confusion, undercut important policymaking processes, and act as alternative "evidence" in industry-driven litigation.

For obvious reasons, food and beverage companies typically sponsor studies that focus on the positive aspects of their products, for example, producing meta-analyses and reviews to influence federal nutrition programs. For example, PepsiCo sponsored a 2021 review of under-consumed food groups and nutrients in the United States, which included policy recommendations for SNAP [33]. Based on federal data sets, the review determined that "foods such as oatmeal, RTE cereals, milk, carrots and citrus juice were among the most cost-effective food sources of multiple under-consumed food groups and nutrients" and highlighted oatmeal, popcorn, rice, yeast bread, and pasta/noodles/cooked grains as the five most cost-effective sources of whole grains. PepsiCo brands such as Quaker Oats and

Smartfood produce oatmeal, RTE cereals, popcorn, rice, and pasta/noodles/cooked grains. And PepsiCo subsidiary Tropicana Products is "the leading producer and marketer of branded fruit juices" worldwide [34]. The review ultimately concluded that the very items PepsiCo produces "could easily be included (if not already in) in the USDA's Thrifty Food Plan" which serves as the basis for SNAP benefit allotments.

Industry-sponsored studies not only highlight the positive aspects of their products, but such studies can also shift the responsibility for products' negative health impacts [35]. For example, decades-worth of research funded by the sugar industry minimized the link between sugar and heart health [36]. There is evidence that as far back as 1967 that the Sugar Association was working closely with scientists to shift the blame for cardiovascular disease away from sugar and onto fat. In one case, in an article published in the *New England Journal of Medicine*, the Association recommended studies for the authors, Harvard scientists, to review and also revised their drafts [36].

The links between sugar consumption and diet-related disease are now well-established, but industry-funded research would have you believe otherwise. A literature review of studies looking at the link between sugary drink consumption, obesity, and diabetes revealed 34 studies that found an association, and 26 that did not. Of the studies finding no association, all were sponsored by industry [37].

Countering industry-sponsored studies can consume valuable agency resources. Additional research, communications campaigns, and media events may be necessary to debunk distorted science. The National Institutes of Health (NIH) and the USDA—the two government agencies that fund the bulk of nutrition research—cannot afford to waste limited research dollars on industry-directed distractions. Their budgets are already too small relative to the task. A review of the 2018 federal budget revealed that only 7% of the USDA's Agricultural Research Service dollars were dedicated to human nutrition. At NIH, funding for cancer, which affects approximately 9% of the population, was $6.3 billion whereas funding for obesity, which affects roughly 30% of the population, was only $1 billion [38].

Another illustration of the threat that industry-sponsored science presents to sound policy is provided by the process that led to the *2020–2025 Dietary Guidelines for Americans* (DGA). In 2020, for the first time, federal agencies solicited comments on the topics to be covered. More than two-thirds of the comments submitted were from industry and included "ill-cited and baffling recommendations aimed at skewing the 2020–2025 DGA in favor of the food and beverage industry." [39] For example, the Calorie Control Council, an industry group backed by Coca-Cola, cited research by the International Life Sciences Group (ILSI) stating that low- and no-calorie sweeteners are "safe and effective tools in reducing sugar and overall calories." Founded by a former Coca-Cola executive, ILSI is funded largely by corporations to investigate clinical questions. The organization has been criticized for championing business interests that undermine health, such that the World Health Organization (WHO) revoked ILSI's access to its meetings. Even candy maker Mars withdrew its membership from the group, citing ILSI's support for "advocacy-led studies" as the reason [40].

A group responsible for producing and promoting distorted science should not be in a position to influence nutrition policy, but that was exactly the case with the 2020–2025 DGA. The DGA committee is responsible for reviewing the most current dietary science and writing a report. This report influences national education messages, consumer materials, and nutrition programs. In 2020, more than half the DGA committee members had ties to ILSI [39].

Finally, industry's manipulation of data matters because it impacts the outcome of court cases. When policies have the potential to reduce companies' profits, industry may turn to litigation. In 2015, San Francisco passed a law that would have required warning labels on sugary drink advertisements across the city, including on bus stops and billboards. Specifically, advertisements had to include the following: "WARNING: Drinking beverages with added sugar(s) contributes to obesity, diabetes, and tooth decay. This is

a message from the City and County of San Francisco."

The American Beverage Association, the California Retailers Association, and the California State Outdoor Advertising Association contested the law, alleging that it violated plaintiffs' freedom of speech and unjustly targeted sugar-sweetened beverages as a factor in the obesity epidemic [35]. The court considered whether the required warning was "purely factual and uncontroversial" and concluded that by focusing on a single category—sugar-sweetened beverages—, but not specifying a quantity consumed, the warning unfairly conveyed that these beverages were more likely than other sources of added sugars and calories to harm health. The court relied heavily on studies presented by industry, studies that public health advocates say contradict well-established scientific evidence. Following appeals, an *en banc* Ninth Circuit decided for industry on different, procedural grounds. Nevertheless, the litigation demonstrates how industry-sponsored research can undermine evidence-based warnings and threaten government efforts to protect consumers' health.

Turning the Tide on Industry Influence

With industry resistance to contend with, policy change is slow. Despite the concerted efforts by industry to undermine sound nutrition policy, officials are continuing to develop laws and regulations to improve the food environment. Policies can be low-cost, long-lasting, and designed to improve the diets of those most in need. Recent actions at the federal, state, and local levels indicate that a range of legal and policy interventions are feasible. Looking again at the food retail environment, the following section describes the promising actions that could begin to turn the tide so that policies help to ensure that the food environment supports, rather than undermines, healthy eating.

Federal Action

Changes in policymaking at the federal level are difficult given the level of consensus needed and the powerful industry efforts opposing national change. Still, policymakers within federal agencies and Congress are taking steps to improve the food environment. For example, after two decades and multiple requests from advocacy groups such as the Center for Science in the Public Interest, in late 2021, the FTC launched an investigation of industry practices in supermarkets [41]. A better understanding of the problem is the first step to developing better interventions. Many of industry's largest players, including Walmart, Amazon, Tyson Foods, and Kraft Heinz, will be required to share their strategies regarding pricing, marketing, promotions, and brand selection with the FTC. Shining a light on practices that have too long been in the dark could lead to enhanced public understanding and, possibly, policies to protect consumers from unhealthy in-store marketing.

Another policy action that could help improve the retail food environment is the *Stop Subsidizing Obesity Act*, first introduced by Senators Blumenthal and DeLauro in 2016. At present, companies can deduct marketing expenses from their taxes. The proposed bill would end the tax subsidy for unhealthy food and beverages marketed to children. Manufacturers would no longer be able to write off the fees they pay for "advertising displays and promotions at the retail site, including preferential placement," as well as for character licensing, toy cobranding, celebrity endorsements, and a host of other practices aimed at making unhealthy products appealing to children [42]. With more political momentum, policies along these lines could hold

industry accountable for the high public health cost of food marketing to children.

State Action

State attorneys general (AGs) may present another opportunity to develop and enforce innovative nutrition policies [43]. State AGs can file cases on behalf of their citizens through a power known as *parens patriae*. They can also enact rules and regulations, protect consumer interests, educate the public, and draft amicus briefs to inform cases brought by other actors. This menu of actions enables state AGs to bring needed attention to public health issues, prompting national action. For example, in 2009, an AG investigating industry's Smart Choices Program, an industry self-regulatory initiative that labeled store products such as Frosted Flakes as healthy, prompted the FDA to initiate its own investigation and ultimately ended the program.

More recently, state AGs have successfully sued the federal government to challenge cuts to SNAP, a program that increases low-income consumers' buying power in supermarkets [44]. They have also increased enforcement of and education around data privacy. If such actions were extended to grocery platforms, state AGs could help prevent industry from using personal data to promote individuals' least healthy purchases. Increased enforcement and education at the state level could put pressure on the FTC to take broader, bolder action to protect the public from unhealthy food marketing nationwide.

Local Action

Enacting national policy often involves holding industry accountable at the local and state levels first. For example, many industries put up aggressive opposition to calorie labeling on menus, claiming that listing calories would be *too* difficult given the combinations of foods; *too* cluttered given the information already on menu boards; and *too* expensive given the number of outlets. But, as a result of the many state and local calorie labeling policies that were implemented under pressure from public health advocates and community members, industry accepted the writing on the wall, literally [45]. One benefit of a national policy, rather than a patchwork of policies, is that it is easier for industry to comply with.

At the local level, there are a number of promising retail policies that are gaining momentum. Recently passed sugary drink taxes, healthy checkout policies, and dollar store restrictions have the potential to make unhealthy food and beverages less affordable, less prominent, and less prevalent. As each approach becomes more familiar, it is likely to become less controversial and, ultimately, easier to pass elsewhere.

Sugary drink excise taxes demonstrate how momentum can build behind a local policy. Though technically levied on the manufacturer, excise taxes get passed on to the consumer at the point of purchase, usually the supermarket. These taxes discourage consumption, raise local government revenue, and encourage manufacturers to reduce the sugar content of their products. In 2014, Berkeley, California, became the first US jurisdiction to pass such a tax. An evaluation 3 years later showed sugary drink consumption in low-income neighborhoods had fallen by more than 52% [46]. Following this bold action, six additional jurisdictions have implemented sugary drink taxes.

Another local policy that could gain traction is healthy checkout. In 2020, Berkeley again passed the nation's first such policy, requiring supermarkets to offer healthier food and beverages—not candy and chips—near the register [47]. Limiting the placement of unhealthy food and beverages is an important step to reduce their purchase. In the United Kingdom, where 9 supermarket chains totaling 90% of the food retail market have implemented healthy checkouts, consumers now buy 17% less candy and chips [48]. As public health groups like the Center for Science in the Public Interest continue to work with local advocates across the country on placement policies like these, the influence industry exerts over store design may fall.

An additional retail policy that could potentially reduce the prevalence of unhealthy food and beverages limits the expansion of discount variety stores, also known as dollar stores, in a community. There are currently more than 30,000 such stores in America, more than the top ten grocery chains combined [49]. Most are located in low-income communities and communities of color [50]. The food these stores sell is predominantly ultra-processed, and the healthy items are even more limited in selection [51]. Members of rural communities tend to value dollar stores more than members of suburban and urban communities, possibly because they are the only store in a sparsely populated area with affordable options for select products [52]. But critics assert that dollar stores, particularly in urban areas, have capitalized on the retail void in low-income communities of color, offering a restricted range of products where competition was already sparse. To address the lack of healthy food options in their communities, more than 25 municipalities, typically in metropolitan areas, have passed policies to limit the spread of dollar stores. Several of these policies allow new dollar stores to open but on the condition that they dedicate at least 15% of the floor area for fresh produce, meat, and dairy. The number and recent popularity of such measures suggest that there are localized, politically powerful models of civic engagement that could be replicated to chip away at industry's influence over food stores.

Conclusion

Food and beverage manufacturers produce most of the salty, sweet, and tempting foods that currently clutter the food environment. Money, relationships, and research are key to their sales strategy. They use these tools to influence both the food environment and nutrition policy. The supermarket is one of the most important places where Americans acquire food, and in this setting the tools of the food industry take shape using their tried-and-tested methods. These include trade promotion fees; direct store delivery and category management; and manipulation of personalized data. We see similar methods at work in the political arena including political spending and sponsorships; relationships developed through the revolving door; and self-serving research. These methods provide the leverage that industry needs in order to create an un-leveled playing field.

Recent actions at the federal, state, and local levels could help to ensure that public health interests prevail over special interests. Evaluation of these actions—real research, not distorted science—will help determine what combination of policies best support healthy eating. And, with more food and beverage manufacturers—typically smaller, newer companies—now producing healthier items, support for such policies is likely to grow, creating a positive feedback loop that supports healthy eating.

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Dietary Supplements and Health: One Part Science, Nine Parts Hype

31

Norman J. Temple

Key Points

- Use of dietary supplements has much increased over recent decades; around half of people in North America regularly use supplements.
- A wide variety of supplements are sold.
- In some cases there is firm evidence supporting their efficacy but in most cases there is little or no supporting evidence.
- Some herbal preparations have toxic effects and should therefore only be used with much caution.
- Supplements are marketed by a variety of different methods, including health food stores, advertisements in newspapers and on TV, multilevel marketing, bulk mail, spam e-mails, and Internet websites.
- Marketing of supplements often involves giving unreliable or dishonest information that is not supported by scientific studies.
- The marketing of supplements in the United States is only weakly regulated.

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

Introduction

Hope springs eternal in the human breast.

A. Pope, Essay on man, Epistle i.

Dietary supplements refer to any substance taken in addition to regular food. Supplements include vitamins, minerals, amino acids, herbs, enzymes, and various substances extracted from plants and animals. Some of these products are not technically dietary supplements but are included here as they are marketed and used much like true dietary supplements. By definition, these products are not conventional foods but are intended to supplement the diet, generally with the intent of improving health and body functioning, and of preventing or treating disease.

There has been a substantial increase over the past few decades in the sales of dietary supplements in the USA. Much of the rise can be traced to the passing of the Dietary Supplement and Health Education Act (DSHEA) in 1994, a law that gave the supplement industry much wider freedom in their marketing claims. Sales in North America were roughly $50.1 billion in 2020 and are projected to grow at a rate of 5.6% per year for the next several years [1]. Surveys reveal that around half of adults in the USA take supplements regularly [2–4]. Canadian numbers are broadly similar [5]. The people most likely to use dietary supplements are female, older, white,

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_31

nonsmokers, regular exercisers, and better educated [2, 3].

Clearly, dietary supplement manufacturers have succeeded in convincing many millions of consumers to buy their products. This chapter examines the possible benefits that consumers receive from the billions of dollars they spend on supplements. This chapter looks at the ways by which supplements are marketed (including examples of egregious marketing strategies and claims) and reviews the current regulatory status of dietary supplements in Canada and the United States. This chapter then suggests ways in which consumers can protect themselves from unscrupulous or dishonest marketing.

Common Supplements

A wide variety of supplements are sold, but space permits only a limited number to be discussed here. The quality of the evidence supporting their efficacy covers a wide spectrum.

Vitamins and Minerals

The story of vitamin D in recent years has been both fascinating and confusing. It had been well-known for decades that vitamin D plays a critical role in calcium balance and bone health. Starting around the year 2000 epidemiological studies generated impressive evidence suggesting that poor intake increases the risk of cardiovascular disease, cancer, and osteoporosis (and therefore of bone fractures). Based on these findings it was widely believed that supplements of vitamin D would help prevent these major health problems. Many randomized controlled trials (RCTs) have been carried out but the results have been mostly negative [6, 7]. In one particularly informative RCT, healthy older adults (average age of 75) were given a daily supplement of vitamin D for 3 years [8]. At the end of that period, no evidence was detected of a benefit with respect to risk of infections, cognitive function, fractures, or blood pressure.

It must be stressed that as the evidence is full of contradictions, conclusions are tentative. Our best evidence at present is that only limited groups of people would benefit from a supplement. One is frail older people [7]. The other is people who are likely to have low blood levels of the vitamin, including those with dark skin and those with little skin exposure to the sun. A major problem group is inhabitants of northern latitudes, including the northern states of the USA and the whole of Canada. For these people, the amount of UV is insufficient to generate vitamin D for around 5 months each year. An appropriate supplement provides about 400–800 IU (10–20 μg) per day [7]. A recent review by three experts went one step further. They argued that people with a low body level of vitamin D, a group that includes most Black people who live in northern latitudes, should take a supplement that provides 4000 IU (100 μg) per day. They believe that this would lower their risk of several diseases [9].

Another popular supplement is calcium, often taken by middle-aged and older women in the hope that it will help protect against osteoporosis. Alas, findings from RCTs have been mostly negative regarding the value of this supplement [7]. An additional reason to avoid calcium supplements is that they have been linked to a 15% increased risk of cardiovascular disease in postmenopausal women [10].

The lesson from vitamin D and calcium is that we must be hesitant before accepting a widely held opinion that supplements of particular micronutrients will improve health and prevent disease. But we must also avoid going to the other extreme and dismiss the value of supplements of all micronutrients; with several micronutrients, many people have a low intake and a strong case can be made for the benefit of supplements.

Iron and folic acid are two examples of this. Many women are lacking in these micronutrients during their reproductive years and may benefit from a supplement. In the case of iron, this is due to a combination of poor intake and menstrual loss which results in anemia. As meat is a rich

source of iron, vegetarians are at most risk. A low intake of folate is also common because a large section of the population eats an unhealthy diet with a low content of nutritious foods, especially fruit and vegetables. This problem is a serious concern as it may lead to the development of a type of congenital malformation during pregnancy called neural tube defects, such as spina bifida.

Multivitamins—meaning pills containing a broad spectrum of vitamins and minerals that are typically taken once a day—are the most popular type of dietary supplement. These are certainly advisable for people at risk of malnutrition such as people who habitually consume a low-calorie diet which is often the case with elderly people and those with anorexia, drug addiction, or advanced cancer. But what about healthy adults? Much valuable evidence has come from prospective cohort studies. Findings consistently reveal that people who consume a multivitamin supplement gain no benefit in terms of reduced all-cause mortality [11–13]. These findings are supported by the results of RCTs. Several such trials have taken place in order to determine whether multivitamins have any value in the areas of all-cause mortality, cardiovascular disease, cancer, or cognitive impairment. A paper published in 2013 in the journal *Annals of Internal Medicine* summarized the findings and drew a firmly negative conclusion [14]. The paper had the unambiguous title: "*Enough is enough: Stop wasting money on vitamin and mineral supplements.*"

Antioxidants

Many supplements are sold with a claim of being "rich in antioxidants," the obvious implication being that these products improve health or prevent disease. In support of this, it has been firmly established that antioxidants are important components of some of the body's defense mechanisms. In particular, they help prevent oxidative damage to essential molecules such as lipids and DNA. Based on these findings it seemed logical to assume that supplements of antioxidants will help prevent various diseases. This possibility was tested in the following studies.

Several dozen RCTs have been conducted in order to test the three major antioxidant vitamins: beta-carotene, vitamin C, and vitamin E. The goal of the RCTs was to determine the effectiveness of these vitamins for either primary or secondary prevention. The dose has typically been several times higher than the RDA. Very little evidence has been forthcoming from these RCTs that either beta-carotene or vitamin C prevents disease [6]. The results with respect to beta-carotene and cancer were discussed in Chap. 10. More importantly, meta-analyses of RCTs indicate that supplementing with these vitamins does nothing to reduce all-cause mortality [6, 15]. Vitamin E presents a more confusing story. It seems to have modest value in the prevention of cardiovascular disease [6] but other evidence suggests that it may lead to a slight increase in all-cause mortality [6].

There is convincing evidence that foods naturally rich in antioxidants, such as fruit and vegetables, reduce the risk of various diseases including heart disease and cancer. But these benefits are likely to be the result of the combined action of many different substances including phytochemicals, antioxidants, various vitamins and minerals, and dietary fiber. There is no reason to believe that the health benefits obtained from foods rich in antioxidants can also be obtained from purified antioxidants. Therefore, when advertisements for supplements state that a product is "rich in antioxidants," that is weak evidence that it will have a positive impact on health.

Probiotics

The study of the microbiome and its relationship to health has emerged as a hot topic in recent years. The focus has been on the bacteria present in the colon. The rationale for giving supplements of probiotics, preparations containing particular bacteria in a concentrated form, is to boost the number of beneficial bacteria in the colon. Findings from RCTs provide some supporting

evidence that specific probiotics are of value for a small number of medical purposes, such as preventing antibiotic-associated diarrhea.

Some evidence suggests that probiotics may also improve immune function [16] and help with weight loss [17]. Supplement manufacturers have seized on this limited evidence; they are marketing probiotics to healthy people by exaggerating the possible benefits [18]. Advertisements for such supplements are commonly seen on TV.

Herbs

A great many different herbal preparations are being sold in North America and around the world. They are employed for both prevention and treatment of a wide variety of disorders. It is misleading to characterize these products as dietary supplements; they more closely resemble drugs.

Supporting evidence for the value of herbal supplements is highly contentious. Unlike conventional drugs, herbal supplements generally lack standardization of their active ingredients. There can be much variation between different brands of what is supposedly the same herb; this is due to such factors as the actual species of plant used, the part of the plant used, and the extraction method. Adding to these problems many herbal products sold in North America do not contain the herbal product stated on the label. This was shown in a study published in 2013 which reported that about half the samples of herbal products tested did not contain the species stated on the label [19].

Let us suppose that a RCT is carried out and the findings strongly suggest that a particular herbal product is effective for the prevention or treatment of a particular condition. Does this mean that we can be confident that the product will work equally well if a person buys that herbal product from a health food store? The answer must be no. This is because the various problems stated above with the formulation of herbal products mean that one cannot be confident that a herbal product purchased by patients will contain the same active ingredients at a similar concentration as that present in the product tested in the RCT.

Here we look at some examples of herbal treatments that have been much researched and are widely used.

- Echinacea. This herb is widely used for the prevention and treatment of the common cold. A review concluded that: "The overall evidence for clinically relevant treatment effects is weak" [20].
- St John's Wort. Evidence suggests that it may be effective in the treatment of mild to moderate depression [21]. This herb therefore appears to be in the small minority where there is solid supporting evidence of efficacy.
- Ginkgo biloba. This herb is used by many people in the belief that it helps maintain cognitive health in aging, especially for the memory. In 2009 the results were published of a randomized, double-blind trial in which 3070 people across the USA, aged 72–96, were given either the herb or a placebo [22]. After 6 years there was no difference in the rate of cognitive decline between the two groups. No benefits were seen for memory function. The overall findings from RCTs suggest some benefit in treating patients with mild cognitive impairment or Alzheimer's disease [23].
- Ginseng. This very popular herb is often claimed to boost mental and physical performance. But this claim relies in no small part on its use in traditional Asian medicine over many centuries. As is often the case with herbal products, research studies are inconsistent regarding the benefits of ginseng. Another potential problem is that there are several species of plant that are called ginseng. The evidence from RCTs indicates that ginseng may improve glucose metabolism and may possibly be useful for psychomotor performance and cognitive function, but it has no positive effect on physical performance [24].
- Cinnamon. This supplement is often used by persons afflicted with type 2 diabetes. It is claimed to improve blood glucose levels. This product may achieve a modest beneficial effect [25].

These examples illustrate the general problem with herbal treatments. First, many have little or no supporting evidence. Second, even where clinical trials have generated positive results in clinical trials (often using a carefully selected preparation of known composition), it is hit or miss whether the herb will achieve similarly positive results when used for self-treatment by the average consumer.

Detoxification and Boosting the Immune System

Detoxification is, of course, a well-established biochemical process. However, herbal treatments, in particular, are routinely sold with the promise that they will stimulate the liver—and perhaps other organs as well—so that detoxification is accelerated and the body is cleansed. This will then lead to all sorts of benefits. However, supporting empirical evidence is lacking.

Many supplements come with the claim that they somehow stimulate the immune system. Much like detoxification this is usually associated with herbs. For a few herbs, echinacea, for example, there is some supporting evidence. But in most cases the claims come minus credibility.

The claims being made for supplements that supposedly speed detoxification and boost the immune system resemble those for antioxidants. In each case, these terms provide an apparently scientific reason why a particular product will do wonders for health.

Glucosamine and Chondroitin

Supplements of these substances have become popular for the treatment of osteoarthritis. While some positive effects have been reported in a few trials, especially for chondroitin, our most reliable evidence is that neither supplement is of clinical value [26].

Prevagen

This supplement is frequently advertised on TV in North America. It is claimed that it aids the memory. The marketing campaign was so grossly dishonest that in 2017 the Federal Trade Commission and the New York State Attorney General took action [27, 28]. These agencies: charged the marketers of the dietary supplement Prevagen with making false and unsubstantiated claims that the product improves memory, provides cognitive benefits, and is 'clinically shown' to work." New York Attorney General Eric Schneiderman stated: "The marketing for Prevagen is a clear-cut fraud…. It's particularly unacceptable that this company has targeted vulnerable citizens like seniors in its advertising for a product that costs more than a week's groceries, but provides none of the health benefits that it claims." Incredibly, 5 years later, in 2022, the advert was still appearing on TV.

In one major respect things have gone from bad to worse. Other supplement manufacturers have jumped on the memory supplement bandwagon and are advertising their own products on TV. Memory supplements are best forgotten.

CoQ

Another supplement frequently advertised on TV in North America is CoQ (also known as CoQ10 or coenzyme Q10). It is most commonly marketed as an aid to heart health. Findings from RCTs are not consistent and do not justify claims that supplements will improve health [29].

Weight-Loss Products

With the huge obesity epidemic that has swept North America, it is scarcely surprising that supplement manufacturers have seen a golden opportunity for fat profits. Many products have been marketed. Typically, such products come with thin promises based on even thinner evidence.

Table 31.1 Features of common ingredients found in weight-loss supplements[a]

Supplement	Claimed action	Effectiveness	Safety[b]	Is it recommended?
Bitter orange	Increases energy metabolism and the breakdown of fat; decreases appetite	Possible small increase in metabolism. Effect on weight probably negligible.	Some concerns	No
Caffeine	Increases energy metabolism	Small increase in metabolism. Possible small increase in weight loss.	Safe	No
Green tea	As caffeine	Effect on weight probably negligible	Safe	No
Chitosan	Reduces fat absorption	Possible small decrease in fat absorption. Effect on weight probably negligible.	Safe	No
Chromium	Increases muscle mass and fat loss and decreases appetite and food intake.	Possible small increase in weight loss	Safe	No
Conjugated linoleic acid (CLA)	Reduces body fat	Possible small increase in loss of body fat and weight	Safe	No
Garcinia cambogia (hydroxycitric acid)	Suppresses the appetite	Effect on weight probably negligible	Some concerns	No
Hoodia	Suppresses the appetite	None	Possibly unsafe	No

[a]Sources of information: Medline Plus http://medlineplus.gov and National Center for Complementary and Alternative Medicine http://nccam.nih.gov
[b]All products are potentially hazardous if taken in excess

But what they do produce, very often, is a photo of a young woman with a BMI of about 20. Recent reviews have evaluated the effectiveness of various supplements promoted for weight loss and concluded that they are unlikely to contribute to meaningful weight loss [30–32]. Table 31.1 briefly describes some of the more commonly sold supplements that come with the claim of enhancing weight loss.

A Repeating Story

What we see, time and time again, is weak evidence dressed up as solid science. The following are the types of evidence that are commonly used to promote the sale of supplements:

- A physiological or biochemical change in the body. Often this is based on mere speculation or even pure invention; for example, that health will be improved because a herbal mixture induces detoxification or because a supplement is rich in antioxidants.
- Weak clinical evidence (e.g., a particular herb has been used for centuries as a treatment and therefore it must be effective; or evidence based on one or two small studies of dubious importance).
- Anecdotal evidence, often from an unqualified person with a serious conflict of interest. A slight variation of anecdotal evidence is the use of testimonials ("Jim from Miami says: 'Thanks to Speedy Fat Burn I have lost 25 pounds in one month.'").

In order for claims to have real credibility we need to see hard scientific evidence. Ideally, there should be consistent evidence from well-conducted RCTs, with clinical endpoints, showing health benefits, and published in peer-reviewed journals. But such evidence is seldom available.

Dietary supplements are a multibillion dollar industry, but integral to its success has been the

widespread use of blatantly misleading marketing. The marketers of supplements often use scientific evidence the way a drunk uses a lamp post: more for support than illumination. This strategy has been so successful because most of the population has a weak grasp of biomedical science [33].

Potential Hazards from Supplements

A common mantra from those in the supplement industry is that their products are safe. However, many hundreds of cases of undesired side effects induced by supplements have been reported [34]. The true figure likely runs into the thousands as most cases are probably never reported. A study published in 2015 estimated that 23,000 visits occur each year to emergency departments in the USA as a result of harm caused by supplements [35]. This is likely to be a substantial underestimate as it excludes cases where the emergency room physician failed to make a connection between the medical problem and the use of supplements. The type of supplements most often linked to this problem is those recommended for energy and weight loss.

Supplements can be hazardous in a variety of ways. Many herbal supplements have toxic effects. Some supplements sold with the claim that they enhance sexual function have been shown to be adulterated with drugs [36]. A chemical analysis was conducted on traditional Ayurvedic medicines that were being sold in the USA via the Internet. The findings revealed that 21% of these herbal preparations exceeded one or more standards for acceptable daily intake of lead, mercury, or arsenic [37]. Recent studies carried out in the USA and Canada have reported that many supplements contain high levels of fillers or contaminants [19, 38]. Again, this problem is most often associated with herbal products. Quite apart from toxic contaminants, many herbs interact with various drugs. St John's wort is especially problematic in that regard [39]. Compounding this problem patients often do not tell their physician about their use of supplements.

How Dietary Supplements are Marketed

Dietary supplements are marketed in diverse ways [40]. They can be purchased in pharmacies, supermarkets, and health food stores (HFS); directly from people engaged in multilevel marketing; and through websites. Their sales are promoted using all forms of marketing methods, including advertisements in newspapers, bulk mail, spam e-mails, and Internet websites, as well as by advertising and infomercials on TV. This section describes some marketing strategies used by manufacturers and sellers.

Health Food Stores, Drugstores, and Supermarkets

HFS are a popular source of dietary supplements. They typically carry hundreds of different products. HFS staff seldom have any proper scientific knowledge regarding the topics on which they freely dispense advice. But what they do have is a strong economic incentive to sell products. As a result, a request for advice will typically be responded to by a recommendation to take a particular supplement: advice that usually suffers from a serious lack of credible supporting evidence. In addition, studies in Hawaii, Canada, and the UK have shown that when the same question is asked in different HFS, there is a huge variation in the advice that is given [40].

In recent years it seems that every drugstore has given over a generous amount of shelf space to the display of supplements. The same is seen in the pharmacy section of supermarkets. However, these stores are quite different from HFS in one important respect: customers requesting advice are far less likely to be recommended to buy useless supplements. This is not surprising as pharmacists are trained health professionals and must abide by a code of ethics.

This was confirmed in a study conducted in Canada [41]. Visits were made to 260 HFS and drugstores (or the pharmacy section of supermarkets). It was found that 88% of the time that questions were asked in HFS, customers were given

recommendations that were either unscientific (6%) or poorly supported by the scientific literature (82%). By contrast, this occurred for only 27% of questions in pharmacies. Conversely, on two-thirds of visits to drugstores/supermarkets, the staff gave advice considered to be fairly accurate or accurate, but this seldom occurred in HFS (68% vs. 7%).

Multilevel Marketing

Many products—from Avon cosmetics to Tupperware—are sold by multilevel marketing, a strategy in which company salespeople recruit other salespeople. The foot soldiers and everyone up the chain receive a commission from the sales.

The people who control this form of marketing often engage in unscrupulous activities. On one occasion flyers were distributed in Edmonton promoting a particular product where the person behind it was described as "the world's leading viroimmunologist." In another case, the mastermind was referred to as "Widely regarded as the world's #1 nutritionist" and the product as "The biggest discovery in nutrition in the last 40 years!"

Advertising

Dietary supplements are advertised in diverse ways. In the last few years, there seems to be far more advertising of supplements during regular TV programs. Infomercials are another method. They resemble regular TV programs. They typically last for 30 min and air during the night. Newspapers are one common method, sometimes as multi-page supplements.

Bulk mail ("junk mail") is a common form of advertising, especially for supplements that promise weight loss. Spam e-mails are a cheap and easy way for manufacturers to promote their dietary supplements to tens of thousands, if not millions, of people. As a result, large numbers of products are being touted. In recent years vast numbers of spam e-mails have been sent out promoting sex-related nutritional supplements. Spam e-mails typically work by directing potential customers to a website. There are many websites selling all types of supplements; they are, in effect, virtual HFS. They often flout US law [42].

Regulations on the Marketing of Supplements

United States

The principal agency of the US government that regulates supplements is the Food and Drug Administration (FDA). However, product advertising is regulated by the Federal Trade Commission (FTC).

In 1994 Congress passed a law regulating the marketing of dietary supplements: the Dietary Supplement and Health Education Act (DSHEA). This law freed dietary supplement manufacturers from many FDA regulations [43]. Whereas under the former law, manufacturers were required to prove that a dietary supplement is *safe*, now, under DSHEA, the onus is on the FDA to prove that a supplement is *unsafe*. This shift in regulatory policy places burdens on a federal agency with important public health responsibilities but limited resources.

As a result of DSHEA, marketers of supplements are free to make health-related claims (structure/function claims) but are not permitted to state explicitly that the product will cure or prevent disease. They must also state that the FDA has not evaluated the agent. What this means is that a marketer may now claim that a supplement "boosts the immune system," "makes the body burn fat while you sleep," or "fights cholesterol" provided they stop short of saying that the supplement prevents infectious disease, cures obesity, or prevents heart disease. Needless to say, most consumers will be confused by the distinction between the two sets of claims. One potentially dangerous feature of the labeling regulations is that manufacturers are not required to provide information about possible adverse effects.

Another major flaw in DSHEA is that herbal preparations are regulated together with vitamins and minerals. As a result, herbal preparations escape proper regulation. As mentioned earlier, it would be more accurate to call these products drugs rather than dietary supplements [44].

Put bluntly, the 1994 law, together with the lack of resources at the FDA to properly enforce regulations, has given supplement manufacturers *carte blanche* to employ deceptive marketing that often looks and smells like fraud.

DSHEA was passed by Congress after heavy lobbying that was orchestrated by the supplement industry [43]. Over the years following the passage of DSHEA, sellers of supplements took full advantage of the law. This led to sharply increased sales of dietary supplements.

In 2003 the serious problems with the current regulatory climate were addressed by the editors of the *Journal of the American Medical Association* (JAMA) [45] published an editorial deploring this state of affairs:

> Manufacturers of dietary supplements are trying to have it both ways. They claim their products are powerfully beneficial, on the one hand, but harmless on the other. To claim both makes no sense, and to claim either without trials demonstrating efficacy and safety is deceptive. The public should wonder why dietary supplements have effectively been given a free ride. New legislation is needed for defining and regulating dietary supplements.

A similar article was published in 2002 in the *New England Journal of Medicine* with a focus on herbal supplements and a more general editorial in 2009 [44]. These comments are as true today as when they were written.

Canada

Canada provides an object lesson for the USA on how not to reform the system for the production and marketing of supplements. In 1999 the government of Canada created a new organization, the Natural Health Products Directorate, to regulate dietary supplements. The regulations require a pre-market review of products to assure consumers that label information is truthful and health claims are supported by scientific evidence. When these regulations were announced, the clear impression was given that the marketing of supplements would become much more evidence-based and honest. Much evidence, some of which was referred to in this chapter, indicates that the new regulations have failed to achieve any real impact [46]. In that respect, the situation in Canada is still every bit as bad as that in the USA. The clear lesson is that regulations are worth little if the regulators are unable or unwilling to enforce the regulations.

Advice for Consumers

Given the diverse and innovative forms of marketing of dietary supplements, consumers need help sorting through the health claims. Untrustworthy claims for supplements often have the following features:

- Money-back guarantee.
- A reliance on anecdotal evidence, especially testimonials.
- A claim that the product is a "scientific breakthrough" or an "ancient remedy."
- Touting the product as an effective treatment for a broad range of ailments. If things are too good to be true, they probably are.

Additional guidelines that can be helpful are:

- Ignore advice given by anyone who has a financial interest in selling supplements, especially when they appear to have no relevant qualifications. This includes staff in health food stores and people engaged in multilevel marketing; and statements on flyers that arrive in the mail, on infomercials, and on the websites of supplement manufacturers.
- If in doubt about a supplement, obtain advice from a licensed healthcare professional, such as a physician, dietitian, or pharmacist.
- Always use common sense. People should view all types of marketing of supplements with a healthy dose of skepticism.

- For further information check credible sources of information. This is a consumer's best protection against fraudulent and misleading marketing. Information on supplements is easily found on the websites of several health-related organizations. Here are three of the best:

Mayo Clinic http://www.mayoclinic.org/drugs-supplements

National Center for Complementary and Alternative Medicine (NCCAM) http://nccam.nih.gov

Medline Plus http://medlineplus.gov

Conclusion

The general population is exposed to enormous amounts of marketing activity for supplements. Alas, when we look closely at this marketing, we see that ethics, honesty, and a sincere desire to improve the health of consumers have taken a backseat to maximize sales and profit. Compounding this problem, the vast majority of people do not have the knowledge to critically evaluate the claims being made. As a result, the marketing of supplements has been highly successful: millions of people have embraced the use of dietary supplements.

Supplements can pose hazards, including both harmful side effects and interference with the action of prescription drugs. These problems arise most often with herbs. Patients often do not tell their physician about their use of supplements. Physicians and other healthcare professionals need to be aware of these problems. But, unfortunately, most physicians receive very little training in this area.

But there is a positive side to dietary supplements. There is good supporting evidence for several supplements, which was briefly reviewed earlier in this chapter. There is no good reason why we cannot have the best of both worlds: promote the use of supplements when there is solid supporting evidence while proscribing those that lack such evidence. A vital step in this direction is stricter regulation of the industry by government agencies. In the final analysis, an educated consumer is the best consumer when it comes to dietary supplements. And the need for education also applies to health professionals.

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A Plague of False and Misleading Information

32

Norman J. Temple

Key Points

- False and misleading information is widespread across many areas of nutrition.
- This chapter briefly examines some examples including Dr. Oz and his TV show, unscientific weight-loss treatments, diets for treating illnesses based on a person's blood group, approaches to the prevention and treatment of disease based on detoxification, and the use of stem cells for treatment of disease.
- This chapter also looks at nutritionist training programs that lack scientific credibility.
- Problems of food companies meddling in scientific research and conflict of interest in research are discussed.

Introduction

The previous chapter discussed dietary supplements, including how they are marketed. That chapter stressed that much of this marketing is based on delivering false and misleading information to potential customers. This chapter continues the subject of how the problem of false and misleading information is widespread in other areas of nutrition and medicine. This problem has a long history across the medical sciences. In Victorian times a common belief was that masturbation was a major cause of blindness and insanity. In the 1970s a great many people believed that if they were always feeling irritable and lacking in energy, this was a sure sign of low blood sugar. This epidemic mysteriously disappeared only to be replaced by newer epidemics such as an allergy to gluten, an overload of toxins, and a yeast infection (Candida). More recently millions of parents have become convinced that some types of vaccination pose a significant risk to children. The resulting decrease in the proportion of children who have been vaccinated has led to many cases of measles and some deaths. The scope of the problem of false and misleading information is enormous and is continuously evolving. The Internet serves as an efficient vehicle by which false information can spread around the world at lightning speed. It is clearly impossible therefore to cover all aspects of this problem. This chapter is intended only to present some illustrative examples of the problem.

The Case of DR Oz

Dr. Mehmet Oz was for many years a highly accomplished heart surgeon at Columbia University, New York. He has had a TV show since 2009 that has been watched by millions of

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_32

people across North America. He dispenses advice on many topics in the general area of health. Researchers from the University of Alberta in Edmonton, Canada, made a careful analysis of the accuracy of his claims [1]. They estimated that 39% of his advice was in the area of diet. The researchers were able to find evidence in support of 46% of the recommendations while 15% were contradicted by the evidence. That left 39% of the recommendations where no supporting evidence could be found. In other words, at least half of the recommendations made by Dr. Oz lacked supporting scientific evidence.

One of his claims landed him in hot water. Dr. Oz was called before Congress to testify at a Senate hearing about deceptive advertising for over-the-counter diet supplements after he sang the praises of green coffee bean extract as a "miracle" weight-loss pill [2]. Sen. Claire McCaskill, who chairs the Senate's Consumer Protection panel, blasted him for making such claims on his show when "you know it's not true."

Weight-Loss Treatments

If diet books worked, then the obesity epidemic would have been vanquished years ago. But for the past several decades the diet book industry has been growing at the same rate as American waistlines. A search at Amazon shows that thousands of books are published each year on the subject. A perusal of the titles reveals obvious indicators that false and misleading information is a common ingredient. For example, 170 books were published in 2018 that included the words "quick and easy weight loss" in the title (or a slight variation of these words). Similarly, the words "belly fat" appeared in the titles of 120 books. This problem extends to magazines. Woman's World is a supermarket tabloid sold across North America. It regularly features the latest "lose a pound per day" diet on its front page.

Blood Types and Health

In 1991 James D'Adamo published a book titled "*The Blood Type Diet: Your Personalized Diet and Exercise Program.*" The theme of this book is that people should select their diet, as well as their exercise program, based on their ABO blood group. Over the years several other authors jumped on the publishing bandwagon with books making similar claims. These books claim that a person's blood group is an effective means to both prevent and treat an assortment of health problems including cancer, heart disease, diabetes, arthritis, and overweight.

How much evidence is there to justify the many claims made in these books? There is, in fact, surprisingly strong evidence that blood groups do affect health. Folks who have blood group O have a significantly reduced risk of cardiovascular disease, some types of cancer, as well as of all-cause mortality [3]. This suggests that the antigens that are the basis of blood groups have complex effects on disease etiology. Perhaps one day this information will be translated into practical advice on reducing risks to health if your parents bequeathed you a less desirable blood group. But there is no evidence to support the claims of those promoting particular diets, or other types of treatment, based on a person's blood group. A systematic review on this subject was published in the *American Journal of Clinical Nutrition* [4]. The researchers concluded that: "No evidence currently exists to validate the purported health benefits of blood type diets."

Detoxification

Detoxification was discussed in the previous chapter where it was pointed out that many dietary supplements, mainly herbal ones, are sold with the claim that they enhance health by speeding detoxification. This claim is devoid of supporting evidence. However, the claims made in the area of detoxification go well beyond supplements.

The American chapter of the story started a century ago. Benedict Lust emigrated to the USA from Germany late in the nineteenth century. In 1918 he wrote the following: "The natural system for curing disease is based on….the employment of various forces to eliminate the poisonous products in the system…" [5]. Lust later became one of the founding fathers of naturopathy in the USA.

The concept of detoxification is based on the general claim that the accumulation of toxins in the body is involved in much sickness and that disease can be both prevented and cured using treatments to eliminate these toxins. This concept is still the basis for various naturopathic therapies today. Indeed, a survey of naturopaths in the USA reported that 92% stated that they employ detoxification therapies [6]. Detoxification is often advocated to enhance weight loss. The treatment at the center of detoxification is fasting, often accompanied by fruit or vegetable juices. As noted above and in the previous chapter the supplement industry has jumped on the bandwagon and promotes many products as aids to detoxification. In recent years, the concept has gained much popularity in nutritional and health circles that clearly lie well outside the mainstream. There has also been an explosion of books on the subject in recent years.

A variation of this approach is autotoxicity. Here the focus is on removing toxins from the colon, often with the aid of an enema. A more extreme variation is colonic irrigation, a procedure that is potentially harmful as it can hyperextend the colon [7, 8]. The irony of this treatment is that the same effect can be achieved by a few teaspoons of wheat bran at far less risk, far less discomfort, and far less cost!

There is very little credible evidence that detoxification treatments, such as dietary changes, consumption of herbs and supplements, fasting, or colonic irrigation, can remove toxins from the body [9]. Moreover, there is no evidence that these treatments improve health.

Stem Cells

Stem cells are the cells that develop into blood, brain, bones, and all of the body's organs. They are at the center of an exciting area of medical research. They have the potential to repair and regenerate cells. This opens up the possibility that stem cells may one day be used to treat many medical conditions and diseases. For example, it may be possible to use stem cells to repair major injuries to the spinal cord that has left people confined to a wheelchair.

The use of stem cells in the treatment of patients ("regenerative medicine") is regulated by the Food and Drug Administration (FDA) [10]. But as we saw in the previous chapter with dietary supplements and in this chapter with some other forms of treatment, the public is being targeted with treatments that are scientifically worthless. According to the FDA: "These regenerative medicine products have risks but are often illegally marketed by clinics as being safe and effective for the treatment of a wide range of diseases or conditions, even though they haven't been adequately studied…" [11].

Training Programs for Nutritionists

The usual dietitian training program in North America is a 4-year degree in nutrition followed by a supervised clinical internship. But do a Google search using the term "nutritionist training program" and many programs pop up, most of which are seriously lacking in scientific credibility.

Here is one example of a program. Graduates receive a certificate of knowledge (or probably lack thereof). The American School of Natural Health (http://www.americanschoolofnaturalhealth.com) offers a training course to become a "nutrition consultant." Their courses emphasize the importance of "Detoxification & Cleansing." Programs of this type typically take about 1 or

2 years to complete which is considerably less than conventional nutrition programs. But for many people that is too long. One option for people in a rush is the American Fitness Professionals & Associates (www.afpafitness.com). They will train a person to become a "Certified Nutrition & Wellness Consultant" in only 100 h.

Some schools offer a more in-depth program. The International College of Natural Health and Traditional Chinese Medicine (http://www.internationalhealthcollege.com), based in Ontario, Canada, has a 24-month program called the "Orthomolecular Nutrition Diploma Program." Some indications of what students will learn during the program are indicated by a description of books from the approved reading list:

(i) "The 4-Week Ultimate Body Detox Plan shows you how to get rid of toxins using a simple and effective step-by-step approach."
(ii) "Control the level of acid in your body and reclaim your health with this simple, step-by-step program. Beginning a healthier lifestyle can be as easy as starting your day sipping a glass of water with a squeeze of lemon juice. Drinking this simple drink is only one of the many ways, all outlined in The Ultimate pH Solution, that you can change your body's pH and ward off disease."
(iii) "The only Self-Help Guide to make alternative cancer therapies work for YOU. A bold revelation of what this [20th] century's early naturopaths learned about not only the causes of cancer, but also effective treatments and what you CAN DO NOW to save your life with this vital knowledge."

The Problem of Food Companies Meddling in Scientific Research

Commercial organizations have a long history of meddling in the scientific process so as to distort the outcomes of research in ways that help enhance the sale of particular products. The tobacco industry and Big Pharma have been playing this game for decades. Here we look at how this takes place in the area of food and nutrition.

There is an enormous amount of money tied up in the results of research studies in the area of nutrition science. Reports have appeared that suggest that conflict of interest exists and is distorting the findings of some research studies. Here is one illustrative example. An analysis was made of research studies and review papers published between 1999 and 2003 on soft drinks, juice, and milk [12]. Those reports where the authors had industry financing were at least seven times more likely to report a finding favorable to the industry that provided the finance than was the case with reports where there was no industry financing. Much the same has been reported concerning research on olestra, a fat substitute [13].

These findings do not necessarily indicate that deliberate dishonesty has taken place. Rather, they raise suspicion that the research process has been corrupted. This can occur in various ways such as by designing randomized trials so that the results desired by the funders are more likely to be observed, by analyzing the data so as to make the conclusions as close as possible to what the paymasters want to hear ("if you torture the data long enough, it will eventually confess"), and by only allowing the findings of studies to be published if they report the "right" results.

Journals are well aware of this problem, especially in the area of drug research. As a result most journals now insist that all authors of papers state whether there is any potential conflict of interest. But that is only a partial solution to the problem as the following example illustrates. A paper was published in a nutrition journal in 2014 that reviewed the value of vitamin supplements [14]. The paper strongly argued the case that such supplements are of much value. A note at the end of the paper stated that funding for the work came from Pfizer but failed to mention that Pfizer is the manufacturer of Centrum multivitamins, which is the leading brand of multivitamins sold in North America.

Much evidence has appeared in recent years linking sugar-sweetened beverages with the epidemic of obesity. This poses an obvious threat to Coca-Cola. They have responded by funding

research that emphasizes the role of physical activity in obesity while ignoring the role of diet [15]. In China, Coca-Cola succeeded in taking a large measure of control over obesity research and policy development. As a result the Chinese policy on obesity, especially during the years 2000–2013, emphasized physical activity over diet [16]. In another significant action, Coca-Cola set up an organization called the Global Energy Balance Network [17]. The game plan was for the organization to be perceived as being both independent and scientifically credible while promoting interpretations of the science of obesity that are favorable to the commercial interests of Coca-Cola.

Chapter 30 has more examples that describe how the food industry has carried out distortions of research in the area of nutrition and health.

Conclusion

Much of what has been written in this chapter will doubtless be out of date within a few years. But creative minds will dream up many new forms of false and misleading information. Some will do it because they are deluded, some because they love the publicity, and others because of greed. There is little that can be done to stop these people. A society that values free speech allows people to say that megadoses of vitamin C cure cancer and that COVID-19 is a fake illness. The general public is easily misled by this misinformation as only a small minority has the scientific education that allows them to identify which claims are probably correct and which should be ignored.

Various proposals have been made for how to mitigate this serious problem [18–20]. Accurate information is the best antidote. This places the onus on health professionals, scientists, and journalists to provide sound information to the general public. What is especially important is to provide the public with accurate information on all areas of nutrition, health, and medicine, written by highly credible experts, and in language that the average person can easily understand. Fortunately, this need is being met by several excellent websites that are now available at no cost. Here are a few:

http://www.mayoclinic.com; http://www.healthfinder.gov; http://medlineplus.gov; http://www.eatright.org

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Postscript: An Overview of Nutrition—Much Progress but Challenges Ahead

33

Norman J. Temple, Ted Wilson, David R. Jacobs, Jr., and George A. Bray

Key Points

- Nutrition in the twentieth century was mainly concerned with the individual substances found in food.
- At the same time it became firmly established that the disease pattern seen across the Western world is a direct result of lifestyle, and that diet plays a major role in this.
- This information has been of tremendous value in showing how health may be enhanced and diet-related diseases prevented. There is clearly a great opportunity to achieve a major improvement in the well-being of the population
- Moreover, as the cost of achieving this is relatively modest, the benefits for public health would be highly cost-effective.
- We now present a summary of the key lessons from this book and the top priorities for action.

Nutrition in the twentieth century was mainly concerned with the individual substances found in food. Up until the 1960s the major focus was on vitamins, minerals, protein, carbohydrates, and fats. In the 1970s dietary fiber emerged as an important topic, followed later by *trans* fatty acids, n-3 fatty acids, and phytochemicals. At the same time it became firmly established that the disease pattern seen across the Western world is a direct result of lifestyle, and that diet plays a major role in this. This information has been of tremendous value in showing how health may be enhanced and diet-related diseases prevented. Indeed, it is no exaggeration to say that these discoveries in nutrition science represent one of the most important advances in the field of public health since the 1950s. There is clearly a great opportunity to achieve a major improvement in the well-being of the population. Moreover, as the cost of achieving this is relatively modest, the benefits for public health would be highly cost-effective.

Many efforts have been made to turn this information into nutrition education for the general public. This has taken various forms, such as

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

T. Wilson
Department of Biology, Winona State University, Winona, MN, USA
e-mail: twilson@winona.edu

D. R. Jacobs, Jr.
Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA
e-mail: jacob004@umn.edu

G. A. Bray
Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA, USA
e-mail: George.Bray@pbrc.edu

N. J. Temple et al. (eds.), *Nutritional Health*, Nutrition and Health,
https://doi.org/10.1007/978-3-031-24663-0_33

food guides and health promotion. The results of these efforts have been mixed. Some sections of the population have paid attention to the nutrition messages, followed the advice, and achieved improved health. But much more often the information has been all but ignored. The worsening obesity epidemic is the clearest demonstration of this. One major reason for this weak degree of success is because the best efforts by health professionals in the area of nutrition education have often been thwarted by the power and enormous budgets of the food industry which typically promote unhealthy patterns of eating.

The rivers of Montana serve as an illustration of the problem. One river flows west to the Pacific Ocean, a second goes north through Canada to Hudson Bay and thence to the Arctic Ocean, and the third joins the Missouri, then the Mississippi, and continues to the Gulf of Mexico. These rivers resemble the world of nutrition and health: many streams flow into major rivers of ideas, action, and direction, but these rivers can flow in opposite directions and interact in complex ways with the total landscape of nutritional health. Over the last two decades several new streams have merged with the rivers.

The contents of this book describe these issues as illustrated by the following brief summary of the book.

- Chapters 1 and 2 describe the methodology for carrying out nutrition research. This includes a close examination of the strengths and weaknesses of the different methods. These methods are the basis for most of our knowledge in nutrition science, past, present, and future.
- Chapters 5–10 provide a detailed survey of our present knowledge of the relationship between diet and the prevention and therapy of type 2 diabetes, obesity, heart disease, hypertension, and cancer. Chap. 6 on obesity and Chap. 8 on coronary heart disease present recent findings that many readers will find especially interesting.
- There is growing interest in phytochemicals and their relationship to health and disease. This topic is examined in Chap. 12.
- Chapters 13 and 14 explore the impact of alcoholic and nonalcoholic beverages on health and the risk of various diseases. Chapter 13 presents recent evidence that suggests that the recommendations regarding a safe upper limit for alcohol intake should be lowered.
- A growing trend is the development of so-called functional foods. These are claimed to be healthier as a result of either addition or removal of various bioactive substances. Their potential value is looked at in Chap. 15.
- There has been enormous interest in recent years on the potential health benefits of various dietary patterns. Chapters 16–19 examine four such diets, namely the Mediterranean diet, the DASH diet, the vegetarian/flexitarian diet, and low-carbohydrate diet.
- Chapter 20 looks at trends in dietary recommendations as they pertain to nutrient intakes, dietary guidelines, and food guides. One particular trend that is especially noteworthy is the adoption of a food guide based on a plate design for depicting the recommended diet. It is now used in the USA and several other countries.
- Food labels are described in Chap. 21. There is growing interest around the world in front-of-package food labels. Various designs have been developed and these are discussed.
- Chapter 22 surveys health promotion and nutrition policy by governments. The latter covers such topics as lowering the salt content of food, placing restrictions on the advertising of unhealthy foods, and the use of taxes and subsides so as make healthy foods more affordable relative to less healthy foods. The chapter presents the case that health promotion is of limited effectiveness and that a strategy based on government policy is likely to achieve much more success in encouraging the population to adopt a healthier lifestyle including a healthier diet. An important advantage of this strategy is that it is cost-effective.
- Chapter 23 explains how the concept of food synergy is the surest route to a better understanding of the relationship between diet and disease. The key aspect of this is a focus on foods and dietary patterns rather than single substances.

- The potential importance of genomics and gene-based personalized nutrition is examined in Chap. 24.
- Chapter 25 summarizes current knowledge on the relationship between the gut microbiome, health, and risk of various diseases.
- There is a strong relationship between the changing global environment, including climate change, and food production. Nutrition scientists are now recognizing the great importance of this subject. This has led to the emerging field of food sustainability which is discussed in Chap. 27.
- There have been many developments in recent years in the application of technology to food production, a subject examined in Chap. 28. This includes the much-debated subject of how genetic engineering is changing the DNA of the foods we eat (i.e., genetically modified organisms).
- The food industry routinely invests its enormous resources in marketing unhealthy foods. Advertising is a major component of this. At the same time the industry regularly uses its political influence to oppose any regulatory change by governments whenever this might threaten their profits. As a result opportunities to improve population health are lost. This subject is discussed in Chap. 30. One inevitable result of the actions of the food industry is the thwarting of the hard work carried out by health professionals in their efforts to encourage the population to consume a healthier diet.
- The food industry is by no means alone in the damage it causes. Chapter 31 describes how the dietary supplement industry also shows little hesitation in displaying disreputable behavior whenever this helps it boost sales of its products. More generally, there is a serious problem with the widespread dissemination of false and misleading information. This is documented in Chap. 32. One aspect of this is that thousands of books on diverse topics related to nutrition have been published in recent decades, but a great many of them are worse than useless.

When we take a broad overview of where nutrition science and nutrition practice stand in the third decade of the twenty-first century, we see overwhelming evidence that the application of our present knowledge can deliver major advances in public health. What this means is that nutrition is on track to move to a new higher level. We can call this strategic nutrition.

To paraphrase Churchill, advances in the field of nutrition science in recent years represent "not the beginning of the end but, perhaps, the end of the beginning." In the opinion of the editors of this book we are ready to move from the hors d'oeuvres to the main course.

We now present a summary of the key lessons from this book and the top priorities for action:

1. The funds allocated to nutritional research are far less than the need. A much expanded nutrition research program would generate the information needed. We think government, industry, and the general public would be responsive. This is a tall order but not impossible. The concept of food synergy should serve as a guide to nutrition research. Accordingly, the focus should be on foods and dietary patterns rather than on single substances. A reduced emphasis on mechanistic research also makes good sense.
2. There is great need for much expanded educational efforts, including health promotion campaigns. Closely related to this we need better designs for food guides. Another priority should be improved food labels, especially user-friendly front-of-package food labels.
3. Governments should implement policies geared more towards population health rather than the commercial demands of the food industry. Just as society supplies safe drinking water, society should also make healthy food readily available rather than requiring every member of the public to be a nutrition expert. Based on these principles the following actions should be taken. Adverts for unhealthy foods must be more strictly regulated. Of most importance adverts for unhealthy foods

("junk food") should be banned when the target audience is children. Other actions should include setting strict limits on the food content of unhealthy substances such as salt. Healthy foods must, as far as possible, be the affordable choice. This can be achieved by providing subsidies on healthier foods combined with adding taxes on unhealthy foods. Achieving these goals will require much determination in order to overcome the powerful resistance from the food industry and its lobbyists.

4. Nutrition policies in the future will increasingly embrace food sustainability.

This fourth edition of *Nutritional Health* provides the reader with a wide-ranging review of where the different directions of nutritional thought are going and how they interact. The authors have indicated the impediments that restrict the downward flow of this information to the consumer. This book presents some solutions for improving this flow. We have laid down the groundwork that is needed for implementing nutritional policies that are strategic and all encompassing. Changes in nutrition are coming and this book will help the reader understand these changes and the need for implementing them.

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