
Nutrition and Health

Series Editors:

Adrianne Bendich, PhD, FACN, FASN
Wellington, FL, USA

Connie W. Bales, PhD, RD
Durham VA Medical Center
Duke University School of Medicine
Durham, NC, USA

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. Nutrition and Health is a major resource of relevant, clinically based nutrition volumes for the professional that serve as a reliable source of data-driven reviews and practice guidelines.

More information about this series at <http://www.springer.com/series/7659>

Peter Weber • Marc Birringer
Jeffrey B. Blumberg
Manfred Eggersdorfer • Jan Frank
Editors

Vitamin E in Human Health

Editors

Peter Weber
University of Hohenheim
Institute of Nutritional Sciences
Stuttgart
Germany

Jeffrey B. Blumberg
Friedman School of Nutrition Science
and Policy, Jean Mayer USDA Human
Nutrition Research Center on Aging
Tufts University
Boston, MA
USA

Marc Birringer
University of Applied Sciences Fulda
Nutritional, Food and Consumer
Sciences
Fulda
Germany

Manfred Eggersdorfer
University Medical Center Groningen
Hanzepluin 1
Groningen
The Netherlands

Jan Frank
University of Hohenheim
Institute of Nutritional Sciences
Stuttgart
Germany

Nutrition and Health

ISBN 978-3-030-05314-7 ISBN 978-3-030-05315-4 (eBook)
<https://doi.org/10.1007/978-3-030-05315-4>

Library of Congress Control Number: 2019934811

© Springer Nature Switzerland AG 2019

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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

We dedicate this book to the diverse community of biochemical, molecular, clinical, and public health scientists exploring the many roles of vitamin E in human health. We especially appreciate the commitment shown by the many devoted scientists who have contributed directly to this book. Last but not the least, we are most grateful to the unending support of our families for the work we do in nutrition science to promote health and treat disease.

Peter Weber, MD, PhD
Marc Birringer, PhD
Jeffrey B. Blumberg, PhD
Manfred Eggersdorfer, PhD
Jan Frank, PhD

Foreword

Progress in nutrition science is continuing at an ever more rapid pace. New data from experimental and preclinical studies are emerging at the same time as advanced designs in prospective cohorts, metabolic studies, and clinical trials are providing evidence that needs to be evaluated and translated into dietary guidelines for health promotion and disease prevention. This is no small challenge when nutrition research is criticized as based on confounded or inaccurate methods and scorned for changing recommendations to follow or avoid specific nutrients, foods, and dietary patterns. In fact, when properly evaluated, there is a great deal of concordance between conclusions drawn from multiple research approaches, while changes in the science and recommendation largely follow these advances. When there is a discordance between these results, for example, between observational studies and clinical trials, then we need to examine them more closely. By doing so, we often gain valuable insights and learn to ask new and more targeted questions. A book like this one provides an opportunity to bring together the disparate information collected from basic research and human studies to be considered jointly in a broad context of applications from food science to public policy.

The early reductionist approaches in nutrition research focused on the discovery of individual nutrients and their mechanisms in the prevention of corresponding deficiency syndromes. However, much like more recent holistic approaches to tackling complex biological pathways and to addressing socio-cultural factors that underlie health outcomes, parallels exist for individual nutrients like vitamin E. Most micronutrients have pleiotropic effects on multiple physiological systems, including the microbiome, and interact broadly with other dietary components as well as drugs and environmental toxins. We need to understand better how the various congeners of vitamin E and their metabolites affect the molecular and cellular functions and structures of the body that ultimately impact human health. These issues are urgent because the consumption of vitamin E from foods falls below recommended intakes in about 90 percent of populations around the globe. Together with other under-consumed micronutrients and healthy foods, we continue to be faced with the problem of “hidden hunger” where the effect of these chronic shortfalls may not be immediately apparent but whose consequences can be long

term and profound. After being studied for close to a century, we are far from knowing all that is relevant about vitamin E and other micronutrients. This volume brings together the history and the science of vitamin E and looks to its future in human health.

Dariusz Mozaffarian, MD, DrPH
Friedman School of Nutrition Science and Policy
Tufts University
Boston, MA, USA

Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes (1) a synthesis of the state of the science; (2) timely, in-depth reviews by the leading researchers and clinicians in their respective fields; (3) extensive, up-to-date, fully annotated reference lists; (4) a detailed index; (5) relevant tables and figures; (6) identification of paradigm shifts and the consequences; (7) virtually no overlap of information between chapters but targeted, interchapter referrals; (8) suggestions of areas for future research; and (9) balanced, data-driven answers to patient as well as health professional questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter and in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research- and practice-oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed *de novo*, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

Vitamin E in Human Health edited by **Peter Weber, MD, PhD; Marc Birringer, PhD; Jeffrey B. Blumberg, PhD; Manfred Eggersdorfer, PhD, and Jan Frank, PhD**, is a very welcome and timely addition to the Nutrition and Health Series and fully exemplifies the series' goals. There has been a continuous stream of basic as well as clinical research over the last decade on the associations between oxidative stress and increased risk of cellular damage that provide increasing evidence of the critical antioxidant role of vitamin E. Moreover, the recent findings of non-antioxidant functions of the vitamin, including biological activities of metabolites as well as activation of enzymes and, of great significance, vitamin E-gene interactions, are reviewed in depth so that the reader is brought up-to-date on the many new findings at the cellular and intracellular levels. With regard to vitamin E, the major lipid-soluble antioxidant capable of reducing the adverse effects of oxidative stress, significant clinical research has been published on the importance of vitamin

E in reducing the damage to the vessels and organs of the cardiovascular and cerebrovascular systems in aging populations as well as in the very youngest newborns. Of equal importance are the detailed studies of the critical role of vitamin E in tissues of the nervous and immune systems. Contemporary data on the vitamin E status in at-risk populations, especially in children and women of childbearing potential, are also of great importance; these studies alone warrant the development of this 31-chapter tome.

Vitamin E, as an essential fat-soluble nutrient for humans and animal species, plays key roles in the retina and related brain tissues, lymphocytes, macrophages and other immune cells, red cells, sperm and ova, and basically every cell membrane in the body. As a former vitamin E researcher, and Roche colleague of Dr. Peter Weber, I am personally very pleased to note the thoughtful organization of this new volume. There are chapters that review data on the biology and biochemistry of the vitamin, its metabolism and metabolomics, and effects on gene regulation and the genetic defect that results in severe neurological and muscular defects associated with ataxia in isolated vitamin E deficiency; intakes and status in healthy individuals are included as well as an extensive section that is devoted to clinically relevant discussions of safety in healthy individuals as well as in patient populations. The volume is designed as an important resource for nutritionists and dietitians, research and public health scientists, diabetes specialists, ophthalmologists, nephrologists, cardiologists, gastroenterologists, and related physicians and healthcare professionals who interact with clients, patients, and/or family members. The volume provides objective, relevant information for professors and lecturers, advanced undergraduates and graduates, researchers, and clinical investigators who require extensive, up-to-date literature reviews, instructive tables and figures, and excellent references on all aspects of the importance of vitamin E in human health and disease.

The editors of this volume are experts in their respective fields. Dr. Peter Weber, MD, PhD, is Adjunct Professor of Nutrition at the Institute of Nutritional Sciences at the University of Hohenheim, Germany. Dr. Weber received his PhD in Nutritional Sciences from the University of Bonn, Germany, and his MD degree from the University of Mainz, Germany. He then worked at the Research Institute of Child Nutrition in Dortmund, Germany, and then trained in Internal Medicine with a subspecialty in endocrinology at the University of Mainz, Germany. Dr. Weber practiced medicine and clinical research for 10 years before joining the vitamins R&D area at Hoffmann-La Roche in New Jersey, USA, and following the purchase of the Vitamins Division by DSM, he continued to lead the research and development team human nutrition in various functions until his recent retirement. Dr. Weber has more than 70 peer-reviewed publications in the fields of iodine deficiency and goiter, thyroid diseases, metabolic syndrome, postprandial lipid metabolism, vitamin K, vitamin status of populations, and the role of vitamins and polyunsaturated fatty acids in human health. He is a Coeditor of several books on micronutrients and health. His scientific interests include the role of micronutrients in the prevention of chronic diseases, nutritional status in risk groups such as the elderly, and the emerging topic of nutrition security.

Dr. Marc Birringer received his PhD in Chemistry from the University of Siegen (Germany). His postdoctoral research included investigations of the

anticancer activity of seleno-amino acids at the University of Albany and examination of human vitamin E metabolism and anticancer properties of newly synthesized tocopheryl derivatives at the German Institute of Human Nutrition. Dr. Birringer co-founded a biopharmaceutical company where he was Head of R&D and developed a high-throughput synthesizer for peptide libraries and the development of tissue-specific drug-peptide conjugates. He also researched diet-induced mitochondrial activation and aging. Dr. Birringer was appointed Full Professor for Applied Nutritional and Environmental Biochemistry in the Department of Nutritional, Food and Consumer Sciences at Fulda University of Applied Sciences. His current research is focused on the metabolism of dietary lipophilic micronutrients. Dr. Birringer is President of the Gesellschaft für Angewandte Vitaminforschung eV and Member of the Editorial Board of *NFS Journal* and has authored more than 80 scientific articles and reviews.

Dr. Jeffrey B. Blumberg, PhD, is a Full Professor in the Friedman School of Nutrition Science and Policy and also serves as the Senior Scientist in the Antioxidants Research Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University (USA). His research is focused on the biochemical basis for the role of antioxidant nutrients and their dietary requirements in promoting health and preventing disease during the aging process via changes in the status of oxidative stress, glucoregulation, and inflammation. He has published more than 400 scientific articles and serves on the Editorial Boards of several scientific journals. Dr. Blumberg was included in the 2015 Thomson Reuters' top 1% of cited researchers in his field. He has been the Recipient of the ASN Mary Swartz Rose Senior Investigator Award for outstanding research on the safety and efficacy of bio-active compounds for human health. Dr. Blumberg participates in activities relevant to the incorporation of sound nutrition science into public health policy and has served as a Member of the Workshop on Health Promotion and Aging in the Office of the US Surgeon General, Sports Medicine Committee of the US Olympic Committee, Consultation on Preparation and Use of Food-Based Dietary Guidelines for the WHO/FAO, Food Advisory Committee of the FDA, and other committees.

Dr. Manfred Eggersdorfer is Professor for Healthy Ageing at the University Medical Center in Groningen, Netherlands. He received his PhD in Organic Chemistry at the Technical University of Munich, Germany, and undertook postdoctoral work at Stanford University, California, working with Dr. Carl Djerassi on the isolation and characterization of sterols from marine origin. Dr. Manfred Eggersdorfer worked for BASF and was Head of R&D for the Fine Chemicals Division and then joined Roche as Head of Research Vitamins and DSM where he was responsible for Nutrition Science & Advocacy. Dr. Eggersdorfer is a Member of the Advisory Board of Johns Hopkins Bloomberg School of Public Health, a Board Member of the Gesellschaft für Angewandte Vitaminforschung eV, and Member of the Tufts Nutrition Council. He is an Honorary Member of the Oxygen Club of California and Author of numerous publications, reviews, and book chapters in the field of vitamins, carotenoids, and innovation in nutritional ingredients. He is a Reviewer for several scientific journals as well as Associate Editor of the *International Journal of Vitamin and Nutrition Research*.

Professor Frank graduated with a Diploma in Nutrition from Bonn University and obtained his PhD in Food Science at the Swedish University of Agricultural Sciences. He received postdoctoral training at the Universities of Kiel and Hohenheim and was a Visiting Scientist at the Linus Pauling Institute (USA), the University of Reading (UK), and the University of Surrey (UK). Dr. Frank served as Professor of Human Metabolomics at the Institute of Nutrition and Food Science at the University of Bonn and is now Full Professor and Head of the Division of Food Biofunctionality at the Institute of Nutritional Sciences at the University of Hohenheim (Germany). He is the Founding President of the Society of Nutrition and Food Science (www.snfs.org), Member of the Board of Directors of the Society for Applied Vitamin Research (Gesellschaft für Angewandte Vitaminforschung eV), and Editor-in-Chief of *NFS Journal*, Associate Editor of *Nutrition*, and Member of the Editorial Boards of *The Journal of Nutritional Biochemistry*, *BioFactors*, and *Plant Foods for Human Nutrition*. His primary research interests lie in factors that determine the absorption, metabolism, and elimination of phytochemicals and different vitamin E congeners, especially long-chain vitamin E metabolites.

The 31 chapters in this comprehensive volume are organized in five parts: historic perspective and basic biochemical review; intake and status data; safety, drug-nutrient interactions, and nutrient-nutrient interactions; cardiovascular, neurological, and immune functions; and public health implications.

Part I: Biochemistry, Metabolism, and Molecular Effects of Vitamin E

The first of the four introductory chapters of the volume, Chap. 1, written by the editors, provides readers with the rationale for this timely review of vitamin E. Chapter 2, *the first chapter in Part One*, examines the first 100 years of vitamin E research using a historical perspective of the discovery of the vitamin, its importance in the maintenance of growth and animal reproduction, and the gradual appreciation of its essentiality for human life. We learn that vitamin E has eight forms that provide the biological activities associated with the broad term. The vitamin is ubiquitously distributed throughout the body as it is a critical component of all membranes. Chapter 3 describes in detail the physical structures and biological activities of the eight forms of vitamin E and concentrates on their antioxidant activities in both foods and living organisms. α -Tocopherol's role in cell membranes is to protect unsaturated fatty acids from oxidation and maintain membrane integrity. Even though the concentration of α -tocopherol in membranes is small, ranging 0.1–1 mol% relative to phospholipids, it efficiently prevents the oxidation of these fatty acids. The extensively referenced chapter describes the process of scavenging free radicals and the detailed movement of vitamin E within cell membranes in animal tissues as well as the protective role in food production involving oils and other lipids. Chapter 4 reviews the absorption, metabolism, and excretion of vitamin E. We learn that vitamin E has a high bioavailability of about 50–80% and follows the general absorptive route of dietary fats; the

liver preferentially incorporates α -tocopherol into lipoproteins that are released into the blood stream for the distribution of lipids to peripheral tissues. Metabolism is described in detail and outstanding research questions are included.

Chapters 5 and 6 examine the bioactivities of some of the vitamin E derivatives and metabolites. Chapter 5, containing 11 detailed figures and over 100 relevant references, reviews the new data concerning the biosynthetic steps leading to a chromanol ring system found only in photosynthetic organisms, such as plants, algae, and cyanobacteria as well as fungi, corals, sponges, and tunicates. The chapter focuses on the structural diversity and bioactivity of minor vitamin E derivatives, meroditerpenes (135 in number that have so far been described) that belong to the class of chromanols and chromenols. This unique chapter provides details concerning the biosynthesis of these compounds and lists of plants that contain these compounds and their functions. Chapter 6 expands our knowledge of new research concerning the bioactivities of vitamin E metabolites by explaining that during hepatic metabolism of vitamin E, the long-chain metabolites, 13-hydroxychromanol and 13-carboxychromanol, are formed by oxidative modification of the vitamin E side chain. These metabolites have been detected in human serum, indicating a physiological relevance for the human body. Given that only 1% of the total body tocopherol is transported in blood, the determination of the long-chain metabolites in extrahepatic tissues is important for assessing the total value of vitamin E for human health. Methodologies are described in detail, and preliminary in vitro studies show activities with regard to anti-inflammatory functions, lipid metabolism, chemoprevention, and xenobiotic metabolism.

New research into the gene-regulatory functions of vitamin E is reviewed in Chap. 7. The chapter examines the non-antioxidant properties of vitamin E including α -tocopherol's inhibition of protein kinase C and 5-lipoxygenase and activation of protein phosphatase 2A and diacylglycerol kinase. Vitamin E can modulate the immune response and activities of many of the immune cells resulting in reduced inflammation and enhanced responses to certain pathogens (discussed in more detail in Chaps. 25 and 26). There is a discussion of the long-term effects of vitamin E deficiency on hepatic gene expression by regulating specific hepatic factors and messenger RNA responses (as reviewed in Chap. 20). The authors' animal studies indicate that dietary vitamin E induces changes in steroidogenesis by affecting cholesterol homeostasis in the testes and adrenal glands. The chapter includes informative figures, an extensive and detailed table, and 120 key references. Another relatively new research area, looked at in Chap. 8, is the study entitled "Metabolomics." Metabolomics is a technology that examines all of the metabolites in a given sample and the changes in these metabolites when challenged with a substance such as vitamin E. The chapter reviews the technologies used to examine the metabolome (all of the metabolites in a sample). The chapter describes the studies in humans that have demonstrated changes to the urinary and the plasma metabolome with vitamin E supplementation and the studies in animals that have found changes to the metabolome with models of vitamin E deficiency. As examples, in humans, vitamin E supplementation influences phospholipid metabolism and amino acid metabolism. Metabolomic studies in animal models, including studies with zebra fish, showed changes to anti-

oxidant status and lipid peroxidation with vitamin E deficiency; rodent models of vitamin E deficiency showed influences on central metabolism.

Chapter 9 provides an in-depth review of the structure and function of the specific α -tocopherol transfer protein (TTP) which serves as the major determinant for the distribution of newly absorbed dietary tocopherol throughout the body. The authors present a model for the directional transport of tocopherol from endosomal membranes to the plasma membrane of hepatocytes and review recent data showing that regulation of TTP serves to maintain vitamin E homeostasis in cells and tissues. Expression of TTP is highest in the liver and is also expressed in the brain and placenta and that expression in these tissues is of high physiological importance. Mutations in the TTP gene are the only known cause for the autosomal recessive disorder ataxia with isolated vitamin E deficiency (AVED). AVED patients present with progressive neurodegeneration and low (or undetectable) serum levels of α -tocopherol.

As discussed in earlier chapters, there is growing interest in the biological activities of a number of vitamin E isoforms. New data on the in vitro studies of the effects of γ -tocotrienol on cancer cell types in cell culture are described in Chap. 10. The chapter reviews the importance of lipid rafts, which are specialized micro-domains within the plasma membrane that are required for receptor tyrosine kinase dimerization, activation, and signal transduction. Recent studies demonstrate that the antiproliferative effects of γ -tocotrienol are associated with its accumulation in the lipid raft micro-domain where it appears to interfere with the tyrosine kinase dimerization and activation in human breast cancer cells. Additional experiments showed that γ -tocotrienol added to cell cultures directly disrupted lipid raft integrity by directly interfering with HER receptor dimerization that is linked to breast cancer cell viability. This early evidence of the bioactivity of γ -tocotrienol is critical to moving to the next step of laboratory animal testing in breast cancer models.

The final chapter in this Part, Chap. 11, describes, in detail, the interactions between vitamin E and polyunsaturated fatty acids (PUFA) and reviews the mechanisms of uptake, transport, distribution, metabolism, interaction, and regulatory roles of both these classes of essential nutrients in signal transduction, gene expression, and maintenance of normal cell membrane physiology. Vitamin E protects PUFA in cellular membranes from oxidative damage, and the key tissues and organs most affected by either nutrient deficiency are described. Emphasis is placed on the review of research in brain function and the roles of active lipids and vitamin E and how each has independent effects and interdependent effects.

Part II: A Global View on Vitamin E Intake and Status

The five chapters in this part examine the processes behind setting healthful intake levels of vitamin E and review the current intake levels in populations based upon age, sex, and the types of foods that are consumed. Chapter 12 describes the challenges facing regulators, academicians, and clinicians in setting recommended intakes for vitamin E. The chapter summarizes the current approaches used by national organizations around the world to set vitamin E intake recommendations and compares the most recent

recommendations. The authors posit that new research on the importance of increased omega-3 long-chain (LC) PUFA intakes should also result in further increases in vitamin E intake to protect the PUFA from oxidation. Specifically, even though the current intake of omega-3 LC PUFA is low and below the recommended dietary intakes of most Western nations, vitamin E intakes are even lower than needed to protect PUFA. In fact, a worldwide review of nutritional surveys showed that only 45 of the 266 countries achieved the recommended PUFA intake level. Similarly, the current vitamin E intakes are below recommended levels in more than 90% of North American as well as in some European countries. Even so, national recommendations have increased for LC PUFA. Thus, the authors suggest that the ratio of vitamin E to PUFA is even more critical and requires a deeper examination by regulatory authorities. Chapter 13 reviews the current data from over 120 relevant references on vitamin E intakes globally and clearly indicates that, virtually, all populations examined had low intakes relative to whatever their country recommended. Likewise, serum vitamin E concentrations reflected the low intakes, and given that the standard for adequacy is also relatively low, based upon PUFA intakes, these even lower serum levels attest to the validity of the intake data across nations. Of importance are the data that show that plasma vitamin E concentrations less than 8 $\mu\text{mol/L}$ are associated with neurologic disturbances and diseases including peripheral neuropathy, spinocerebellar ataxia, and skeletal myopathy. Concentrations lower than 12 $\mu\text{mol/L}$ have been seen in women with miscarriages and in patients with increased erythrocyte fragility. Preliminary data suggest that low plasma α -tocopherol concentrations are associated with increased risk of developing mild cognitive impairment and Alzheimer's disease. The studies that have correlated higher serum vitamin E with health benefits are reviewed. Chapter 14 presents the current reference values for vitamin E intake and compares these values to the published data on vitamin E intake as well as on vitamin E status for toddlers, elementary school-age children, and adolescents. The chapter includes tables and text that contain the published dietary intakes in these age groups, including infants (preterm and term) from the USA, Mexico, and Brazil and several European countries and a discussion of the rationale used to determine these values. The studies that determined serum/plasma vitamin E in children are reviewed, and the data, like that of intake, are inconsistent.

Chapter 15 provides new research concerning the determination of vitamin E status and its correlation with other biological factors. Vitamin E, as a lipid-soluble molecule, has a high affinity for circulating lipids, resulting in a strong correlation with total cholesterol and fasting triacylglycerols. Many studies correct this by analyzing vitamin E serum/plasma concentrations as a ratio of vitamin E concentrations divided by total cholesterol plus fasting triglycerides. The authors are concerned that there is also a positive correlation between total cholesterol and fasting triglycerides, the summation of total cholesterol and fasting triglycerides to calculate total lipids, and correction for this by dividing vitamin E concentrations may result in an unintended double correction for variance shared by total cholesterol and fasting triglycerides and unwanted weakening, disappearance, or even inversion of existing associations with vitamin E. The chapter, using data from the LifeLines Cohort Study, calculates linear regressions of vitamin E serum concentrations

with numerous other clinical factors and found the association between circulating α -tocopherol and γ -tocopherol to be positive, while most of the associations of γ -tocopherol with biological variables, if present, were opposite to those that were observed for α -tocopherol. The associations are described in detail in the text and included tables.

Chapter 16 reviews the major sources of vitamin E in the diet with emphasis on natural sources. The effects of food processing are also included and examined from the point of harvest until the product is consumed. Wheat germ oil contains about 149 mg of α -tocopherol per 100 g, making it the edible oil that has the highest amount of total vitamin E. Other edible oils that are excellent sources of α -tocopherol include sunflower, safflower, and olive oils. In addition to oils, the comprehensive chapter examines numerous foods and types of preparation that are further summarized in relevant tables and figures.

Part III: Safety of Vitamin E and Interactions with Other Nutrients and Drugs

This clinically important part of the volume provides the reader with three chapters that examine the safety of supplementation with vitamin E, its potential interaction with commonly used pharmaceuticals, as well as the reported interactions with vitamin K. Chapter 17 reviews the analyses of data associating vitamin E supplementation with potential increased risk of death. The author performed a meta-analysis with 68 published studies. The total numbers of study participants were 124,836 in the vitamin E group and 124,925 in the control group. Dosages of vitamin E supplementation ranged from 16.5 to 5000 IU/d. Vitamin E supplementation, regardless of the length of use or dose, age, or sex of participant, did not affect mortality risk. The comprehensive chapter provides all citations, methods of the multiple types of analyses, and findings. Additionally, vitamin E intake is considered to be safe up to an established upper tolerable intake (UL) level of 300–1,000 mg/day (depending on the regulatory authority and the age and sex of the individual) and in any amount that is naturally occurring in foods or in multivitamin supplements. These values are agreed upon by expert groups of the US-IOM, EFSA, and the UK's Expert Group on Vitamins and Minerals (EVM).

Chapter 18 looks at the potential for vitamin E supplementation to affect the drugs commonly used to treat medical conditions often associated with reported beneficial vitamin E effects. The chapter reviews the basics of nutrient-drug interactions: interactions affecting the pharmacokinetics (the metabolism of a drug) or pharmacodynamics (the effect of a drug) of drugs. There is also a review of the evidence in the scientific literature on the potential for any of the eight vitamin E congeners to interact with drugs. Hepatic metabolism is reviewed in detail, and it appears that vitamin E does not affect these enzyme systems at dosage levels known to be consumed, including high doses of supplements. No evidence for vitamin E-drug interactions at vitamin E intakes achievable by diet was found. High-dose (≥ 300 mg/d) supplementation of vitamin E, especially of α -tocopherol, however, may lead

to interactions with aspirin, warfarin, tamoxifen, and cyclosporine A. For the majority of drugs, interactions with vitamin E, even at high doses, have not been observed and are considered by the authors to be unlikely. Chapter 19 looks at the nutrient-nutrient interactions with emphasis on the interactions between vitamin E and another fat-soluble vitamin, vitamin K. Vitamin K is required for normal blood clotting, and vitamin E supplementation can affect platelet membranes, and thus there is the potential for vitamin E to affect the clotting function of vitamin K. However, the extensive review of in vitro as well as clinical studies with and without the anticlotting drug, warfarin, indicates that vitamin E supplementation did not affect clotting time or other indices of clotting.

Part IV: Benefits of Vitamin E on Human Health and Disease

The next four chapters examine the clinical data associating vitamin E status and/or supplementation with beneficial effects on the cardiovascular system and related data in individuals with diabetes or the metabolic syndrome. The final chapter looks at nonalcoholic fatty liver disease (NAFLD). Chapter 20 focuses on the clinical trials evaluating vitamin E supplementation and various cardiovascular outcomes. The chapter examines the major primary prevention peer-reviewed studies published starting in 1998 and ends with the study published in 2015. Secondary prevention studies are then reviewed including studies looking at vitamin E as well as those testing vitamins E and C, β -carotene, and certain pharmacological agents. All data are tabulated; the authors posit that there may be specific patient populations that will benefit from vitamin E supplementation, however, to date; the published studies do not support vitamin E supplementation for either primary or secondary prevention of cardiovascular disease.

One possible reason that the intervention studies have not shown statistically positive effects of vitamin E may be that the populations are genetically heterogeneous and vitamin E may benefit some and harm other patients, resulting in an overall null effect. Chapter 21 reviews the important finding that a polymorphism in the haptoglobin (Hp) gene strongly defines individuals with diabetes who are at greater risk of vascular disease. The chapter describes the three polymorphisms and their effects on the removal of free hemoglobin from the bloodstream. The Hp 2-2 genotype is an independent risk factor for incident atherosclerotic cardiovascular disease (CVD) in type 1 and type 2 diabetes patients. Vitamin E supplementation benefits diabetics with the Hp 2-2 genotype. The data from clinical trials as well as the pharmacogenomic consequences of the polymorphism are examined in detail.

Chapter 22 examines the factors associated with the metabolic syndrome (MetS) which is considered an early risk factor for diabetes, cardiovascular, as well as nonalcoholic liver diseases. MetS is defined by the presence of a cluster of conditions that includes at least three of the five risk factors: hypertension, hyperglycemia, central obesity, hypertriglyceridemia, or depressed high-density lipoprotein (HDL). Compared with healthy individuals,

individuals with MetS often have increased oxidative stress that is evidenced by circulating biomarkers of lipid peroxidation including F₂-isoprostanes and oxidized LDL and low antioxidant capacity. Similarly, inflammatory responses, including circulating pro-inflammatory interleukins, tumor necrosis factor- α , C-reactive protein, myeloperoxidase, and other inflammatory mediator concentrations, are increased. The chapter explains the consequences of the metabolic aberrations seen in the syndrome and focuses on obese patients with MetS as a clinical model and emphasizes the dysregulation of α -tocopherol trafficking and catabolism and related health consequences. Individuals with MetS have poor α -tocopherol intakes and compromised α -tocopherol status. The inability to efficiently achieve adequate α -tocopherol serum concentrations can create a vicious cycle of increasing inflammatory damage that further provokes the depletion of α -tocopherol.

Chapter 23 provides a clinical perspective on the hepatic disease, nonalcoholic fatty liver disease (NAFLD), which is one of the leading causes of chronic liver disease worldwide, especially in Western countries where obesity and metabolic syndrome have been on the rise. NAFLD is broadly subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NASH, characterized by histological hallmarks of steatosis, lobular inflammation, and hepatocellular ballooning, can progress to fibrosis and liver cancer. Intracellular evidence points to oxidative damage to the liver mitochondria and other organelles in NAFLD. At the same time, antioxidant capacity of the liver is reduced, resulting in further damage. Laboratory animal studies of NASH and human clinical trials with vitamin E are reviewed and tabulated

Chapter 24 examines the rationale for looking at vitamin E status and supplementation in the prevention and/or slowing of progression of Alzheimer's disease (AD) or mild cognitive impairment (MCI). Vitamin E, as an essential antioxidant micronutrient, is a significant factor in protecting cells from oxidative damage, such as the harmful effects of free radicals observed in brain aging and AD. The chapter reviews the animal studies that showed sufficient evidence to consider treatment with vitamin E for patients suffering from AD. However, the results of clinical studies with AD patients are conflicting. To date, there are no convincing data from meta-analyses of randomized, placebo-controlled trials that vitamin E alone or in combination with other antioxidants prevents the progression or improves cognitive function in people with MCI or AD.

Two major functions of the human immune system are to protect from pathogens and also to recognize our own cells, tissues, and organs. If the immune system is not working properly, there is a greater risk of infections, and, as important, there is also a greater risk of allergies and asthma and other auto-immune diseases. Certainly, genetics plays a critical role, but environmental factors, including nutrients, like vitamin E, can affect these risks. Chapter 25 looks at the development of allergies and asthma and identifies the opposite responses to two isoforms of vitamin E, α -tocopherol and γ -tocopherol. The complex responses seen during allergy and asthma episodes are described as are the specific components of the immune system that respond to these challenges. We learn that in addition to antioxidant functions of tocopherols, the non-antioxidant functions of tocopherol regulate allergic inflammation. Important for interpretation of tocopherol regulatory effects is

that although γ -tocopherol is at tenfold lower concentrations in vivo, γ -tocopherol is very potent and, at these tenfold lower concentrations, can block the benefit of α -tocopherol during allergic inflammation and asthma. Data, from the over 200 important references cited, are presented from laboratory animal studies, epidemiological data globally, and from clinical studies including maternal to child transmission of vitamin E, increased use of soybean oil rich in γ -tocopherol in infant formula and other relevant factors that help to explain the potential benefits and risks of examining vitamin E in allergy and asthma without paying attention to the particular isoforms. Chapter 26 reviews the data showing the immunoenhancing capabilities of vitamin E that can beneficially affect responses to infections. The authors present their data as well as that of others that increased vitamin E intake (α -tocopherol) above recommended levels enhances T-cell function, particularly in aged animals and humans. The mechanisms for this effect of vitamin E involve both a direct effect of enhancing T-cell activation and effector function, and a suppressing effect on the production of prostaglandin E₂, a T-cell-suppressing lipid mediator known to increase with aging. Vitamin E's enhancement of immune functions has significant clinical implications as supplementation is associated with increased resistance to respiratory infections in both aged mice and older adults. The chapter reviews the mechanism of action of the immune system and the detailed analysis of the role of vitamin E in assuring that responses to pathogens, especially respiratory infections, are optimal. The authors indicate that the intake level of vitamin E needed to assure robust immune responses in seniors is about 200 mg/d as compared to the US recommended level of 15 mg/d.

Two other important topics are included in this part of the impressive volume: vitamin E and air pollution, and pregnancy. The chapter on vitamin E's role in reproductive function is especially apt as the first establishment of the international units of activity (IU) of vitamin E was based upon the prevention of fetal reabsorption in a rat model. Chapter 27, containing over 200 relevant references, reviews the sources of air pollution, their adverse health effects, and ways to mitigate these effects with primary decreases in the sources as well as secondary measures to help protect the lungs and overall health. Air pollution is mainly caused by vehicle engine combustion, fossil fuel combustion, power plants, and other industrial sources. Compounds found in air pollution discussed include particulate matter from various sources, carbon monoxide, lead, nitrogen dioxide, sulfur dioxide, and ozone. Children, the elderly, and individuals with health conditions such as asthma, chronic obstructive pulmonary disease (COPD), hypertension, ischemic heart disease, obesity, and diabetes are more susceptible than other populations to the toxicity of air pollution. Both laboratory and clinical studies, where vitamin E, often with vitamin C, is given to at-risk populations, are reviewed. We learn that exposure to pollutants increases the risk of many common diseases, including asthma, COPD, and cardiovascular, metabolic, gastrointestinal, skin, and CNS diseases. While the specific mechanisms leading to the development and progression of each of these diseases vary, all have a common underlying pathology of inflammation and oxidative stress.

Chapter 28 describes our current understanding of vitamin E's role in pregnancy. The vitamin E status of the pregnant woman and its impact on the developing fetus are reviewed. Complications of pregnancy and the neonatal

period, including, but not limited to, infection, chronic lung disease, necrotizing enterocolitis, and intraventricular hemorrhage, are characterized by inflammation. Also, pregnancy outcomes such as length of gestation, mode of delivery, and associations with preeclampsia, pregnancy-induced hypertension, and gestational diabetes are discussed. The authors acknowledge that considerable scientific work remains to fully understand the role of vitamin E in fertility, pregnancy, and its ability to optimize maternal and neonatal outcomes.

Part V: Public Health Implications of Vitamin E

The last part of this comprehensive volume explores unique questions concerning important public health issues. The first chapter examines the health economics of vitamin E supplementation followed by an investigation of consumer choices including vitamin E use and, finally, a critical examination of the current knowledge gaps which are always linked to research priorities and funding sources. Chapter 29 describes the applications of health economic theories and models to an example of clinical use of vitamin E to obtain a better understanding of the possible impact of this essential micronutrient on healthcare costs. The chapter includes a general introduction into health economics and the main concept of the cost per quality-adjusted life year (QALY) gained. This calculation is used to determine the value of vitamin E supplementation using the clinical data discussed in Chap. 20, where there was a reduction in the risk of cardiovascular complications in type 2 diabetes mellitus patients with the haptoglobin Hp 2-2 genotype. The author calculated that, irrespective of Hp genotype, there was an incremental cost-effectiveness ratio (ICER) of £ 684 per QALY gained compared with patients who did not take vitamin E supplementation. Given that in the UK, the value of one QALY is about £40,000, the data indicate that vitamin E supplementation is a very cost-effective intervention for this indication. Different scenarios are provided, and the factors that are used to determine the health economics of an intervention in different healthcare environments are discussed.

Chapter 30 takes a pragmatic perspective on consumer nutrition knowledge and extrapolates to the degree of consumer awareness of vitamin E and its functions as these are critical issues in making the decision to use vitamin supplements. We learn that most consumers have learned that there is a link between the food consumed and their health. Using consumer feedback, it is also clear that not everyone is highly motivated to eat healthily, because food serves other purposes than maintaining a healthy body. The chapter discusses the concept of nutrition knowledge, presents insights on how and from which sources consumers obtain their nutrition knowledge and how this nutrition knowledge affects their food choices and other decisions relevant to their dietary intake, and, finally, reviews possible options for behavioral change regarding the intake of micronutrients such as vitamin E. The author notes that the instruments used to ask consumers about their nutrition knowledge rarely include questions about any vitamins, but when vitamins and minerals were included in questions, consumers rated their importance as high. Recent data indicate that the Internet is a significant resource for nutrition informa-

tion for consumers. The complexity of affecting consumer intake of any food, let alone a single nutrient such as vitamin E, appears from this analysis to be daunting. The conclusion is that the role of vitamin E in consumer decision-making is probably very small and that attempts to change vitamin E intake will be difficult.

The final chapter, Chap. 31, describes the difficulties in comparing study findings between healthy individuals and those with clinical disease; moreover, there is not a clear definition of the term “healthy individual.” Thus, building a totality of the evidence of a consistent biological effect of vitamin E supplementation on any outcome remains quite difficult. Even when the finding is accepted, as with the haptoglobin data in Chap. 20, the finding is so specific, it affects individuals with diabetes and thus not healthy individuals, and the benefits are quite difficult to explain to the general consumer. The chapter includes several examples of basic knowledge gaps including the fact that in the case of vitamin E, the Institute of Medicine (IOM) acknowledges that persons consuming a diet high in polyunsaturated fatty acids (PUFA) require a higher intake of vitamin E to meet the estimated average requirement (EAR) levels for adults in the USA. However, since studies used to support the current EAR levels for vitamin E were conducted in men only, the IOM lacked the scientific data to deliberate a potential EAR for women or any other subpopulations based on age, as an example. The chapter presents insights into the process used for the funding of nutrition research from the National Institutes of Health and other national sources of funding. As with consumer interest, funding research studies are based upon many disparate factors, and priorities are constantly in flux, resulting in the difficulty in comparing results over time. Of note, there are many new initiatives that are being implemented to broaden the scope of research funding, including collaboration across national borders and collaboration with private companies.

Conclusions

The above description of the volume’s 31 chapters attests to the depth of information provided by the 50 highly respected chapter authors and volume editors. Each chapter includes complete definitions of terms with the abbreviations fully defined and consistent use of terms between chapters. Key features of the comprehensive volume include over 100 detailed tables and informative figures; an extensive, detailed index; and more than 2600 up-to-date references that provide the reader with excellent sources of worthwhile practice-oriented information that will be of great value to health providers as well as graduate and medical students.

In conclusion, *Vitamin E in Human Health*, edited by **Peter Weber, Marc Birringer, Jeffrey B. Blumberg, Manfred Eggersdorfer, and Jan Frank**, provides health professionals in many areas of research and practice with the most current and well-referenced volume on the importance of vitamin E in the maintenance of the overall health of the individual as well as reducing the risk of adverse effects in patients with chronic and/or infectious diseases that increase the risk of oxidative stress. The volume serves the reader as the benchmark for integrating the complex interrelationships

between vitamin E intake and the consumption of dietary and supplemental sources of lipids, especially omega-3 long-chain PUFA. Moreover, the physiological, genetic, and environmental interactions between vitamin E, its eight isoforms, metabolites, and cofactors are clearly delineated so that students as well as practitioners can better understand the complexities of these interactions. Practice-oriented chapters examine the clinical importance of a specific vitamin E transfer protein, metabolomics effects of vitamin E, its use as an antioxidant in foods, the clinical value of vitamin E in asthma and allergy, respiratory disease prevention, exposure to air pollution, and human reproduction. The final chapters of this valuable volume provide unique and relevant data on the positive health economic value of vitamin E supplementation in certain patient populations and the importance of understanding the drivers of consumer use of specific supplements, such as vitamin E, and a final chapter provides valuable insights into the processes involved in determining the funding for health research in the USA and how vitamin E research funding fits into these objective processes. The broad scope as well as in-depth reviews of each chapter's topic makes this excellent volume a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, PhD, FACN, FASN
Series Editor

About the Series Editor



Adrienne Bendich PhD, FASN, FACN, has served as the “*Nutrition and Health*” *Series Editor* for more than 20 years and has provided leadership and guidance to more than 200 editors that have developed the 80+ well-respected and highly recommended volumes in the series.

In addition to *Vitamin E in Human Health* edited by Peter Weber, Marc Birringer, Jeffrey B. Blumberg, Manfred Eggersdorfer, and Jan Frank, major new editions published in 2012–2019 include:

1. *Handbook of Nutrition and Pregnancy, Second Edition*, edited by Carol J. Lammi-Keefe, Sarah C. Couch, and John P. Kirwan, 2019
2. *Dietary Patterns and Whole Plant Foods in Aging and Disease*, edited as well as written by Mark L. Dreher, PhD, 2018
3. *Dietary Fiber in Health and Disease*, edited as well as written by Mark L. Dreher, PhD, 2017
4. *Clinical Aspects of Natural and Added Phosphorus in Foods*, edited by Orlando M. Gutierrez, Kamyar Kalantar-Zadeh, and Rajnish Mehrotra, 2017
5. *Diet, Nutrition, and Fetal Programming* edited by Rajendram Rajkumar, Victor R. Preedy, and Vinood B. Patel, 2017
6. *Nutrition and Diet in Maternal Diabetes*, edited by Rajendram Rajkumar, Victor R. Preedy, and Vinood B. Patel, 2017
7. *Nitrite and Nitrate in Human Health and Disease, Second Edition*, edited by Nathan S. Bryan and Joseph Loscalzo, 2017
8. *Nutrition in Lifestyle Medicine*, edited by James M. Rippe, 2017
9. *Nutrition Guide for Physicians and Related Healthcare Professionals, Second Edition* edited by Norman J. Temple, Ted Wilson and George A. Bray, 2016
10. *Clinical Aspects of Natural and Added Phosphorus in Foods*, edited by Orlando M. Gutiérrez, Kamyar Kalantar-Zadeh, and Rajnish Mehrotra, 2016
11. *L-Arginine in Clinical Nutrition*, edited by Vinood B. Patel, Victor R. Preedy, and Rajkumar Rajendram, 2016

12. *Mediterranean Diet: Dietary Guidelines and Impact on Health and Disease* edited by Donato F. Romagnolo, PhD, and Ornella Selmin, PhD, 2016
13. *Nutrition Support for the Critically Ill* edited by David S. Seres, MD, and Charles W. Van Way, III, MD, 2016
14. *Nutrition in Cystic Fibrosis: A Guide for Clinicians*, edited by Elizabeth H. Yen, MD, and Amanda R. Leonard, MPH, RD, CDE, 2016
15. *Preventive Nutrition: The Comprehensive Guide For Health Professionals, Fifth Edition*, edited by Adrienne Bendich, PhD, and Richard J. Deckelbaum, MD, 2016
16. *Glutamine in Clinical Nutrition*, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015
17. *Nutrition and Bone Health, Second Edition*, edited by Michael F. Holick and Jeri W. Nieves, 2015
18. *Branched Chain Amino Acids in Clinical Nutrition, Volume 2*, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015
19. *Branched Chain Amino Acids in Clinical Nutrition, Volume 1*, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015
20. *Fructose, High Fructose Corn Syrup, Sucrose and Health*, edited by James M. Rippe, 2014
21. *Handbook of Clinical Nutrition and Aging, Third Edition*, edited by Connie Watkins Bales, Julie L. Locher, and Edward Saltzman, 2014
22. *Nutrition and Pediatric Pulmonary Disease*, edited by Dr. Youngran Chung and Dr. Robert Dumont, 2014
23. *Integrative Weight Management: A Guide for Clinicians*, edited by Dr. Gerard E. Mullin, Dr. Lawrence J. Cheskin, and Dr. Laura E. Matarese, 2014
24. *Nutrition in Kidney Disease, Second Edition*, edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes, and Dr. Glenn M. Chertow, 2014
25. *Handbook of Food Fortification and Health: From Concepts to Public Health Applications, Volume I*, edited by Dr. Victor R. Preedy, Dr. Rajaventhana Srirajaskanthan, and Dr. Vinood B. Patel, 2013
26. *Handbook of Food Fortification and Health: From Concepts to Public Health Applications, Volume II*, edited by Dr. Victor R. Preedy, Dr. Rajaventhana Srirajaskanthan, and Dr. Vinood B. Patel, 2013
27. *Diet Quality: An Evidence-Based Approach, Volume I*, edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013
28. *Diet Quality: An Evidence-Based Approach, Volume II*, edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013
29. *Handbook of Clinical Nutrition and Stroke*, edited by Mandy L. Corrigan, MPH, RD; Arlene A. Escuro, MS, RD; and Donald F. Kirby, MD, FACP, FACN, FACC, 2013
30. *Nutrition in Infancy, Volume I*, edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
31. *Nutrition in Infancy, Volume II*, edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
32. *Carotenoids and Human Health*, edited by Dr. Sherry A. Tanumihardjo, 2013

33. *Bioactive Dietary Factors and Plant Extracts in Dermatology*, edited by Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013
34. *Omega-6/3 Fatty Acids*, edited by Dr. Fabien De Meester, Dr. Ronald Ross Watson, and Dr. Sherma Zibadi, 2013
35. *Nutrition in Pediatric Pulmonary Disease*, edited by Dr. Robert Dumont and Dr. Youngran Chung, 2013
36. *Nutrition and Diet in Menopause*, edited by Dr. Caroline J. Hollins Martin, Dr. Ronald Ross Watson, and Dr. Victor R. Preedy, 2013
37. *Magnesium in Human Health and Disease*, edited by Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2012
38. *Alcohol, Nutrition, and Health Consequences*, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
39. *Nutritional Health: Strategies for Disease Prevention, Third Edition*, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012
40. *Chocolate in Health and Nutrition*, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
41. *Iron Physiology and Pathophysiology in Humans*, edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren, 2012

Earlier books included *The Vitamin D Solution, 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: From Basic Biology to Clinical Medicine* edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; *Nutrition Guide for Physicians* 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: A Comprehensive Handbook* 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 is President of Consultants in Consumer Healthcare LLC and is the Editor of ten books including *Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fifth Edition*, coedited 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 & 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.

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 an Adjunct Professor at Rutgers University. She is listed in Who's Who in American Women.



Connie W. Bales is a Professor of Medicine in the Division of Geriatrics, Department of Medicine, at the Duke University School of Medicine and Senior Fellow in the Center for the Study of Aging and Human Development at Duke University Medical Center. She is also Associate Director for Education/Evaluation of the Geriatrics Research, Education, and Clinical Center at the Durham VA Medical Center. Dr. Bales is a well-recognized expert in the field of nutrition, chronic disease, function, and

aging. Over the past two decades, her laboratory at Duke has explored many different aspects of diet and activity as determinants of health during the latter half of the adult life course. Her current research focuses primarily on enhanced protein as a means of benefiting muscle quality, function, and other health indicators during geriatric obesity reduction and for improving perioperative outcomes in older patients. Dr. Bales has served on NIH and USDA grant review panels and is Past-Chair of the Medical Nutrition Council of the American Society for Nutrition. She has edited three editions of the *Handbook of Clinical Nutrition and Aging*, is Editor-in-Chief of the *Journal of Nutrition in Gerontology and Geriatrics*, and is a Deputy Editor of *Current Developments in Nutrition*.

About the Editors



Peter Weber, MD, PhD Professor of Nutrition, University of Stuttgart-Hohenheim, Stuttgart, Germany

Peter Weber received his PhD in Nutritional Sciences from the University of Bonn, Germany, and his MD from the University of Münster, Germany. After working for 2 years at the “Research Institute of Child Nutrition,” Dortmund,

Germany, he trained in Internal Medicine with a subspecialty in endocrinology at the University of Mainz, Germany, obtaining 10 years of experience in patient care and clinical research. He is a Professor of Nutrition at the University of Hohenheim, Stuttgart, Germany, and gives lectures in Human Nutrition and Health. He has more than 70 peer-reviewed publications in the field of iodine deficiency and goiter, thyroid diseases, metabolic syndrome, postprandial lipid metabolism, vitamin K, vitamin status of populations, and the role of vitamins and polyunsaturated fatty acids in human health, and he is a Coeditor of several books on micronutrients and health. His scientific interests include the role of micronutrients in the prevention of chronic diseases, nutritional status in risk groups such as elderly, and the emerging topic of nutrition security. After a successful career in various R&D functions at Hoffmann-La Roche in New Jersey, USA, and as Corporate Scientist for Human Nutrition & Health in DSM Nutritional Products in Kaiseraugst, Switzerland, he retired from his industrial appointment in August 2017.



Marc Birringer, PhD Professor for Applied Nutritional and Environmental Biochemistry at the Department of Nutritional, Food and Consumer Sciences of Fulda University of Applied Sciences, Germany

Dr. Marc Birringer started his academic career at the University of Siegen (Germany), where he received his PhD in Chemistry. In 1998, he studied the anticancer activity of seleno-amino acids with Eric Block at the University of Albany (NY/USA). In 1999, he joined the lab of Regina Brigelius-Flohé at the German Institute of Human Nutrition where he investigated human vitamin E metabolism and anticancer properties of newly synthesized tocopheryl derivatives.

In 2002, Dr. Birringer co-founded *peptides&elephants* GmbH, where he was Head of the Research and Development Unit and responsible for the conception of a high-throughput synthesizer for peptide libraries and the development of tissue-specific drug-peptide conjugates. From 2005 to 2010, he worked in the laboratory of Michael Ristow at the University of Jena on diet-induced mitochondrial activation and aging. During that time, he received his *habilitation* in human nutrition.

In 2011, Marc Birringer was appointed Full Professor for Applied Nutritional and Environmental Biochemistry in the Department of Nutritional, Food and Consumer Sciences of Fulda University of Applied Sciences. His current research is focused on the metabolism of dietary lipophilic micronutrients, such as vitamin E and coenzyme Q10. Dr. Marc Birringer is President of the Gesellschaft für Angewandte Vitaminforschung eV, member of the Editorial Board of *NFS Journal*, and author and coauthor of more than 80 scientific articles and reviews.



Jeffrey B. Blumberg, PhD, is a Professor in the Friedman School of Nutrition Science and Policy and also serves as the Senior Scientist in the Antioxidants Research Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University. His research is focused on the biochemical

basis for the role of antioxidant nutrients and their dietary requirements in promoting health and preventing disease during the aging process via changes in the status of oxidative stress, glucoregulation, and inflammation. He has published more than 400 scientific articles and serves on the editorial boards of several scientific journals. Dr. Blumberg was included in the 2015 Thomson Reuters' top 1% of cited researchers in his field. He has been the recipient of the ASN Mary Swartz Rose Senior Investigator Award for outstanding research

on the safety and efficacy of bioactive compounds for human health. Dr. Blumberg also participates in activities relevant to the incorporation of sound nutrition science into public health policy and has served as a member of the Workshop on Health Promotion and Aging in the Office of the US Surgeon General, Sports Medicine Committee of the US Olympic Committee, Consultation on Preparation and Use of Food-Based Dietary Guidelines for the WHO/FAO, Food Advisory Committee of the FDA, and other committees.



Manfred Eggersdorfer, PhD Professor for Healthy Ageing, University Medical Center, Groningen, Netherlands

Dr. Manfred Eggersdorfer studied chemistry at the Technical University of Munich, Germany, and did his PhD in Organic Chemistry on the synthesis and characterization of unusual amino acids. He undertook postdoctoral work at Stanford University, California, working with Carl Djerassi on the isolation and characterization of sterols from marine origin.

Dr. Manfred Eggersdorfer worked for BASF in various positions, including Head of R&D Fine Chemicals, joined Roche as Head of Research Vitamins, and continued

in this position after the acquisition by DSM. In the last years, he was responsible for Nutrition Science & Advocacy.

Dr. Manfred Eggersdorfer is member of the Advisory Board of Johns Hopkins Bloomberg School of Public Health, Baltimore, a board member of the Gesellschaft für Angewandte Vitaminforschung eV, and member of the Tufts Nutrition Council, Boston. He is an Honorary Member of the Oxygen Club of California and author of numerous publications, reviews, and book chapters in the field of vitamins, carotenoids, and innovation in nutritional ingredients. He is a reviewer for several scientific journals as well as Associate Editor of the *International Journal for Vitamin and Nutrition Research*.



Jan Frank, PhD Professor of Food Biofunctionality, Institute of Nutritional Sciences, University of Hohenheim, Stuttgart, Germany

Professor Frank graduated with a Diploma in Nutrition from Bonn University (2000), obtained a PhD in Food Science at the Swedish University of Agricultural Sciences (2004), and received postdoctoral training at the Universities of Kiel and Hohenheim. He was a Visiting Scientist at the Linus Pauling Institute (USA), the University of Reading (UK), and the University of Surrey (UK).

Dr. Frank was appointed Professor of Human Metabolomics at the Institute of Nutrition and Food Science at the University of Bonn in 2012 and, in 2013, Full Professor and Head of the Division of Food Biofunctionality at the Institute of Nutritional Sciences at the University of Hohenheim.

He is the Founding President of the Society of Nutrition and Food Science (www.snfs.org), member of the board of directors of the Society for Applied Vitamin Research (Gesellschaft für Angewandte Vitaminforschung eV), and Editor-in-Chief of *NFS Journal*, Associate Editor of *Nutrition*, and member of the editorial boards of *The Journal of Nutritional Biochemistry*, *BioFactors*, and *Plant Foods for Human Nutrition*.

His research interests lie in factors that determine the absorption, metabolism, and elimination of phytochemicals and different vitamin E congeners and, in particular, long-chain vitamin E metabolites. Dr. Frank and his team examine novel strategies to overcome the low intrinsic oral bioavailability of phytochemicals and investigate their biological activities.

Contents

1	Introduction: Why (Another) Book on Vitamin E?	1
	Peter Weber, Marc Birringer, Jeffrey B. Blumberg, Manfred Eggersdorfer, and Jan Frank	
Part I Biochemistry, Metabolism and Molecular Effects of Vitamin E		
2	History of Vitamin E Research	7
	Marc Birringer, Jeffrey B. Blumberg, Manfred Eggersdorfer, Jan Frank, and Peter Weber	
3	Antioxidative Activity of Vitamin E	19
	Afaf Kamal-Eldin	
4	Bioavailability and Metabolism of Vitamin E	31
	Sandra Flory, Marc Birringer, and Jan Frank	
5	Occurrence and Bioactivities of Minor Vitamin E Derivatives	43
	Marc Birringer and Jan Frank	
6	Bioactivity of Vitamin E Long-Chain Metabolites	61
	Stefan Kluge, Martin Schubert, Lisa Schmölz, Maria Wallert, Marc Birringer, and Stefan Lorkowski	
7	Gene Regulatory Activity of Vitamin E	81
	Alexandra Fischer and Gerald Rimbach	
8	Metabolomic Approaches in Vitamin E Research	99
	John K. Lodge	
9	The Tocopherol Transfer Protein: Regulator of Vitamin E Status	111
	Jeffrey Atkinson, Varsha Thakur, and Danny Manor	
10	The Role of Lipid Rafts in Mediating the Anticancer Effects of γ-Tocotrienol	125
	Paul W. Sylvester	
11	Interaction Between Vitamin E and Polyunsaturated Fatty Acids	141
	Jean-Marc Zingg and Mohsen Meydani	

Part II A Global View on Vitamin E Intakes and Status

- 12 **The Challenge of Defining Daily Intake Recommendations:
Vitamin E and Polyunsaturated Fatty Acids** 163
Daniel Raederstorff, Szabolcs Péter, and Peter Weber
- 13 **Vitamin E Intake and Serum Levels in the General
Population: A Global Perspective** 175
Szabolcs Péter, Manfred Eggersdorfer, and Peter Weber
- 14 **Vitamin E Intakes and Status in Toddlers, School
Kids and Adolescents: What Do We Know?** 189
Volker Böhm
- 15 **Vitamin E Serum Levels and the Challenge to Correct for Lipids:
Accounting for the Usual Double Correction for Variance Shared
by Total Cholesterol and Fasting Triglycerides Reveals New
Insights into the Association with the One-Carbon Pathway** .. 201
Isidor Minović, Camilo G. Sotomayor, Manfred Eggersdorfer,
Ineke J. Riphagen, Martin H. de Borst, Louise H. Dekker,
Gerjan Navis, Ilja M. Nolte, Sander K. R. van Zon,
Sijmen A. Reijneveld, Jan C. van der Molen,
Wilhelmina H. A. de Jong, Jenny E. Kootstra-Ros,
Ido P. Kema, and Stephan J. L. Bakker
- 16 **Stability of Vitamin E in Foods** 215
Marc Pignitter, Silke Grosshagauer, and Veronika Somoza

Part III Safety of Vitamin E and Interactions with Other Nutrients and Drugs

- 17 **Vitamin E and Mortality: A Critical Perspective
of the Conflicting Meta-analysis Outcomes** 235
Wolfgang Köpcke
- 18 **Vitamin E-Drug Interactions** 247
Maren C. Podszun and Jan Frank
- 19 **Vitamin E: Interactions with Vitamin K and Other Bioactive
Compounds** 261
M. Kyla Shea and Sarah L. Booth

Part IV Benefits of Vitamin E on Human Health and Disease

- 20 **Clinical Cardiovascular Disease Trials: The Vitamin E Case** .. 273
Joshua B. Wiener, Elliot M. Berinstein, and Andrew P. Levy
- 21 **Haptoglobin Genotype and a Promising Pharmacogenomic
Approach to Prevent Diabetic Atherothrombosis
with Vitamin E Supplementation** 283
Howard N. Hodis and Wendy J. Mack
- 22 **Vitamin E and Metabolic Syndrome** 295
Richard S. Bruno

23	Vitamin E in Nonalcoholic Fatty Liver Disease	311
	Bubu A. Banini and Arun J. Sanyal	
24	The Role of Vitamin E in Aging and Alzheimer's Disease	325
	Gunter P. Eckert	
25	The Impact of Vitamin E Isoforms on Asthma and Allergy	345
	Joan M. Cook-Mills	
26	Vitamin E, Immune Function, and Protection Against Infection	371
	Dayong Wu and Simin Nikbin Meydani	
27	Vitamin E and Air Pollution	385
	Rebecca F. McLoughlin, Bronwyn S. Berthon, Evan J. Williams, and Lisa G. Wood	
28	The Role of Vitamin E in Pregnancy	405
	Ann L. Anderson Berry and Corrine K. Hanson	
 Part V Public Health Implications of Vitamin E		
29	Vitamin E and Healthcare Costs: Models to Assess the Impact	421
	Mark Nuijten	
30	Do Consumers Care About Micronutrients? A Perspective on the Possible Role of Vitamin E in the Dietary Choices of Consumers	435
	Klaus G. Grunert	
31	Addressing Key Knowledge Gaps in Nutrition Research and the Impact of Funding Priorities in Human Nutrition	445
	La Verne L. Brown and Paul M. Coates	
	Index	457

Contributors

Ann L. Anderson Berry University of Nebraska Medical Center, Omaha, NE, USA

Nebraska Perinatal Quality Improvement Collaborative (NPQIC), Omaha, NE, USA

NICU and Newborn Nursery/Nebraska Medicine, University of Nebraska Medical Center, Omaha, NE, USA

Jeffrey Atkinson Department of Chemistry and Centre for Biotechnology, Brock University, St. Catharines, ON, Canada

Volker Böhm Institute of Nutritional Sciences, Friedrich Schiller University Jena, Jena, Germany

Stephan J. L. Bakker Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Bubu A. Banini Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA, USA

Elliot M. Berinstein The Ruth and Bruce Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel

Bronwyn S. Berthon Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, University of Newcastle, Newcastle, NSW, Australia

Marc Birringer University of Applied Sciences Fulda, Nutritional, Food and Consumer Sciences, Fulda, Germany

Jeffrey B. Blumberg Friedman School of Nutrition Science and Policy, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA

Sarah L. Booth Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA

Martin H. de Borst Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

La Verne L. Brown Office of Dietary Supplements, National Institutes of Health, Bethesda, MD, USA

Richard S. Bruno The Ohio State University, Columbus, OH, USA

Paul M. Coates Office of Dietary Supplements, National Institutes of Health, Bethesda, MD, USA

Joan M. Cook-Mills Herman B Wells Center for Pediatric Research, Department of Pediatrics, Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, IN, USA

Louise H. Dekker Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Gunter P. Eckert Justus-Liebig-University Giessen, Institute of Nutritional Sciences, Giessen, Germany

Manfred Eggersdorfer University Medical Center Groningen, Hanzeplein 1, Groningen, The Netherlands

Alexandra Fischer Institute of Human Nutrition and Food Science, University of Kiel, Kiel, Germany

Sandra Flory Institute of Nutritional Sciences, University of Hohenheim, Stuttgart, Germany

Jan Frank Institute of Nutritional Sciences, University of Hohenheim, Stuttgart, Germany

Silke Grosshagauer Department of Physiological Chemistry, Faculty of Chemistry, University of Vienna, Vienna, Austria

Klaus G. Grunert MAPP Centre, Aarhus University, Aarhus V, Denmark

Corrine K. Hanson Medical Nutrition Education, University of Nebraska Medical Center, College of Allied Health Professions, Omaha, NE, USA

Howard N. Hodis Atherosclerosis Research Unit, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Wilhelmina H. A. de Jong Department of Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Wolfgang Köpcke Institute of Biostatistics and Clinical Research, University Clinic Münster, Münster, Germany

Afaf Kamal-Eldin Department of Food Science, College of Food & Agriculture, United Arab Emirates University, Al Ain, United Arab Emirates

Ido P. Kema Department of Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Stefan Kluge Institute of Nutritional Sciences, Friedrich Schiller University Jena, Jena, Germany

Competence Cluster for Nutrition and Cardiovascular Health (nutriCARD), Halle-Jena-Leipzig, Germany

Jenny E. Kootstra-Ros Department of Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Andrew P. Levy The Ruth and Bruce Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel

John K. Lodge Department of Applied Sciences, Faculty of Health and Life Sciences, Northumbria University, Newcastle upon Tyne, UK

Stefan Lorkowski Institute of Nutritional Sciences, Friedrich Schiller University Jena, Jena, Germany

Competence Cluster for Nutrition and Cardiovascular Health (nutriCARD), Halle-Jena-Leipzig, Germany

Wendy J. Mack Atherosclerosis Research Unit, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Danny Manor Department of Nutrition, Case Western Reserve University, Cleveland, OH, USA

Department of Pharmacology, Case Western Reserve University, Cleveland, OH, USA

Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH, USA

Rebecca F. McLoughlin Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, University of Newcastle, Newcastle, NSW, Australia

Mohsen Meydani Vascular Biology Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA

Simin Nikbin Meydani Nutritional Immunology Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA

Isidor Minović Department of Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Jan C. van der Molen Department of Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Gerjan Navis Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Ilja M. Nolte Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Mark Nuijten A2M – Minerva, Amsterdam, The Netherlands
Department of Economics, ITU, Istanbul, Turkey

Szabolcs Péter DSM Nutritional Products Ltd., Kaiseraugst, Switzerland

Marc Pignitter Department of Physiological Chemistry, Faculty of Chemistry, University of Vienna, Vienna, Austria

Maren C. Podszun Institute of Nutritional Sciences, University of Hohenheim, Stuttgart, Germany

Daniel Raederstorff R&D Human Nutrition & Health, DSM Nutritional Products Ltd, Basel, Switzerland

Sijmen A. Reijneveld Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Gerald Rimbach Institute of Human Nutrition and Food Science, University of Kiel, Kiel, Germany

Ineke J. Riphagen Department of Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Arun J. Sanyal Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA, USA

Lisa Schmölz Institute of Nutritional Sciences, Friedrich Schiller University Jena, Jena, Germany

Competence Cluster for Nutrition and Cardiovascular Health (nutriCARD), Halle-Jena-Leipzig, Germany

Martin Schubert Institute of Nutritional Sciences, Friedrich Schiller University Jena, Jena, Germany

Competence Cluster for Nutrition and Cardiovascular Health (nutriCARD), Halle-Jena-Leipzig, Germany

M. Kyla Shea Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA

Veronika Somoza Department of Physiological Chemistry, Faculty of Chemistry, University of Vienna, Vienna, Austria

Camilo G. Sotomayor Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Paul W. Sylvester College of Pharmacy, University of Louisiana at Monroe, Monroe, LA, USA

Varsha Thakur Department of Nutrition, Case Western Reserve University, Cleveland, OH, USA

Maria Wallert Institute of Nutritional Sciences, Friedrich Schiller University Jena, Jena, Germany

Baker Heart and Diabetes Institute, Melbourne, VIC, Australia

Peter Weber Institute of Nutritional Sciences, University of Hohenheim, Stuttgart, Germany

Joshua B. Wiener The Ruth and Bruce Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel

Evan J. Williams Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, University of Newcastle, Newcastle, NSW, Australia

Lisa G. Wood Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, University of Newcastle, Newcastle, NSW, Australia

Dayong Wu Nutritional Immunology Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA

Jean-Marc Zingg University of Miami, Miller School of Medicine, Miami, FL, USA

Sander K. R. van Zon Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands