

WORKING GROUP REPORT

Nutrition research to affect food and a healthy life span^{1,2}

Sarah Ohlhorst,^{3*} Robert Russell,⁴ Dennis Bier,⁵ David M. Klurfeld,⁶ Zhaoping Li,⁷ Jonathan R. Mein,⁸ John Milner,^{9,12}
 A. Catharine Ross,¹⁰ Patrick Stover,¹¹ and Emily Konopka

³American Society for Nutrition, Bethesda, MD; ⁴NIH Office of Dietary Supplements, Bethesda, MD, and Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA; ⁵USDA/Agricultural Research Service Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, TX; ⁶Human Nutrition Program, USDA/Agricultural Research Service, Beltsville, MD; ⁷Center for Human Nutrition, University of California Los Angeles, and David Geffen School of Medicine at UCLA, Los Angeles, CA; ⁸Monsanto Center for Food and Nutrition Research, Monsanto Vegetable Seed, Kannapolis, NC; ⁹NIH National Cancer Institute, Bethesda, MD; ¹⁰Department of Nutritional Sciences, Pennsylvania State University, University Park, PA; and ¹¹Division of Nutritional Sciences, Cornell University, Ithaca, NY.

ABSTRACT

Proper nutrition offers one of the most effective and least costly ways to decrease the burden of many diseases and their associated risk factors, including obesity. Nutrition research holds the key to increasing our understanding of the causes of obesity and its related comorbidities and thus holds promise to markedly influence global health and economies. After outreach to 75 thought leaders, the American Society for Nutrition (ASN) convened a Working Group to identify the nutrition research needs whose advancement will have the greatest projected impact on the future health and well-being of global populations. ASN's Nutrition Research Needs focus on the following high priority areas: 1) variability in individual responses to diet and foods; 2) healthy growth, development, and reproduction; 3) health maintenance; 4) medical management; 5) nutrition-related behaviors; and 6) food supply/environment. ASN hopes the Nutrition Research Needs will prompt collaboration among scientists across all disciplines to advance this challenging research agenda given the high potential for translation and impact on public health. Furthermore, ASN hopes the findings from the Nutrition Research Needs will stimulate the development and adoption of new and innovative strategies that can be applied toward the prevention and treatment of nutrition-related diseases. The multidisciplinary nature of nutrition research requires stakeholders with differing areas of expertise to collaborate on multifaceted approaches to establish the evidence-based nutrition guidance and policies that will lead to better health for the global population. In addition to the identified research needs, ASN also identified 5 tools that are critical to the advancement of the Nutrition Research Needs: 1) omics, 2) bioinformatics, 3) databases, 4) biomarkers, and 5) cost-effectiveness analysis. *Am J Clin Nutr* doi: 10.3945/ajcn.113.067744.

INTRODUCTION

The attainment of good nutrition depends on and encompasses the entire food supply. Plant and animal foods and their various components are the primary vehicles that provide nourishment to human beings. Nutrition is vital, not only in the growth and

development of humans and animals but also in the prevention and treatment of disease. Nutrition is also fundamental to the maintenance of good health and functionality. Basic and applied research on the interrelations between nutrition and non-communicable diseases, nutrient composition, and nutrition monitoring represents the underpinning for healthy populations and robust economies. Thus, innovative nutrition research and education provide the basis for solutions to larger health-related issues, allowing individuals to live healthier, more productive lives.

The importance of nutrition, as an integral part of the solution to many societal, environmental, and economic challenges facing the world, has just started to be fully appreciated. The American Society for Nutrition (ASN) has identified the "grand" challenges facing nutrition research and science in the 21st century, termed "Nutrition Research Needs." Findings from these Nutrition

¹ This article was written, reviewed, and approved by all Nutrition Research Needs Working Group members. The American Society for Nutrition's (ASN's) Board of Directors also reviewed this document. Final review and approval were provided by ASN 2012–2013 President Teresa A Davis. This article did not undergo editorial peer review by the editors of *The American Journal of Clinical Nutrition*. Because of the broad import and nature of the information included in this article and the need to achieve the widest possible distribution of this information, the article is being copublished in ASN's 2 other journals, *The Journal of Nutrition* and *Advances in Nutrition*.

² Author disclosures: S Ohlhorst, R Russell, D Bier, DM Klurfeld, Z Li, J Milner, AC Ross, P Stover, and E Konopka, no conflicts of interest. JR Mein is employed with Monsanto Company, which commercializes vegetable and commodity crop seeds.

¹² Present address: USDA/ARS, Beltsville Human Nutrition Research Center, Beltsville, MD.

¹³ Formerly an ASN intern and now a graduate of Nazareth College, Rochester, NY.

*Address correspondence to S Ohlhorst, American Society for Nutrition, 9650 Rockville Pike, Bethesda, MD 20814. E-mail: sohlhorst@nutrition.org. doi: 10.3945/ajcn.113.067744.

Research Needs will elucidate strategies that can be applied toward the prevention and treatment of both infectious and noncommunicable diseases, including cardiovascular disease, diabetes, and cancer. Nutrition research holds the key to increasing our understanding of the underlying causes of obesity and its related comorbidities and thus holds promise to markedly influence global economies. Knowledge about adequate nutrition also has an important role in reducing or ending global and domestic food insecurity through direct and purposeful agricultural practices. Population growth will undeniably lead to increased global demand for a safe, available, sustainable, and affordable food supply, while continuing to demand nutritional adequacy.

The ASN Nutrition Research Needs project was originally conceptualized by ASN's Public Policy Committee to identify worldwide nutrition research needs. This effort will be used to educate and communicate to policy makers and other stakeholders the need and value of increased nutrition research funding to meet societal needs. ASN's Public Policy Committee reached out to nearly 75 thought leaders in September 2011 to develop a draft list of nutrition research needs.

In February 2012, ASN convened a Working Group of nutrition scientists and researchers representing a cross-section of the Society's membership to determine the nutrition research needs that will have the greatest impact on the health and well-being of global populations. The names of the Working Group members are listed in the Acknowledgments. Starting with the draft list, the Working Group narrowed down and pulled together 6 nutrition research needs for which advancement would have the greatest projected impact on future health and well-being.

The ASN then informed its membership of the 6 priority research needs and sought further member input. A workshop was held during ASN's 2012 Scientific Sessions and Annual Meeting in San Diego, CA, with nearly 250 attendees. The research needs were also shared via ASN's member newsletter, which reaches the entire membership base of nearly 5000 individuals, to inform and seek input from members who did not attend the annual meeting or the workshop. Member feedback on the Nutrition Research Needs was incorporated during development of the final document.

THE TOP NUTRITION RESEARCH NEEDS

The top 6 nutrition research needs cut across the entire research spectrum from basic science to health policy, from discovery to application. Specific research areas are listed under each research need. These 6 nutrition research needs are highlighted in the hope that they will prompt scientists from all disciplines to collaborate to advance these challenging research needs that have high potential for translation and public health impact. Although the topics presented focus principally on human nutrition research, the Working Group recognized that nutrition research using animal models is an essential foundation for making new discoveries that can be translated to advances in human nutrition. Furthermore, the importance of animal nutrition research is emphasized within these research needs in particular: "Understanding the role of nutrition in

health maintenance" and "Understanding the food supply/environment." The research community will benefit from clearly articulated nutrition research priorities that will lead to science-based information, help to shape policy and enhance future funding for nutrition research, and thereby further promote the field of nutrition science.

1) Understanding variability in individual responses to diet and foods

A top priority for future nutrition research is the need to better understand variability in metabolic responses to diet and food. Enormous variability exists in individual responses to diet and food components that affect overall health. Discoveries underpinning this variability will lead to advances in personalized nutrition interventions and will better inform health and food policies, including Dietary Reference Intakes (DRIs) for nutrient needs and, ideally, future recommendations for known bioactive food components. Research in the following areas is necessary to determine the origins and architecture of variability and to explain similar or dissimilar responses to diet and food components by subpopulations, as influenced by genetic, epigenetic, and ethnic and/or racial differences.

Omics

Omics research, such as nutrigenetics and nutrigenomics (eg, epigenetics, transcriptomics, proteomics, and metabolomics), will help to determine how specific nutrients interact with genes, proteins, and metabolites to predict an individual's health. Omics provide information on individualized nutrient requirements, including how nutrients are digested, absorbed, and metabolized, and their functions in the body. Omics will help to determine and reflect an individual's nutritional status and will aid in the creation of new nutritional and disease biomarkers.

Microbiome

Diverse microbes, such as bacteria and viruses, live in and on the body and contribute to the microbiome, which is estimated to have 10 times as many cells as the body itself (1). Microbes can vary in type and quantity, making each organism's microbiome unique—although subpopulations may have similar microbiome characteristics. The microbiota needs to be better defined, and changes due to diet, age, physiologic state, and disease need to be determined. Research is needed to determine the microbiome's role in varying biological responses to diet and food components and its importance in disease prevention and progression. Conversely, research is also needed to determine how the microbiome is influenced by diet and other environmental factors.

Biological networks

Basic research is needed to provide a better understanding of biological networks, such as an individual's genome (DNA/RNA protein profiles), and how these networks affect metabolic responses to diet and food. Environmental interactions, including nutrients and other dietary components, bacteria, viruses, and

chemical contaminants, all may affect the responsiveness of biological networks to specific foods and the entire diet.

Tissue specificity and temporality

Research is needed to describe the mechanisms by which dietary factors affect variability in development and functioning, including which tissues are most influenced by dietary factors and when during the most critical stages in life this influence occurs.

2) Understanding the impact of nutrition on healthy growth, development, and reproduction

Epigenetics/imprinting

Epigenetics and imprinting research examines how exposures to dietary components during critical periods of development may “program” long-term health and well-being. Research is needed to determine how early nutritional events contribute to disease later in life and alter normal developmental progression.

Early nutrition

Research is necessary to better understand the role of diet and individual food components on normal growth and development. This includes the role of parents’ preconception diets, the maternal diet during pregnancy, and early nutritional events. Studies indicate that the timing of an infant’s introduction to solid foods may increase the likelihood of becoming obese later in life (2). These findings are important given that the number of overweight children in the United States has increased dramatically in recent years (3). Research is now needed to determine the best approaches to influence these factors during early life. The important role of nutrition throughout early life on growth and development, as well as on health and well-being, needs to be continually assessed.

Nutrition and reproductive health

The impact of nutrition on reproductive health, including before and after conception, requires further research. Nutrition has a direct impact on both maternal and paternal fertility and the ability to conceive and also plays a key role in preventing diseases related to reproductive organs, including prostate and ovarian cancers. Although numerous studies have investigated how fruit and vegetable consumption may affect risk of breast, prostate, and other cancers, there is no clear consensus in the scientific literature. Thus, well-designed controlled intervention studies are needed to determine whether effects are limited to subpopulations, what factors influence a response, and what mechanisms may account for changes in health.

3) Understanding the role of nutrition in health maintenance

Health maintenance includes noncommunicable disease prevention and treatment as well as weight management. The role that food components, particularly novel ingredients, contribute to health maintenance requires continuing research. Researchers and the public rely on dietary guidance, including the DRIs, to guide nutrition recommendations and health policy. Research is

needed to better define the nutrient needs that best support health maintenance in all populations and their subgroups, from infancy throughout life. Nutrition across life is a fundamental issue that requires investigation so that recommendations will “match” with true biological needs.

Optimal bodily function

Research is needed to determine the roles that nutrition and fitness, both singularly and together, have in maintaining bodily functions, including cognitive, immune, skeletal, muscular, and other functions. Evolving research areas include prevention of disease-related processes, such as inflammation, and definition of mechanisms that have an important role in health maintenance, such as immunocompetence. Animal models are used to understand the requirements for optimal health in humans and production animals.

Energy balance

Research is also needed to examine the use of a systems approach to achieve energy balance including and integrating environmental, biological, psychosocial, and food system factors. A systems approach is preferable because the standard experimental approach of varying one factor at a time has accomplished little to address the populationwide problem of energy imbalance. A solution-oriented approach that is comprehensive in nature and takes into account the complexities of achieving energy balance must be created. Although far more research is needed to identify systemwide changes that maximize energy balance, intriguing examples exist. “Shape Up Somerville, MA,” effectively reduced weight gain in high-risk children through a multifaceted community-based environmental change campaign (4). Shape Up Somerville increased the community’s physical activity and healthful eating through physical infrastructure improvements and citywide policy and programming changes.

4) Understanding the role of nutrition in medical management

The rapid translation of nutrition research advances into evidence-based practice and policy is a priority for ensuring optimal patient care and effective disease management. Nutrition researchers have a key role in bridging the gap between disease prevention and disease treatment by fostering clinical research, providing innovative education for caregivers and patients, and delineating best practices for medical nutrition in primary care settings.

Disease progression

To improve the medical management of disease, research is needed to determine how nutritional factors influence both disease initiation and progression, as well as how nutrition affects a patient’s response to therapy. Genetic and epigenetic variations among individuals can result in both positive and negative responses to diets, to specific foods, and to novel food components. The issue of individual variability is of considerable importance in refining medical management, including nutrition support, and requires continuing research.

Expanded research will allow us to better understand and minimize unfavorable impacts of both reduced and elevated nutrient intakes on disease progression and overall health. Disease/mortality response curves are U-shaped for many nutrients (that is, there is an increased risk of adverse outcomes if the nutrient is ingested in either too low or too high amounts). The importance of achieving a proper nutrient balance is seen in the example of chronic inflammation. Chronic inflammation contributes to many noncommunicable diseases and can result from high intakes of proinflammatory omega-6 fatty acids in the face of low intakes of antiinflammatory omega-3 fatty acids (5). Research will help to determine the desired intake for essential and nonessential nutrients alone and when combined with other nutrients in the diet.

Nutrition support for special subgroups

Nutrition research is needed to establish the required nutritional needs that best support survival, growth, and development in subpopulations, such as in chronically diseased patients, in children, and in aging adults. With the success of medical advances, as have been seen with in vitro fertilization and neonatal care, caring for preterm infants presents a new challenge in early nutritional management. Preterm infants have special nutrition needs that will greatly affect their future growth and development, as well as their eventual health status as adults.

5) Understanding nutrition-related behaviors

Drivers of food choice

Understanding the link between behavior and food choices can help tackle obesity and other nutrition-related issues that are a public health priority. Individual food choices can be influenced by a number of different drivers including the following:

- Government policy
- Environmental cues
- Cultural differences
- Communication tools, such as social networking and food marketing

Research is needed to identify the impact of these various drivers and to understand how they work alone or together to influence nutrition-related behavior. Research will show how these drivers should be altered to have the highest positive influence on individual behavior and therefore public health. For example, the state of Mississippi recorded a 13% decline in obesity among elementary school students from 2005 to 2011 (6). Multiple changes in the environment occurred, such as the setting of standards for foods sold in school vending machines, setting a requirement for more school exercise time, mandating healthier environments in child care settings, and establishing programs that encouraged fruit and vegetable consumption. The challenge now is to determine what effect these combined actions will have on obesity-related behaviors in the long run.

Nutrition and brain functioning

Further explorations of the biochemical and behavioral bases for food choices and intake over time are essential. Brain function as it relates to food desire and choice needs to be clarified through

research, and the multiple hormones that affect eating require further study as well. Factors such as meal frequency and size, speed of meal consumption, and how these factors are influenced by social cues require objective data, which can only be provided by research. Understanding how the marketing of healthy behaviors could help consumers achieve dietary guidance goals should be a priority. As part of this approach, innovative and practical methods for accurately measuring and evaluating food purchases and eating occasions must be developed.

Imprinting

Because of the high propensity of obese children remaining obese as adults (7), additional research is needed to determine how eating and satiety behaviors are imprinted during critical periods of development and to show how food components affect neural biochemistry and brain functioning—and therefore shape behavior. This research will provide us with a better understanding of how and why an individual makes particular food choices. Although scientists recently validated the concept that food availability during pregnancy has permanent effects on gene expression in children (8), human studies are needed to confirm or refute the hypothesis that fetal programming, resulting from maternal obesity, leads to excess weight in children and into adulthood.

6) Understanding the food supply/environment

Food environment and food choice

Simply knowing or understanding what constitutes a healthy diet is not enough to change an individual's diet or lifestyle. Understanding how the food environment affects dietary and lifestyle choices is necessary before effective policies can be instituted that will change a population's diet in a meaningful way. Examples of key questions that should be addressed include the following:

- Is current dietary guidance an effective way of communicating dietary change?
- Do food assistance programs promote positive dietary patterns or have negative dietary and health consequences?
- What role does food advertising play in food decision making among different age groups and educational levels?
- How do farm-to-fork food systems, with an increased emphasis on local agricultural production and consumption, influence dietary patterns and behaviors?
- How can farm-to-fork food systems ultimately be used to promote healthy behaviors and improve public health?
- How can we most effectively measure, monitor, and evaluate dietary change?

Food composition and novel foods and food ingredients

Having an affordable, available, sustainable, safe, and nutritious food supply is also an important underpinning for making significant changes to a population's diet and lifestyle. Examples of key research areas to address include the following:

- Enhancing our knowledge of the nutrient and phytonutrient content and bioavailability of foods produced, processed, and consumed

- Studying how to better align and foster collaboration between nutrition and agricultural production
- Can shifting agricultural focus from principally agronomic to include quality factors (such as taste, flavor, and nutritional value) have positive effects on fruit and vegetable consumption?
- Can we leverage technologies, such as biotechnology and nanotechnology, to develop novel foods and food ingredients that will improve health, both domestically and abroad, and provide credible, tangible functional health benefits?

Public/private partnerships

To tackle these enormous challenges requires the coordinated efforts of public and private partners. The development of public/private partnerships between food and agricultural industries, government, academia, and nongovernmental organizations has the potential to advance nutrition research, enabling meaningful changes to be made to American and global diets (eg, increased fruit and vegetable consumption to match government recommendations). We need to examine successful examples of public/private partnerships that have resulted in improved nutritional status and food security in specific populations (9).

CROSS-CUTTING TOOLS TO ADVANCE NUTRITION RESEARCH

Nutrition research is truly a cross-cutting discipline, and the Working Group identified several tools that are also necessary to advance the priority needs in nutrition research. Adequately powered intervention trials continue to be essential for validating research theories arising from experimental and epidemiologic studies. However, the development of new, impactful tools will help us to more effectively quantify dietary intake and food waste and to determine the effectiveness of nutrition standards, such as DRI values and the *Dietary Guidelines for Americans*. Although not a traditional tool, multidisciplinary partnerships among scientific societies, government, industry, academia, and others are fundamental to advance the nutrition research agenda. ASN and its membership must be proactive not only in efforts to advance nutrition research (including initiating and leading partnerships) but also in developing the tools needed to enhance the field. ASN recognizes the need to facilitate effective communication among academia, industry, government agencies, consumers, and other stakeholders to advance nutrition.

1) Omics

Omics (especially genomics, proteomics, and metabolomics) will enable us to determine how specific nutrients interact with genes, proteins, and metabolites to predict the future health of an individual. A field of study that encompasses technological advances as well as omics-based research, it is sometimes referred to as personalized nutrition. Omics hold the keys to major nutrition breakthroughs in noncommunicable disease and obesity prevention. Omics provide information on how well nutrients are digested, absorbed, metabolized, and used by an individual. Moreover, omics will lead to new biomarkers that reveal a person's nutritional status and health status all at one time.

2) Bioinformatics

Bioinformatics is an interdisciplinary field that uses computer science and information technology to develop and enhance techniques to make it easier to acquire, store, organize, retrieve, and use biological data. Bioinformatics will enable nutrition researchers to manage, analyze, and understand nutrition data and to make connections between diet and health that were not previously possible. Databases are necessary to gain the full benefits of bioinformatics, because they make nutrition data easily accessible in a machine-readable format.

3) Databases

Accurate, up-to-date food and nutrient databases are essential to track and observe trends related to the nutrition and health of individuals. Databases link food and supplement composition and intake data to health outcomes. Nutrient databases should be expanded to cover more foods and their bioactive components, including nonessential nutrients. Nutrition data must be incorporated into databases related to novel research areas, such as nutrigenomics and the microbiome, to adequately link these areas with nutrition. Data collection must also be improved with enhancements such as photographic food intake documentation, direct upload of food composition and sensory characteristics (if not proprietary) from food manufacturers, and biological sample collection.

4) Biomarkers

Intake, effect, and exposure biomarkers allow us to determine and monitor the health and nutritional status of individuals and subpopulations, including ethnic and racial minorities. Biomarkers that are responsive to diet and nutrition will help assess disease progression and variability in response to treatment, while improving early diagnosis and prevention. Biomarkers must continue to be developed and validated to accurately track food and nutrient intake given our rapidly changing food supply.

5) Cost-effectiveness analysis

Cost-effectiveness analysis is a tool used to calculate and compare the relative costs and benefits of nutrition research interventions. Cost-effectiveness analysis helps to determine the most cost-effective option that will have the greatest benefit to public health.

CONCLUSIONS

The multidisciplinary nature of nutrition research requires collaboration among research scientists with differing areas of expertise, many different stakeholders, and multifaceted approaches to develop the knowledge base required for establishing the evidence-based nutrition guidance and policies that will lead to better health and well-being of world populations. Proper nutrition offers one of the most effective and least costly ways to decrease the burden of chronic and noncommunicable diseases and their risk factors, including obesity. Although there is skepticism about the ability to complete large, well-controlled dietary interventions at a reasonable cost in the United States, the

success of the Lyon Diet Heart Study in France (10, 11) and the PREvención con Dieta MEDiterránea (PREDIMED) study in Spain (12), both of which used variations of the Mediterranean diet, show that this approach can be successful, even in the presence of drug treatment of cardiovascular risks in the latter study. Both of these studies showed significant reductions in cardiovascular disease (and cancer in the Lyon study) after relatively modest dietary changes.

Perhaps the greatest barrier to advancing the connections between food and health is the variability in individual responses to diet; it is also the origin of public skepticism to acceptance of dietary advice and the opportunity for entrepreneurship in the private sector. Imagine being able to identify, with certainty, those most likely to benefit from prescriptive nutrition advice through the various omics technologies and then providing these groups of people with customized nutrition advice based on their metabolic risk profiles. This is the new frontier of the nutritional sciences that offers the opportunity to predictably engineer our physiologic networks for health through diet. The confidence this approach would bring to the skeptical consumer would improve adherence to weight management and disease treatment techniques and improve the chances of success for disease prevention. To realize the full positive impact of achieving good nutrition on disease prevention and the health of populations, we must have the will to invest in and support the 6 key areas of nutrition research that have been outlined above.

The Nutrition Research Needs Working Group consisted of Dennis Bier, David M Klurfeld, Zhaoping Li, Jonathan R Mein, John Milner, A Catharine Ross, Robert Russell (Chair), and Patrick Stover. They were supported by ASN staff members Sarah Ohlhorst and Emily Konopka.

REFERENCES

1. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature* 2007;449:804–10.
2. Huh SY, Rifas-Shiman SL, Taveras EM, Oken E, Gillman MW. Timing of solid food introduction and risk of obesity in preschool-aged children. *Pediatrics* 2011;127:e544–51.
3. Skinner AC, Steiner MJ, Perrin EM. Self-reported energy intake by age in overweight and healthy-weight children in NHANES, 2001–2008. *Pediatrics* 2012;130:e936–42.
4. Economos CD, Hyatt RR, Goldberg JP, Must A, Naumova EN, Collins JJ, Nelson ME. A community intervention reduces BMI z-score in children: Shape Up Somerville first year results. *Obesity (Silver Spring)* 2007;15:1325–36.
5. Wijendran V, Hayes KC. Dietary n-6 and n-3 fatty acid balance and cardiovascular health. *Annu Rev Nutr* 2004;24:597–615.
6. Kolbo JR, Zhang L, Molaison EF, Harbaugh BL, Hudson GM, Armstrong MG, Werle N. Prevalence and trends in overweight and obesity among Mississippi public school students, 2005–2011. *J Miss State Med Assoc* 2012;53:140.
7. Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, Byers T. Do obese children become obese adults? A review of the literature. *Prev Med* 1993;22:167–77.
8. Waterland RA, Kellermayer R, Laritsky E, Rayco-Solon P, Harris RA, Travisano M, Zhang W, Torskaya MS, Zhang J, Shen L, et al. Season of conception in rural Gambia affects DNA methylation at putative human metastable epialleles. *PLoS Genet* 2010;6:e1001252.
9. Institute of Medicine. Building public-private partnerships in food and nutrition: workshop summary. Washington, DC: The National Academies Press, 2012.
10. de Lorgeril M, Salen P, Martin JL, Monjaud I, Boucher P, Mamelle N. Mediterranean dietary pattern in a randomized trial: prolonged survival and possible reduced cancer rate. *Arch Intern Med* 1998;158:1181–7.
11. Dalziel K, Segal L, de Lorgeril M. A Mediterranean diet is cost-effective in patients with previous myocardial infarction. *J Nutr* 2006;136:1879–85.
12. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Pharm D, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–90.