Title

Perspective: Council for Responsible Nutrition Science in Session. Optimizing Health with Nutrition-Opportunities, Gaps, and the Future.

Journal

Advances in Nutrition, 14(5)

Authors

Ho, Emily

Drake, Victoria

Michels, Alexander

et al.

Publication Date

2023-09-01

DOI

10.1016/j.advnut.2023.05.015

Advances in Nutrition 14 (2023) 948–958

American Society for Nutrition
Excellence in Nutrition Research and Practice

Advances in Nutrition
AN INTERNATIONAL REVIEW JOURNAL
journal homepage: https://advances.nutrition.org/

Perspective

Perspective: Council for Responsible Nutrition Science in Session. Optimizing Health with Nutrition—Opportunities, Gaps, and the Future

Emily Ho [1,2,*], Victoria J. Drake [1], Alexander J. Michels [1], Yasmeen M. Nkrumah-Elie [3], LaVerne L. Brown [4], Jonathan M. Scott [5], John W. Newman [6], Barbara Shukitt-Hale [7], Amala Soumyanath [8], Floyd H. Chilton [9,10], Stephen R. Lindemann [11], Andrew Shao [3], Susan Hazels Mitmesser [12]

[1] *Linus Pauling Institute, Oregon State University, Corvallis, Oregon;* [2] *Nutrition Program, College of Public Health and Human Sciences, Oregon State University, Corvallis, Oregon;* [3] *ChromaDex External Research Program, Los Angeles, California;* [4] *National Institutes of Health, Office of Dietary Supplements, Bethesda, Maryland;* [5] *Consortium for Health and Military Performance, Department of Military and Emergency Medicine, F. Edward Hébert School of Medicine, Uniformed Services University, Bethesda, Maryland;* [6] *United States Department of Agriculture, Agricultural Research Service, Western Human Nutrition Research Center, Davis, California;* [7] *United States Department of Agriculture, Agricultural Research Service, Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts;* [8] *BENFRA Botanical Dietary Supplements Research Center, Department of Neurology, Oregon Health and Science University, Portland, Oregon;* [9] *Center for Precision Nutrition and Wellness, University of Arizona, Tucson, Arizona;* [10] *School of Nutritional Sciences and Wellness, College of Agriculture and Life Sciences, University of Arizona, Tucson, Arizona;* [11] *Whistler Center for Carbohydrate Research, Department of Food Science, Purdue University, West Lafayette, Indiana;* [12] *Pharmavite, LLC, West Hills, California*

A B S T R A C T

Achieving optimal health is an aspirational goal for the population, yet the definition of health remains unclear. The role of nutrition in health has evolved beyond correcting malnutrition and specific deficiencies and has begun to focus more on achieving and maintaining 'optimal' health through nutrition. As such, the Council for Responsible Nutrition held its October 2022 Science in Session conference to advance this concept. Here, we summarize and discuss the findings of their *Optimizing Health through Nutrition – Opportunities and Challenges* workshop, including several gaps that need to be addressed to advance progress in the field. Defining and evaluating various indices of optimal health will require overcoming these key gaps. For example, there is a strong need to develop better biomarkers of nutrient status, including more accurate markers of food intake, as well as biomarkers of optimal health that account for maintaining resilience—the ability to recover from or respond to stressors without loss to physical and cognitive performance. In addition, there is a need to identify factors that drive individualized responses to nutrition, including genotype, metabotypes, and the gut microbiome, and to realize the opportunity of precision nutrition for optimal health. This review outlines hallmarks of resilience, provides current examples of nutritional factors to optimize cognitive and performance resilience, and gives an overview of various genetic, metabolic, and microbiome determinants of individualized responses.

Keywords: optimal health, nutrition, precision health, resilience, cognition, individual metabolic variability, microbiome, nutrient–gene interactions

Abbreviations used: AfAm, African American; BENFRA, Botanical Dietary Supplements Research Center; CRN, Council for Responsible Nutrition; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DRI, dietary reference intake; EPA, eicosapentaenoic acid; FA, fatty acid; FADS, fatty acid desaturase; NIH, National Institutes of Health; Nrf2, nuclear factor-erythroid-2-related factor 2; PUFA, polyunsaturated fatty acid; RDA, recommended dietary allowance; RSAX, red sorghum arabinoxylan; SFA, saturated fatty acid; VITAL, VITamin D and omegA-3 TriaL; WSAX, white sorghum arabinoxylan.

* Corresponding author. *E-mail address:* emily.ho@oregonstate.edu (E. Ho).

https://doi.org/10.1016/j.advnut.2023.05.015
Received 30 March 2023; Received in revised form 20 May 2023; Accepted 30 May 2023; Available online 1 June 2023

Statement of Significance

There is a critical need to help find nutrition solutions to optimize our health across the lifespan. However, there is a need to advance concepts beyond the prevention of nutrient deficiencies and consider meeting the nutritional needs for optimal health. This review proposes a framework centered around resilience and determinants of individualized responses for evaluating optimal health and nutrition outcomes while also highlighting the gaps and opportunities in this emerging space.

Introduction—Defining Optimal Health

Over the last few decades, the field of nutrition has grown and evolved. Although we continue to define the critical roles that nutrients play as fuel sources, enzyme cofactors, signaling molecules, and vital infrastructure for our bodies, the cutting edge of nutrition research is pushing beyond simply meeting our bodies' basic needs. Indeed, as the population is living longer, an emerging focus for nutrition has been on obtaining and maintaining optimal health over the life course. On 10 October, 2022, the Council for Responsible Nutrition (CRN) held their annual Science in Session conference entitled *Optimizing Health through Nutrition – Opportunities and Challenges*. The audience consisted of scientists (with expertise in nutrition and other disciplines, including biochemistry, toxicology, and health care) and executives from dietary supplement and functional food companies as well as nutrition graduate student awardees of a CRN and ASN Foundation educational scholarship to attend the symposium. CRN is a trade association representing dietary supplement and functional food companies. The goals for this meeting were to propose a definition for optimal nutrition and identify strategies and tools for evaluating optimal health and nutrition outcomes while highlighting the gaps in this emerging space.

Now more than ever in history, our population's health has emerged as a global priority. Currently, 6 in 10 adults in the United States have a chronic disease, and 4 in 10 have 2 or more. In $<$10 y, the number of older adults is projected to increase by ~18 million. This means that by 2030, 1 in 5 Americans is projected to be $\geq$65 y old. As the major risk factor for many chronic illnesses is age, it is anticipated that the rates of all age-related diseases, especially chronic diseases, will skyrocket, potentially overwhelming the health care system. We need to enable the health care system—and the population—to be more proactive rather than reactive toward health outcomes. There is a critical need to help find solutions to optimize health across the lifespan to support living better longer, i.e., healthspan. Ensuring optimal nutrition is a significant and easily modifiable variable in the solution for maintaining and improving healthspan. We need to advance concepts beyond essential health and consider meeting the nutritional needs for optimal health. Although the nutrition science community is moving toward the vision of nutrition to support optimal health, many challenges and gaps still exist, but there are also recent advances and exciting opportunities. The goal of the CRN "Science in Session" workshop was to discuss these challenges, gaps, and opportunities in order to advance the concept of nutrition for optimal health. This review summaries these findings and discussions.

Gaps and Opportunities

The DRIs for individual nutrients, including the Estimated Average Requirement and the RDA, are life stage- and sex-specific recommendations for Americans and Canadians. These reference intakes were established in the 1990s by the Food and Nutrition Board of the National Academies of Sciences, Engineering, and Medicine to prevent deficiency disease and to reduce the risk of chronic diseases [1]. However, incorporating chronic disease endpoints has been extremely challenging, primarily because data are largely lacking. Such end points were used to set the DRIs for only a handful of nutrients [2]. Thus, the current DRIs, including the RDAs that are aimed to cover the nutrient needs of 98% of the population, do not account for the amount of a nutrient that one needs in order to achieve and maintain 'optimal' health.

What is holding us back from defining and realizing optimal health?

A. Better biomarkers for nutrient status are needed. For some nutrients—especially those that are homeostatically regulated—sensitive and specific biomarkers of nutrient status need to be developed [3]. We often rely on self-report dietary recalls or food frequency surveys to assess nutrient status; these tools have inherent flaws and biases that limit their accuracy and precision. The Office of Nutrition at the National Institutes of Health has recently launched a precision nutrition initiative that prioritizes identifying more objective markers of food and nutrient intake. This initiative seeks to innovate both dietary assessment methods and develop biological biomarkers of food and nutrient intake using technologies, such as metabolomics and machine learning methods [4–7].
B. A second gap includes a need to identify better biomarkers of healthspan and optimal health. These biomarkers need to move past identification of deficiency syndromes that link nutrient shortfalls to essential health and toward linking such shortfalls to optimal health. Moreover, there are numerous nonessential bioactives and natural compounds that will contribute to optimal health. This review will introduce concepts of resilience as potential touchstones and markers of optimal health. The concept of resilience encompasses the ability to respond to stress and maintain performance as well as to maintain cognitive processes as we age.
C. A third gap, and opportunity, centers around the concept of precision nutrition in defining optimal health. To realize the promise of optimal health, we need to appreciate that optimal health is different for everybody—one size does

not fit all. Understanding the drivers of differential and individualized responses to food, nutrients, and bioactives will be critical to realize the potential of precision nutrition. There is a critical need to understand the interactions among age, sex, environment, and genetic ancestry on how an individual responds to factors derived from foods. Emerging areas, including the roles of genotype, metabotypes, and the microbiome, will also be discussed in this complex and evolving science. This research and science will need to inform future RDA guidelines and recommendations, where additional subgroups of susceptible populations may be given specific, additional guidance and new biomarkers of health, rather than over deficiency syndromes, are considered.

Hallmarks of Optimal Health: Resilience, Performance, and Cognition

Defining Resilience

The science of resilience is not a new concept—this scientific concept was documented in the literature as early as the 1800s; the terminology entered the biomedical sciences in the mid-1900s and emerged in the early 2000s as a concept to be interconnected in multiple health domains. The questions dominating its broad use and applicability tend to focus on how to define resilience. In 2019, the Trans-NIH Resilience Working Group [8] was formed with a goal to develop an NIH-wide definition of resilience and to achieve consistency and harmony on the design and reporting of resilience research studies. In 1993, an introductory manuscript to a special issue published on the science of resilience included a quote stating, "resilience is at risk for being viewed as a popularized trend that has not been verified through research and is in danger of losing credibility within the scientific community" [9]. The authors of the manuscript also warned against definitional diversity with respect to measures of resilience and urged researchers to clearly operationalize the definition of resilience in all research reports. Remarkably, this call to action served as a primary aim of the Trans-NIH Resilience Working Group when it was organized >25 y after the 1993 special issue on resilience. One of the first activities of the Trans-NIH Resilience Working Group was to host a workshop, in March 2020, which led to the development of a definition of resilience and a conceptual infographic. The definition was intended to be applicable and useful across multiple domains, and it states that resilience encompasses "A system's capacity to resist, recover, grow, or adapt in response to a challenge or stressor" (Figure 1) [10]. A system can represent different domains, levels, and/or processes. Over time, a system's response to a challenge might show varied degrees of reactions that likely fluctuate in response to the severity of the challenge, the length of time exposed to the challenge, and/or innate/intrinsic factors. To show applicability of the definition in resilience research studies, the Resilience Research Design Tool [11] was later developed to help improve consistency in resilience research reports and to facilitate harmony with respect to measures of resilience outcomes. One of the goals of the resilience framework is to reframe the way we ask research questions, particularly about nutritional interventions like dietary supplements, so that we can better understand health outcomes that are not based solely on disease end points.

Going forward, as researchers across various scientific domains and sectors come closer to a unified definition of resilience and perhaps agree to the use of a standard checklist for designing and reporting on resilience studies, there is greater opportunity to harmonize the science and develop more empirical evidence of resilience outcomes.

Optimizing stress response and performance with nutrition

Optimizing performance also includes building resilience in order to enhance the ability to perform tasks and ensuring resilience in order to prevent illness, injury, and disease. Within the US Department of Defense, researchers are able to study different models of physical and psychological stress and the application of different nutritional interventions with Service Members throughout their careers. Various models of stress are introduced, including initial military training (e.g., boot camp or basic training), advanced military training courses (i.e.,

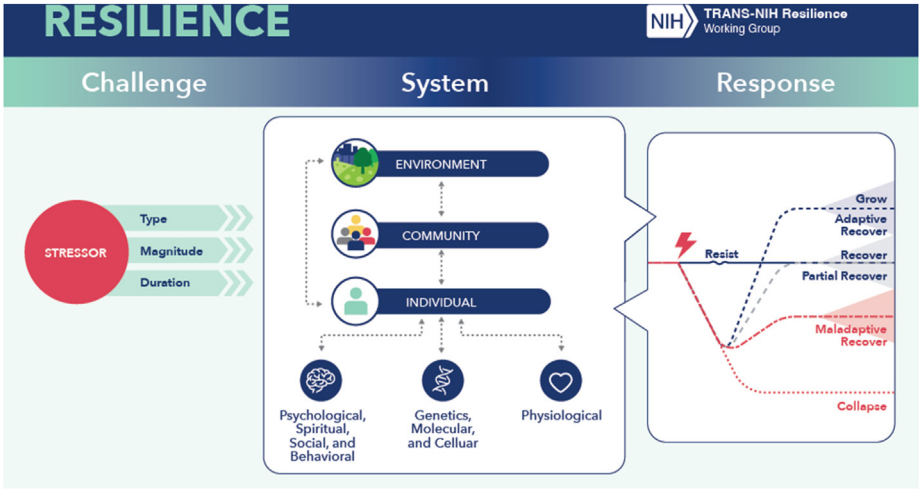

FIGURE 1. Overview of National Institutes of Health (NIH) resilience definition and concept model. Source material from https://ods.od.nih.gov/pubs/resilienceinfographic4.pdf [10].

Mountain Warfare, Jump School, Air Assault, etc.), service academies (i.e., US Air Force Academy, US Military Academy at West Point, or US Naval Academy), and extreme environments (e.g., heat, cold, and alternobarics), along with examples of various interventions and outcome measures collected to date. The importance of nutrition on readiness and resilience was identified in military populations more than a decade ago [12] and continues to be of interest [13]. Two specific examples are provided to further explore nutrition interventions aimed at optimizing performance in the Department of Defense. The first, a completed double-blind, randomized, placebo-controlled trial, used a calcium and vitamin D fortified food product to optimize bone health during initial military training of Marine Corps recruits [14]. Using a supplement or food intervention (with placebo controls) for calcium and vitamin D, participants received 2000-mg calcium and 1000-IU vitamin D per day. The primary outcomes of the study showed that bone markers and vitamin D status improve, but the supplementation did not affect skeletal parameters [14]. Vitamin D also augmented markers of innate mucosal immunity [15].

A second, forthcoming study aims to evaluate the effectiveness of adding spices and herbs to increase vegetable intake among junior-enlisted Service Members. Their current research is focused on the stressors and challenges to enhance resilience. Using a cycle of basic science/discovery that advances to clinical (or field) trials with various review steps (to evaluate outcomes and redesign studies for greater efficacy) helps move the field of nutrition science forward in a "total force fitness" approach. Total force fitness was introduced as a framework to help Service Members, their families, and military units reach and sustain optimal, holistic health, and performance in a way that aligns with their mission, culture, and identity [16]. Other examples of frameworks focused on a holistic approach to research include Whole Person Health proposed by the National Center for Complementary and Integrative Health [17], Whole Health developed by the Department of Veterans Affairs [18], and a recent consensus study report by the National Academies entitled Achieving Whole Health [19]. A focus on improving resilience as a model outcome highlights the opportunities and complexities of conducting optimal health and nutrition research in this space.

Cognition and cognitive resilience

As the number and proportion of older adults in the population increase, the prevalence of age-related deficits in mobility and cognition also increases. Such deficits may be because of normal aging or to pathologic processes. For instance, cognitive impairments like declines in memory and speed of processing may result from normal brain aging or neurodegenerative diseases like dementia. When considering hallmarks of optimal nutrition and health, improving resilience from cognitive decline has strong promise and impact [20]. Although the etiology of age-related mobility and cognitive changes is multifactorial, it is well established that vulnerability to oxidative stress and inflammation increases as we age. Strategies that target oxidative stress and inflammation may improve resilience to processes that lead to cognitive decline [21]. For example, a healthy diet may help combat both oxidative stress and inflammation in the body, but a diet rich in bioactive polyphenolics from fruit, vegetables, walnuts, and coffee may be especially important in improving resilience and health outcomes [22].

Polyphenols have antioxidant and anti-inflammatory activities, so consuming them could slow or prevent age-related changes. As previously shown, foods high in polyphenols, e.g., dark-colored berry fruits, prevent age-related neuronal and behavioral deficits in animal models of aging [23]. In particular, studies from animal models of aging have found that polyphenolic compounds from walnuts and berries hold promise in slowing—and perhaps even reversing—age-related motor and cognitive declines [23]. These polyphenolics possess antioxidant and anti-inflammatory properties and may also influence the brain directly through various mechanisms, including altered cell signaling and increased neurogenesis, arborization (branching) of dendrites, and autophagy in the brain [24].

In recent randomized, double-blind, placebo-controlled pilot studies in healthy older adults (ages 60–75 y), blueberry or strawberry supplementation (1–2 cups/d for 90 d) was able to improve some aspects of cognitive performance, but not gait or balance. In a randomized, double-blind, placebo-controlled trial in 44 healthy older adults (ages 60–75 y), supplementation with freeze-dried blueberry powder (polyphenolic equivalent to ~1 cup/d of blueberries) for 3 months improved 1 measure of executive function (mental flexibility) and 1 measure of learning and memory (verbal learning) [25]. In a similarly designed trial, supplementation of freeze-dried strawberry powder (polyphenolic equivalent to ~1 cup/d of strawberries) in 39 healthy older adults for 3 months improved 2 measures of learning and memory (spatial memory and recognition memory) compared with placebo but had no effect on executive function [26]. Both trials found that berry powder supplementation did not affect mobility, including measures of balance and gait, likely because the study subjects had no mobility detriments at baseline. Berry supplementation did not decrease serum levels of inflammatory biomarkers compared with placebo, but when serum from berry-supplemented subjects was applied directly to cultured microglia cells, there was a reduction in LPS-induced inflammatory markers relative to placebo-treated subjects [27]. Interestingly, the serum was protective when taken during fasting as well as postprandially. Although these studies are preliminary, they add to the evidence that berry supplementation may help protect against age-related cognitive declines. In addition to single nutrients, healthy dietary patterns have been shown to slow the rate of cognitive decline [28]. In particular, the Mediterranean-DASH diet intervention for neurodegenerative delay diet, which highlights increased intake of plant-based foods, such as berries and green leafy vegetables, is associated with lower risk of cognitive impairment in older adults [29].

Further investigations examined mechanisms and other factors involved in the beneficial effects of berry fruits. For example, changes in circulating levels of specific phenolic compounds were correlated with changes in cognition [30]. Furthermore, cognitive performance and inflammation were related, as serum collected from berry-supplemented animals reduced LPS-induced inflammatory-stress-mediated signals (e.g., NO) in stressed highly aggressively proliferating immortalized microglia in vitro relative to serum from placebo-fed controls, and nitrite levels following supplementation were positively correlated with cognitive performance (i.e., escape latency in a maze)

[31]. Therefore, the inclusion of additional servings of polyphenolic-rich foods, such as nuts and berries, in the diet may be one strategy to forestall age-related neuronal deficits, perhaps via decreases in inflammation and suppression of microglial activation, to help increase cognitive resilience and preserve cognitive function.

Other nonnutritive natural compounds derived from plants should also be considered as bioactive compounds that contribute to optimal health and improving resilience. The BENFRA Botanical Dietary Supplements Research Center at Oregon Health & Science University studies Botanicals Enhancing Neurological and Functional Resilience in Aging. Two botanicals of interest are *Centella asiatica* (gotu kola) and *Withania somnifera* (Ashwangandha). The Center has considerable experience with *Centella asiatica*, which is used in Ayurvedic medicine to improve memory. It is a popular dietary supplement for "brain health" and shows potential to be developed as a FDA approved "botanical drug" for the treatment of Alzheimer's disease. The rational use of botanicals, whether as dietary supplements or botanical drugs, requires their evaluation through optimized clinical trials [32,33]. These trials must be based on sound preclinical studies providing evidence for functional effects, mechanisms of action, and active compounds. The use of preclinical models is critical to inform the optimal design and implementation of future nutrient or botanical clinical intervention trials in healthy older adults and in patients with neurologic diseases, such as Alzheimer's disease. However, due to the limitations of preclinical models in representing human health, disease, and responses [34,35], evaluation of the efficacy of an intervention through clinical trials in humans is essential. Research needs to focus on product authentication, identification of the biologically active compounds and their mechanisms of action, and detection of relevant biomarkers that translate to humans. Preclinical studies also need to address efficacy and safety of the botanical to advance translational research in cognitive resilience. Preclinical studies at Oregon Health & Science University have confirmed the cognitive effects of *Centella asiatica* in aged mice [36,37] and that the antioxidant response gene *Nrf2* is a molecular target of this herb [36,38]. Triterpenes and caffeoylquinic acids have been identified as active compounds in *C. asiatica* and may account for its neuroprotection [39–42]. A phase I clinical trial examining the pharmacokinetics of *Centella asiatica* compounds in older adults with mild cognitive impairment was recently published [43]. A recently initiated clinical trial (NCT05591027) will examine safety of *C. asiatica* and also characterize the biologic signatures of its cognitive effects in a population of cognitively impaired older adults.

In the case of Ashwagandha, work at the BENFRA Center has focused on water and hydroethanolic extracts of the root, as these preparations are commonly used in dietary supplements and in previously reported scientific studies. In one study, the effects of aqueous and hydroethanolic extracts of Ashwagandha root were compared in *Drosophila melanogaster* models of sleep, cognition, locomotion (phototaxis), and stress-induced depression [44]. Treatment with the hydroethanolic extract improved age-related sleep fragmentation (defined as an increase in sleep bout number and a decrease in sleep bout length) in male flies. Surprisingly, Ashwagandha root aqueous extract showed stronger effects than the hydroethanolic extract in *Drosophila melanogaster* models of cognition and locomotion (phototaxis) and a model of stress-induced depression. Treatment with the aqueous extract of *W. somnifera* improved age-related locomotor declines in females at lower doses than the hydroethanolic extract. The aqueous extract also provided some resilience against stress-induced depression both when given prophylactically (only before stress) and continuously (before and during stress) in a Drosophila model of depression. By contrast, the hydroethanolic extract was only effective when given continuously. The withanolides, commonly regarded as Ashwagandha's active compounds, are present in greater amounts in the hydroethanolic than aqueous extracts [44]. Together, this suggests that different Ashwangandha compounds may modulate the botanical's effects on cognition, mood, and sleep and that compounds other than the well-known withanolides may be involved in some of its biologic effects. Studies are underway to explore these unknown active compounds in resilience to age-related cognitive decline and stress. Knowledge of the bioactive compounds associated with each potential clinical use of Ashwangandha will be important in optimizing products for clinical trials of Ashwangandha for those conditions.

In summary, as we pivot to emphasize the promotion of optimal health, we need alternative indices of health besides disease outcomes. An individual's ability to be resilient, including the ability to respond to stressors and to thrive and retain functionality (i.e., cognitive function and immunity) while maintaining a high quality of life, should be considered. Moreover, both essential nutrients (vitamins and minerals) as well as other nonessential bioactive compounds should be considered as key factors that promote optimal health.

Individualized Responses and Precision Health

As we define optimal health, it is clear that the potential solutions will vary depending on many individual and environmental factors. Nutritional interventions in healthy adults are known to produce a variety of responses, and work is underway to identify and characterize the different phenotypes that result in unique metabolic needs, with the goal to design personalized dietary approaches to maximize individual health. Although reasonable skepticism regarding the consumer readiness for precision and personalized nutrition exists, efforts to better illuminate the goals and challenges to this emerging technology are being openly discussed in the research community. For instance, in August of 2021, the National Academy of Science, Engineering, and Medicine held a public workshop titled "Challenges and Opportunities for Precision and Personalized Nutrition" [45]. At this workshop, participants raised important perspectives on current opportunities and information gaps in our understanding and approaches to variability in nutritional responses, the shift in the personalized nutrition industry, and numerous studies demonstrating the potential utility for research in this area to aid in our understanding of variable nutritional responses as well as how in certain circumstances they may be beneficial in tooling both dietary guidance for glucose control and therapeutic interventions for weight loss. Addressing these knowledge gaps and refining our expectations and applications for individualized nutrition will be critical to realizing the full potential of this knowledge as another tool in our arsenal to improve human health. In 2020, the NIH also launched a new

strategic plan for nutrition that emphasizes Precision Nutrition [46]. In 2022, the NIH invested $170M in a new Precision Health program that leverages the All of Us research program and will allow unprecedented opportunities to combine metabolism, microbiome, diet assessment methods, and data sciences together to provide new insights in precision nutrition. Instead of a one-size-fits-all, we can envision a time where a person's unique characteristics (e.g., age, genetics, sex, metabolism, health history, known environmental exposures, lifestyle) will be effectively used in a proactive approach to health promotion and disease prevention, and importantly, allowing personalized strategies based on these characteristics. Significant strides in science and technology made over the past decade will be instrumental in our efforts to understand precision nutrition. In this next section, we discuss contributors to individual variability and precision nutrition, including the role of metabolism, genotypes, and the gut microbiome.

Metabolic variability

Variability in responses to nutritional interventions in healthy humans is well-known and suggests that individuals may benefit from more personalized dietary regimens to improve or maintain health. Although the physiologic/genetic underpinnings of these phenotypes and their responsiveness to changes in nutritional status largely remain to be explored, tools to efficiently identify nutritionally responsive phenotypes are emerging. Variable responses to dietary omega-3 FAs are one of the better characterized nutritionally responsive phenotypes, and this research highlights the complexity and nuance needed to fully appreciate physiologically relevant responses [47,48]. For instance, in a secondary analysis of a randomized, double-blind, placebo-controlled trial of short-term fish oil supplementation (2 g/d EPA + 1 g/d DHA for 6 wk) in 83 individuals of African ancestry, a two-thirds by one-third split in 'high responders' compared with 'low responders' was reported with respect to intervention effect on red blood cell long-chain ω-3 FA enrichment, reduction in plasma triglyceride concentrations, and stimulated monocyte inflammatory responses [49]. Although an individual's adiposity, baseline ω-3 FA status, consumed dose, and the ingested ω-3 form (i.e., TG, phospholipid, and ethyl ester) contribute to the ω-3 response [50,51], this variance may also be influenced by an individual's background diet. In particular, the consumption of less than one-third cup of dark-green and orange vegetables and legumes—and the health effects of their accompanying nutrients—was associated with the low response in a secondary analysis of the aforementioned intervention study [49].

Another experimental approach to examine interindividual variability to a nutritional intervention is the mixed meal/macronutrient challenge test [52–55]. Analogous to oral glucose tolerance tests, in which the metabolic response to a standardized carbohydrate challenge is investigated, a mixed macronutrient challenge can be used to probe the metabolic response to a complex meal. Using standard clinical measurements, such a challenge can be used to simultaneously assess insulin sensitivity and fat tolerance [54]. However, by expanding the experimental end points to include both physiologic and broad metabolic responses using modern metabolomic technologies, the potential for phenotypic profiling of an individual's response to such a standardized meal is extraordinary. For instance, an individual's metabolic flexibility (i.e., the ability to switch among available fuels, such as fats, carbohydrates, or proteins), their metabolic health, and the potential for their response to interventions can all be assessed [52,53,55]. Another powerful application of metabolomic phenotyping in nutritional research is the application to twin studies. By employing sets of both dizygotic and monozygotic twins, these approaches have demonstrated the power to segregate and quantify the genetic and environmental factors driving covariance between physiologic and metabolic traits and health outcomes [56,57].

In summary, characterizing the range and nature of both fasting and postprandial nutritional phenotypes based on differences in metabolism in healthy populations offers novel approaches to identify individuals that may benefit from more individualized nutritional guidance to improve and/or maintain their health. Moreover, tools exist today to begin this task. The application of these tools in well-designed clinical trials will be critical to effectively demonstrate their value in aligning nutritional guidance and/or interventions with metabolic phenotypes.

Genotype

Gene-by-diet interactions have the potential to have a tremendous impact on human health. Throughout history, humans evolutionarily adapted to their local environments to move across the globe, including to their changing diets. However, transitions to the modern Western diet in the last 75 y have resulted in maladaptations leading to a high prevalence of various chronic diseases, including obesity, cancer, and cardiometabolic diseases that disproportionately affect certain populations and create ethnic health disparities [58,59]. For example, the adoption of the Western diet brought about a dramatic increase in the intake of PUFAs, specifically dietary ω-6 PUFAs [60]. This shift was initiated by an American Heart Association recommendation in 1961 to replace dietary SFAs with PUFAs [61]. Evidence supporting the recommendation included randomized controlled trials and cohort studies conducted in non-Hispanic White populations showing benefits of increasing ω-6 PUFAs on levels of serum lipids and lipoproteins [62,63]. It was also assumed that only a small proportion of these ω-6 PUFAs (2%–3% of energy ingested) could be converted to proinflammatory/prothrombotic long-chain ω-6 PUFAs, such as arachidonic acid [64], so adding 5%–10% energy as ω-6 PUFAs (as recommended) would have limited detrimental inflammatory/thrombotic effects due to saturation of the biosynthetic pathway.

However, studies began to emerge a decade ago that showed genetic ancestry plays a critical role in determining the metabolic capacity of the long-chain ω-6 PUFA biosynthetic pathway. Specifically, several studies revealed that populations with African ancestry (compared with those of European or Amerind ancestry) have much higher frequencies of genetic variants in the FA desaturase (*FADS*) cluster on chromosome 11 (chr11q12-13.1) that markedly enhance the conversion of dietary ω-6 PUFAs to the long-chain ω-6, arachidonic acid and proinflammatory/prothrombotic oxylipins (including eicosanoids), and endocannabinoids metabolites [65–67]. This underlying pathogenetic mechanism potentially results in a higher risk of chronic disease in those of African ancestry compared with those with European ancestry.

With few exceptions, ω-6 long-chain PUFAs, such as arachidonic acid are proinflammatory/prothrombotic, and ω-3 long-chain PUFAs, such as EPA and DHA are anti-inflammatory/antithrombotic [68–70]. Given the fact that a much higher proportion of populations of African ancestry has the capacity to form higher levels of arachidonic acid and its metabolites from dietary ω-6 PUFAs, it might be expected that ω-3 long-chain PUFAs would have a greater capacity to balance the impact of high dietary ω-6 PUFAs in these populations. Among clinical trials carried out to date, the VITamin D and omegA-3 TriaL (VITAL) is of particular interest when considering African ancestry, as it included $n = 5106$ African-American (AfAm) participants out of $n = 25{,}871$ total participants. Overall, supplementation with marine ω-3 long-chain PUFAs (EPA + DHA, 1g/d as ethyl esters) failed to prevent CVD (composite end point) or cancer events among healthy middle-aged men and women over 5 y of follow-up. Although ω-3 long-chain PUFA supplementation failed to prevent CVD (composite end point) in the full group analysis, in a follow-up subgroup analysis, Manson et al. [71] demonstrated robust risk reductions in AfAm (HR: 0.23; 95% CI: 0.11, 0.47; P interaction by race, 0.001). Similarly, subgroup reanalysis of the VITAL study data based on the *FADS* framework compared the Kaplan–Meier curves for the MI end point, faceted by fish consumption and the number of CVD risk factors, for both European American and AfAm participants [47]. This reanalysis revealed a marked ~80% reduction in MI associated with ω-3 long-chain PUFA supplementation in AfAm participants with baseline CVD risk who did not consume fish (low ω-3 intake) [47]. By contrast, and in accord with our *FADS* framework and the mixed distribution of *FADS* haplotypes in European American populations, these participants failed to benefit similarly, regardless of baseline fish intake or baseline CVD risk. Collectively, these data suggest that AfAm populations may benefit from ω-3 long-chain PUFA supplementation, and both ancestry and *FADS* variability should be factored into future clinical trial designs. Such heterogeneity in the *FADS* cluster and other genes should inform the design of future clinical trials and may offer the opportunity to personalize recommendations of long-chain ω-3 PUFA supplementation to individuals of different ethnicities.

Microbiome

The human gut responds rapidly to significant changes in the diet [72,73], and long-term dietary habits can exert strong effects [74]. The influence of dietary components has had a long history of impact on gut health and maintenance of high gut microbial diversity [75,76]. However, the gut microbiomes in humans are highly diverse and variable among individuals [77]. Moreover, the influence of specific dietary components on the gut microbiome community structure (i.e., diversity and abundance of individual microbes) and microbial metabolic function may vary among individual microbiomes [78]. Thus, diet–microbiome interactions are highly individual and idiosyncratic, especially over one's lifetime [79]. Myriad dietary compounds are known to modulate human gut microbiome structure and function, with impact on disease [80]; among these, dietary fibers were first established for their protective effects against chronic disease at population scales, which are widely believed to be largely mediated by the microbiome [81]. Although dietary fiber intake is widely associated with positive health outcomes (chiefly, prevention of the chronic diseases increasingly prevalent in Western populations) [82–85], persistent public health and nutrition messaging in many such nations has made only modest gains in increasing consumption [86]. Thus, dietary fibers remain, to date, the only microbiome-focused nutrient with established dietary guidelines for population-scale health. If populations are recalcitrant to increasing their overall fiber intake, dietary fiber-based strategies to improve health must seek to identify the fiber types most active in stimulating the appropriate microbiome responses to benefit host physiology [87,88]. This is not trivial in that *1*) as a category, "fiber" simply means the non–human-digestible plant components and includes a vast array of molecular structures, both soluble and insoluble [89]; and *2*) the mechanisms by which these divergent structures alter the structure and function of gut microbiota, thereby influencing health, are poorly understood [90]. Coupled with the fact that many fiber intervention studies do not specify or characterize the fiber structures employed (e.g., fine polysaccharide structures, particle sizes), it is very challenging to discern which structural variables are influential on the responses of gut microbiota, both in vitro and in vivo [91]. Consequently, the ways in which fiber structures differentially influence ecology in the gut and metabolic function suggest that specific fibers can be targeted to desirable microbial consumers, thereby potentially being health beneficial at much smaller daily doses and at population scales ("one size fits many").

Fiber polysaccharide structures contain a dizzying array of linkages among glycosyl residues that, in turn, generate strong differences in higher-order structure of these substrates. Because microbial carbohydrate-active enzymes are highly specific to the bonds they hydrolyze, differences in genome content or regulation of these carbohydrate-active enzymes can drive division of labor in degradation of polysaccharide consumption [92]. The Lindemann laboratory at Purdue University has demonstrated that *1*) metabolism of fibers is emergent across individuals but structural differences select for similar microbiota across donors [93] and *2*) polysaccharides can structure communities and maintain diversity against high-dilution pressure [94]. These data strongly suggest that fiber fine structures are highly selective for consortia of fermenting microbes and sustain them in diverse communities, potentially serving as a basis for targeting these microbiota in the midst of complex and idiosyncratic human gut communities [89,90,93,95–99]. The hypothesis is that there are general ecologic strategies that microbes use to gain advantage with respect to fiber fermentation and possible downstream health benefits [92]. It is believed that these strategies are genetically encoded [100]; thus, they provide a foundation for engineering fibers that will allow the gut microbiome to be manipulated for predictable outcomes across disparate individuals.

To test the hypothesis that subtle differences in polysaccharide structure select for distinct microbial communities, 2 subtly different model polysaccharides, red and white sorghum arabinoxylan (RSAX and WSAX, respectively) were fermented with identical microbiota. RSAX was slightly more complex at the level of branching diversity than WSAX and maintained a more diverse microbiome in which members of *Bacteroides* spp., especially *B. ovatus*, were dominant. In contrast, WSAX promoted the growth of *Agathobacter rectalis* and *Bifidobacterium longum*-dominated communities. Interestingly, these polysaccharides selected for

genomically identical strains across 3 unrelated donors. Alongside the differences in community structure, RSAX and WSAX were fermented to different metabolic outcomes. Further, when fed to mice, WSAX and a human-derived microbial consortium adapted to its use modified the cecal metabolism of mice in sex-specific ways. Interestingly, the effects of transient human microbes could be seen in metabolite profiles and in postantibiotic community resilience in the mice. Our data suggest that *1*) polysaccharide fine structure deterministically selects for fermenting communities; *2*) fine polysaccharide variants often target largely the same microbes across individuals; and *3*) in turn, these differences lead to divergent metabolic outcomes, which are potentially impactful on host physiology and resilience to stress. Together, these results suggest that well-characterized fiber structures may be used to influence human health at population scales and relatively small doses.

Conclusions, Actions, and Next Steps

Defining optimal health is going to be extremely dynamic in nature. As our analytical technologies continue to advance, where we can obtain structural, cellular, organ, and whole-body data—and generate millions of data points around cellular and health outcomes—there is a critical need for collaborative team science approaches. Collaboration among data scientists, biologists, and nutrition experts will help decipher complex data and identify new hypotheses and approaches. This team science approach will be needed to help identify and interpret new markers of resilience and optimal health and to better understand the complexity of factors that lead to interindividual response differences and individualized recommendations. Critical research needs include:

- A harmonization of methods, research design, and outcome measures
- An increase in diversity, equity, and inclusion lens, with more research on understudied populations
- Methodology that facilitates integration of data streams

The field of nutrition is in a critical transition period. Public awareness and interest in the role of nutrition in health have grown exponentially. Yet, a high proportion of the population still does not meet the current dietary guideline recommendations. A transition to defining optimal health, with markers of resilience and retaining optimal function, has the potential to help motivate behavior change as tangible measures of functionality and vitality that can be individualized. However, these scientific efforts will require team communication and close collaboration to properly message and communicate to the population at large, and ultimately, improve the health of the nation.

Funding

Supported by the United States Department of Agriculture (USDA) Project 2032-51530-025-00D (JWN), USDA Project 8050-51000-102-000-D (BSH), Oregon Agricultural Experimental Station (W4002; OR00735) (EH), and USDA Project ARZT-1361680-H23-157 (FHC). Also supported by the National Institutes of Health (NIH) NCCIH U19AT010829 (AS), NIH NCCIH R61 AT009628 (AS), NIH NCCIH R01 0008099 (AS), NCCIH R01 AT008621 (FHC), Alzheimer's Association PTC-REG22-924617 (AS), NIH P30 ES03028 (EH) and NIGMS R35 GM133634 (SL).

Author Disclosures

JMS, JWN, BSH, AS, VJD, LLB, AJM, has no conflicts of interest. SRL is the founder of Ina Microbiome, LLC. EH is a scientific advisor for Haleon and Vytology. AShao and YNE are employees of ChromaDex, Inc. FHC is a cofounder of Tyrian Omega, Inc, and Resonance Pharma, Inc. SHM is an employee of Pharmavite, LLC.

Disclaimers

The opinions and assertions expressed herein are those of the authors and do not reflect the official policy or position of the National Institutes of Health, Uniformed Services University, or the Department of Defense.

The mention of trade names or commercial products in this publication is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the USDA or NIH. The USDA is an equal opportunity provider and employer.

Acknowledgments

The authors' responsibilities were as follows – EH, VJD, AJM: wrote the initial draft of the manuscript; YNE, LLB, JMS, JWN, BSH, ASo, FHC, SRL, ASh, SHM: provided input on, edited, and revised the manuscript; EH: had primary responsibility for the final content; and all authors: read and approved the final manuscript.

References

[1] Institute of Medicine, Dietary Reference Intakes: the Essential Guide to Nutrient Requirements, National Academies Press, Washington, DC, 2006.
[2] M. Sheffer, C.L. Taylor, The development of DRIs 1994-2004: lessons learned and new challenges: Workshop Summary, National Academies Press, Washington, DC, 2008.
[3] D.J. Raiten, S. Namasté, B. Brabin, G. Combs Jr., M.R. L'Abbe, E. Wasantwisut, et al., Executive summary–biomarkers of nutrition for development: building a consensus, Am. J. Clin. Nutr. 94 (2) (2011) 633S–650S, https://doi.org/10.3945/ajcn.110.008227.
[4] A.R. Kristal, N.C. Vizenor, R.E. Patterson, M.L. Neuhouser, A.L. Shattuck, D. McLerran, Precision and bias of food frequency-based measures of fruit and vegetable intakes, Cancer Epidemiol. Biomarkers Prev. 9 (9) (2000) 939–944.
[5] A.R. Kristal, C.H. Andrilla, T.D. Koepsell, P.H. Diehr, A. Cheadle, Dietary assessment instruments are susceptible to intervention-associated response set bias, J. Am. Diet Assoc. 98 (1) (1998) 40–43, https://doi.org/10.1016/S0002-8223(98)00012-1.
[6] D. Aaby, J. Siddique, Effects of differential measurement error in self-reported diet in longitudinal lifestyle intervention studies, Int. J. Behav. Nutr. Phys. Act. 18 (1) (2021) 125, https://doi.org/10.1186/s12966-021-01184-x.
[7] B.Y. Lee, J.M. Ordovás, E.J. Parks, C.A.M. Anderson, A.L. Barabási, S.K. Clinton, et al., Research gaps and opportunities in precision nutrition: an NIH workshop report, Am. J. Clin. Nutr. 116 (6) (2022) 1877–1900, https://doi.org/10.1093/ajcn/nqac237.
[8] Trans-NIH Resilience Working Group [Internet]. Bethesda, MD; National Institutes of Health Office of Dietary Supplements [cited

2023 February 13]. Available from: https://ods.od.nih.gov/Research/resilience.aspx.
[9] D. Cicchetti, N. Garmezy, Prospects and promises in the study of resilience, Dev. Psychopathol. 5 (4) (1993) 497–502, https://doi.org/10.1017/S0954579400006118.
[10] L. Brown, B. Cohen, R. Costello, O. Brazhnik, Z. Galis, Conceptualizing a resilience research framework at the National Institutes of Health, Stress Health, 2023, https://doi.org/10.1002/smi.3260.
[11] L. Brown, B. Cohen, R. Costello, O. Brazhnik, Z.S. Galis, Next steps: operationalizing resilience research, Stress Health, 2023, https://doi.org/10.1002/smi.3256.
[12] D.L. Purvis, C.V. Lentino, T.K. Jackson, K.J. Murphy, P.A. Deuster, Nutrition as a component of the performance triad: how healthy eating behaviors contribute to soldier performance and military readiness, US Army Med. Dep. J. (2013) 66–78.
[13] L.J. Lutz, E. Gaffney-Stomberg, K.W. Williams, S.M. McGraw, P.J. Niro, J.P. Karl, et al., Adherence to the Dietary Guidelines for Americans is associated with psychological resilience in young adults: a cross-sectional study, J. Acad. Nutr. Diet 117 (3) (2017) 396–403, https://doi.org/10.1016/j.jand.2016.09.018.
[14] E. Gaffney-Stomberg, A.T. Nakayama, K.I. Guerriere, L.J. Lutz, L.A. Walker, J.S. Staab, et al., Calcium and vitamin D supplementation and bone health in Marine recruits: effect of season, Bone 123 (2019) 224–233, https://doi.org/10.1016/j.bone.2019.03.021.
[15] J.M. Scott, J.B. Kazman, J. Palmer, J.P. McClung, E. Gaffney-Stomberg, H.G. Gasier, Effects of vitamin D supplementation on salivary immune responses during Marine Corps basic training, Scand. J. Med. Sci. Sports 29 (9) (2019) 1322–1330, https://doi.org/10.1111/sms.13467.
[16] W.B. Jonas, F.G. O'Connor, P. Deuster, J. Peck, C. Shake, S.S. Frost, Why total force fitness? Mil. Med. 175 (8S) (2010) 6–13, https://doi.org/10.7205/MILMED-D-10-00280.
[17] H.M. Langevin. Research on Whole Person Health [Internet]. Bethesda, MD: National Institutes of Health, National Center for Complementary and Integrative Health. [cited 2023 May 15]. Available from: https://www.ama-assn.org/system/files/i22-sps-education-session-whole-person-health.pdf.
[18] [Internet], Whole Health, US Department of Veteran Affairs, Washington, DC, 2023 [cited 2023 May 15]. Available from: https://www.va.gov/wholehealth/.
[19] National Academies of Sciences, Engineering, and Medicine, Achieving Whole Health: A New Approach for Veterans and the Nation, The National Academies Press, Washington, DC, 2023.
[20] M.G. Miller, N. Thangthaeng, S.M. Poulose, B. Shukitt-Hale, Role of fruits, nuts, and vegetables in maintaining cognitive health, Exp. Gerontol. 94 (2017) 24–28, https://doi.org/10.1016/j.exger.2016.12.014.
[21] S.J. Spencer, A. Korosi, S. Layé, B. Shukitt-Hale, R.M. Barrientos, Food for thought: how nutrition impacts cognition and emotion, NPJ Sci. Food 1 (2017) 7, https://doi.org/10.1038/s41538-017-0008-y.
[22] K.R. Gildawie, R.L. Galli, B. Shukitt-Hale, A.N. Carey, Protective effects of foods containing flavonoids on age-related cognitive decline, Curr. Nutr. Rep. 7 (2) (2018) 39–48, https://doi.org/10.1007/s13668-018-0227-0.
[23] P. Pribis, B. Shukitt-Hale, Cognition: the new frontier for nuts and berries, Am. J. Clin. Nutr. 100 (Suppl 1) (2014) 347S–352S, https://doi.org/10.3945/ajcn.113.071506.
[24] M.G. Miller, B. Shukitt-Hale, Berry fruit enhances beneficial signaling in the brain, J. Agric. Food Chem. 60 (23) (2012) 5709–5715, https://doi.org/10.1021/jf2036033.
[25] M.G. Miller, D.A. Hamilton, J.A. Joseph, B. Shukitt-Hale, Dietary blueberry improves cognition among older adults in a randomized, double-blind, placebo-controlled trial, Eur. J. Nutr. 57 (3) (2018) 1169–1180, https://doi.org/10.1007/s00394-017-1400-8.
[26] M.G. Miller, N. Thangthaeng, G.A. Rutledge, T.M. Scott, B. Shukitt-Hale, Dietary strawberry improves cognition in a randomised, double-blind, placebo-controlled trial in older adults, Br. J. Nutr. 126 (2) (2021) 253–263, https://doi.org/10.1017/S0007114521000222.
[27] G.A. Rutledge, D.R. Fisher, M.G. Miller, M.E. Kelly, D.F. Bielinski, B. Shukitt-Hale, The effects of blueberry and strawberry serum metabolites on age-related oxidative and inflammatory signaling in vitro, Food Funct 10 (12) (2019) 7707–7713, https://doi.org/10.1039/c9fo01913h.
[28] P. Devranis, E. Vassilopoulou, V. Tsironis, P.M. Sotiriadis, M. Chourdakis, M. Aivaliotis, et al., Mediterranean diet, ketogenic diet or MIND Diet for aging populations with cognitive decline: a systematic review, Life (Basel) 13 (1) (2023) 173, https://doi.org/10.3390/life13010173.
[29] S. Kheirouri, M. Alizadeh, MIND diet and cognitive performance in older adults: a systematic review, Crit. Rev. Food Sci. Nutr. 62 (29) (2022) 8059–8077, https://doi.org/10.1080/10408398.2021.1925220.
[30] G.A. Rutledge, A.K. Sandhu, M.G. Miller, I. Edirisinghe, B.B. Burton-Freeman, B. Shukitt-Hale, Blueberry phenolics are associated with cognitive enhancement in supplemented healthy older adults, Food Funct 12 (1) (2021) 107–118, https://doi.org/10.1039/d0fo02125c.
[31] B. Shukitt-Hale, N. Thangthaeng, M.G. Miller, S.M. Poulose, A.N. Carey, D.R. Fisher, Blueberries improve neuroinflammation and cognition differentially depending on individual cognitive baseline status, J. Gerontol. A Biol. Sci. Med. Sci. 74 (7) (2019) 977–983, https://doi.org/10.1093/gerona/glz048.
[32] B.C. Sorkin, A.J. Kuszak, G. Bloss, N.K. Fukagawa, F.A. Hoffman, M. Jafari, et al., Improving natural product research translation: from source to clinical trial, FASEB J 34 (1) (2020) 41–65, https://doi.org/10.1096/fj.201902143R.
[33] W.J. Weber, D.C. Hopp, National Center for Complementary and Integrative Health perspectives on clinical research involving natural products, Drug Metab. Dispos. 48 (10) (2020) 963–965, https://doi.org/10.1124/dmd.120.000071.
[34] E. Drummond, T. Wisniewski, Alzheimer's disease: experimental models and reality, Acta Neuropathol 133 (2) (2017) 155–175, https://doi.org/10.1007/s00401-016-1662-x.
[35] S.J. Mitchell, M. Scheibye-Knudsen, D.L. Longo, R. de Cabo, Animal models of aging research: implications for human aging and age-related diseases, Annu. Rev. Anim. Biosci. 3 (2015) 283–303, https://doi.org/10.1146/annurev-animal-022114-110829.
[36] N.E. Gray, C.J. Harris, J.F. Quinn, A. Soumyanath, Centella asiatica modulates antioxidant and mitochondrial pathways and improves cognitive function in mice, J. Ethnopharmacol. 180 (2016) 78–86, https://doi.org/10.1016/j.jep.2016.01.013.
[37] N.E. Gray, J.A. Zweig, M. Caruso, M.D. Martin, J.Y. Zhu, J.F. Quinn, et al., Centella asiatica increases hippocampal synaptic density and improves memory and executive function in aged mice, Brain Behav 8 (7) (2018), e01024, https://doi.org/10.1002/brb3.1024.
[38] J.A. Zweig, M.S. Brandes, B.H. Brumbach, M. Caruso, K.M. Wright, J.F. Quinn, et al., Loss of NRF2 accelerates cognitive decline, exacerbates mitochondrial dysfunction, and is required for the cognitive enhancing effects of Centella asiatica during aging, Neurobiol. Aging 100 (2021) 48–58, https://doi.org/10.1016/j.neurobiolaging.2020.11.019.
[39] N.E. Gray, A. Alcazar Magana, P. Lak, K.M. Wright, J. Quinn, J.F. Stevens, et al., Centella asiatica - phytochemistry and mechanisms of neuroprotection and cognitive enhancement, Phytochem. Rev. 17 (1) (2018) 161–194, https://doi.org/10.1007/s11101-017-9528-y.
[40] N.E. Gray, J.A. Zweig, C. Murchison, M. Caruso, D.G. Matthews, C. Kawamoto, et al., Centella asiatica attenuates Aβ-induced neurodegenerative spine loss and dendritic simplification, Neurosci. Lett. 646 (2017) 24–29, https://doi.org/10.1016/j.neulet.2017.02.072.
[41] N.E. Gray, J. Morré, J. Kelley, C.S. Maier, J.F. Stevens, J.F. Quinn, et al., Caffeoylquinic acids in Centella asiatica protect against amyloid-β toxicity, J. Alzheimers Dis. 40 (2) (2014) 359–373, https://doi.org/10.3233/JAD-131913.
[42] D.G. Matthews, M. Caruso, A. Alcazar Magana, K.M. Wright, C.S. Maier, J.F. Stevens, et al., Caffeoylquinic acids in Centella asiatica reverse cognitive deficits in male 5XFAD Alzheimer's disease model mice, Nutrients 12 (11) (2020) 3488, https://doi.org/10.3390/nu12113488.
[43] K.M. Wright, M. Bollen, J. David, A.B. Speers, M.S. Brandes, N.E. Gray, et al., Pharmacokinetics and pharmacodynamics of key components of a standardized Centella asiatica product in cognitively impaired older adults: a phase 1, double-blind, randomized clinical trial, Antioxidants (Basel) 11 (2) (2022) 215, https://doi.org/10.3390/antiox11020215.
[44] H. Holvoet, D.M. Long, A. Law, C. McClure, J. Choi, L. Yang, et al., Withania somnifera extracts promote resilience against age-related and stress-induced behavioral phenotypes in Drosophila melanogaster; a possible role of other compounds besides Withanolides, Nutrients 14 (19) (2022) 3923, https://doi.org/10.3390/nu14193923.
[45] National Academies of Sciences, Engineering, and Medicine, Challenges and Opportunities for Precision and Personalized

Nutrition: Proceedings of a Workshop—In Brief, The National Academies Press, Washington, DC, 2021.
[46] National Institutes of Health, 2020–2030 Strategic plan for NIH nutrition research: a report of the NIH Nutrition Research Task Force [Internet], 2020. Available from: https://dpcpsi.nih.gov/sites/default/files/2020NutritionStrategicPlan_508.pdf.
[47] F.H. Chilton, A. Manichaikul, C. Yang, T.D. O'Connor, L.M. Johnstone, S. Blomquist, et al., Interpreting clinical trials with omega-3 supplements in the context of ancestry and FADS genetic variation, Front. Nutr. 8 (2021), 808054, https://doi.org/10.3389/fnut.2021.808054.
[48] W. Stoffel, B. Holz, B. Jenke, E. Binczek, R.H. Günter, C. Kiss, et al., Delta6-desaturase (FADS2) deficiency unveils the role of omega3- and omega6-polyunsaturated fatty acids, EMBO J 27 (17) (2008) 2281–2292, https://doi.org/10.1038/emboj.2008.156.
[49] A. O'Sullivan, P. Armstrong, G.U. Schuster, T.L. Pedersen, H. Allayee, C.B. Stephensen, et al., Habitual diets rich in dark-green vegetables are associated with an increased response to ω-3 fatty acid supplementation in Americans of African ancestry, J. Nutr. 144 (2) (2014) 123–131, https://doi.org/10.3945/jn.113.181875.
[50] R.E. Walker, K.H. Jackson, N.L. Tintle, G.C. Shearer, A. Bernasconi, S. Masson, et al., Predicting the effects of supplemental EPA and DHA on the omega-3 index, Am. J. Clin. Nutr. 110 (4) (2019) 1034–1040, https://doi.org/10.1093/ajcn/nqz161.
[51] C.E. Richardson, S. Krishnan, I.J. Gray, N.L. Keim, J.W. Newman, The omega-3 index response to an 8 week randomized intervention containing three fatty fish meals per week is influenced by adiposity in overweight to obese women, Front. Nutr. 9 (2022), 810003, https://doi.org/10.3389/fnut.2022.810003.
[52] S. Wopereis, J.H.M. Stroeve, A. Stafleu, G.C.M. Bakker, J. Burggraaf, M.J. van Erk, et al., Multi-parameter comparison of a standardized mixed meal tolerance test in healthy and type 2 diabetic subjects: the PhenFlex challenge, Genes Nutr 12 (2017) 21, https://doi.org/10.1186/s12263-017-0570-6.
[53] J. Fiamoncini, M. Rundle, H. Gibbons, E.L. Thomas, K. Geillinger-Kästle, D. Bunzel, et al., Plasma metabolome analysis identifies distinct human metabotypes in the postprandial state with different susceptibility to weight loss-mediated metabolic improvements, FASEB J 32 (10) (2018) 5447–5458, https://doi.org/10.1096/fj.201800330R.
[54] J.W. Newman, S. Krishnan, K. Borkowski, S.H. Adams, C.B. Stephensen, N.L. Keim, Assessing insulin sensitivity and postprandial triglyceridemic response phenotypes with a mixed macronutrient tolerance test, Front. Nutr. 9 (2022), 877696, https://doi.org/10.3389/fnut.2022.877696.
[55] J.L. LaBarre, K. Singer, C.F. Burant, Advantages of studying the metabolome in response to mixed-macronutrient challenges and suggestions for future research designs, J. Nutr. 151 (10) (2021) 2868–2881, https://doi.org/10.1093/jn/nxab223.
[56] R. Barron, K. Bermingham, L. Brennan, E.R. Gibney, M.J. Gibney, M.F. Ryan, et al., Twin metabolomics: the key to unlocking complex phenotypes in nutrition research, Nutr. Res. 36 (4) (2016) 291–304, https://doi.org/10.1016/j.nutres.2016.01.010.
[57] K.M. Bermingham, L. Brennan, R. Segurado, R.E. Barron, E.R. Gibney, M.F. Ryan, et al., Exploring covariation between traditional markers of metabolic health and the plasma metabolomic profile: a classic twin design, J. Proteome Res. 18 (6) (2019) 2613–2623, https://doi.org/10.1021/acs.jproteome.9b00126.
[58] L. Cordain, S.B. Eaton, A. Sebastian, N. Mann, S. Lindeberg, B.A. Watkins, et al., Origins and evolution of the Western diet: health implications for the 21st century, Am. J. Clin. Nutr. 81 (2) (2005) 341–354, https://doi.org/10.1093/ajcn.81.2.341.
[59] B.M. Popkin, Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases, Am. J. Clin. Nutr. 84 (2) (2006) 289–298, https://doi.org/10.1093/ajcn/84.1.289.
[60] T.L. Blasbalg, J.R. Hibbeln, C.E. Ramsden, S.F. Majchrzak, R.R. Rawlings, Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century, Am. J. Clin. Nutr. 93 (5) (2011) 950–962, https://doi.org/10.3945/ajcn.110.006643.
[61] Dietary fat and its relation to heart attacks and strokes. Report by the Central Committee for Medical and Community Program of the American Heart Association, JAMA 175 (1961) 389–391.
[62] M. Miller, N.J. Stone, C. Ballantyne, V. Bittner, M.H. Criqui, H.N. Ginsberg, et al., Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association, Circulation 123 (20) (2011) 2292–2333, https://doi.org/10.1161/CIR.0b013e3182160726.
[63] R.P. Mensink, P.L. Zock, A.D.M. Kester, M.B. Katan, Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials, Am. J. Clin. Nutr. 77 (5) (2003) 1146–1155, https://doi.org/10.1093/ajcn/77.5.1146.
[64] H. Sprecher, Metabolism of highly unsaturated n-3 and n-6 fatty acids, Biochim. Biophys. Acta 1486 (2–3) (2000) 219–231, https://doi.org/10.1016/s1388-1981(00)00077-9.
[65] A. Ameur, S. Enroth, A. Johansson, G. Zaboli, W. Igl, A.C.V. Johansson, et al., Genetic adaptation of fatty-acid metabolism: a human-specific haplotype increasing the biosynthesis of long-chain omega-3 and omega-6 fatty acids, Am. J. Hum. Genet. 90 (5) (2012) 809–820, https://doi.org/10.1016/j.ajhg.2012.03.014.
[66] S. Sergeant, C.E. Hugenschmidt, M.E. Rudock, J.T. Ziegler, P. Ivester, H.C. Ainsworth, et al., Differences in arachidonic acid levels and fatty acid desaturase (FADS) gene variants in African Americans and European Americans with diabetes or the metabolic syndrome, Br. J. Nutr. 107 (4) (2012) 547–555, https://doi.org/10.1017/S0007114511003230.
[67] R.A. Mathias, S. Sergeant, I. Ruczinski, D.G. Torgerson, C.E. Hugenschmidt, M. Kubala, et al., The impact of FADS genetic variants on ω6 polyunsaturated fatty acid metabolism in African Americans, BMC Genet 12 (2011) 50, https://doi.org/10.1186/1471-2156-12-50.
[68] C.D. Buckley, D.W. Gilroy, C.N. Serhan, Proresolving lipid mediators and mechanisms in the resolution of acute inflammation, Immunity 40 (3) (2014) 315–327, https://doi.org/10.1016/j.immuni.2014.02.009.
[69] S. Sergeant, E. Rahbar, F.H. Chilton, Gamma-linolenic acid, dihommo-gamma linolenic, eicosanoids and inflammatory processes, Eur. J. Pharmacol. 785 (2016) 77–86, https://doi.org/10.1016/j.ejphar.2016.04.020.
[70] S. Yedgar, M. Krimsky, Y. Cohen, R.J. Flower, Treatment of inflammatory diseases by selective eicosanoid inhibition: a double-edged sword? Trends Pharmacol. Sci. 28 (9) (2007) 459–464, https://doi.org/10.1016/j.tips.2007.07.005.
[71] J.E. Manson, S.S. Bassuk, N.R. Cook, I.M. Lee, S. Mora, C.M. Albert, et al., Vitamin D, marine n-3 fatty acids, and primary prevention of cardiovascular disease current evidence, Circ. Res. 126 (1) (2020) 112–128, https://doi.org/10.1161/CIRCRESAHA.119.314541.
[72] L.A. David, A.C. Materna, J. Friedman, M.I. Campos-Baptista, M.C. Blackburn, A. Perrotta, et al., Host lifestyle affects human microbiota on daily timescales, Genome Biol 15 (7) (2014) R89, https://doi.org/10.1186/gb-2014-15-7-r89.
[73] A.W. Walker, J. Ince, S.H. Duncan, L.M. Webster, G. Holtrop, X. Ze, et al., Dominant and diet-responsive groups of bacteria within the human colonic microbiota, ISME J 5 (2) (2011) 220–230, https://doi.org/10.1038/ismej.2010.118.
[74] J.L. Sonnenburg, F. Bäckhed, Diet-microbiota interactions as moderators of human metabolism, Nature 535 (7610) (2016) 56–64, https://doi.org/10.1038/nature18846.
[75] E.R. Leeming, A.J. Johnson, T.D. Spector, C.I. Le Roy, Effect of diet on the gut microbiota: rethinking intervention duration, Nutrients 11 (12) (2019) 2862, https://doi.org/10.3390/nu11122862.
[76] L.A. David, C.F. Maurice, R.N. Carmody, D.B. Gootenberg, J.E. Button, B.E. Wolfe, et al., Diet rapidly and reproducibly alters the human gut microbiome, Nature 505 (7484) (2014) 559–563, https://doi.org/10.1038/nature12820.
[77] L. Chen, D. Wang, S. Garmaeva, A. Kurilshikov, A. Vich Vila, R. Gacesa, et al., The long-term genetic stability and individual specificity of the human gut microbiome, Cell 184 (9) (2021) 2302–2315.e12, https://doi.org/10.1016/j.cell.2021.03.024.
[78] J.J. Faith, N.P. McNulty, F.E. Rey, J.I. Gordon, Predicting a human gut microbiota's response to diet in gnotobiotic mice, Science 333 (6038) (2011) 101–104, https://doi.org/10.1126/science.1206025.
[79] C. Milani, C. Ferrario, F. Turroni, S. Duranti, M. Mangifesta, D. van Sinderen, et al., The human gut microbiota and its interactive connections to diet, J. Hum. Nutr. Diet 29 (5) (2016) 539–546, https://doi.org/10.1111/jhn.12371.
[80] E. Rinninella, E. Tohumcu, P. Raoul, M. Fiorani, M. Cintoni, M.C. Mele, et al., The role of diet in shaping human gut microbiota, Best Pract. Res. Clin. Gastroenterol 62–63 (2023), 101828, https://doi.org/10.1016/j.bpg.2023.101828.
[81] H. Trowell, D. Burkitt, Physiological role of dietary fiber: a ten-year review, ASDC J. Dent. Child 53 (6) (1986) 444–447.

[82] X. Liu, W. Yang, J.L. Petrick, L.M. Liao, W. Wang, N. He, et al., Higher intake of whole grains and dietary fiber are associated with lower risk of liver cancer and chronic liver disease mortality, Nat. Commun. 12 (1) (2021) 6388, https://doi.org/10.1038/s41467-021-26448-9.
[83] M.K. Szmidt, J. Kaluza, H.R. Harris, A. Linden, A. Wolk, Long-term dietary fiber intake and risk of chronic obstructive pulmonary disease: a prospective cohort study of women, Eur. J. Nutr. 59 (5) (2020) 1869–1879, https://doi.org/10.1007/s00394-019-02038-w.
[84] L. Lu, Y.F. Huang, M.Q. Wang, D.X. Chen, H. Wan, L.B. Wei, et al., Dietary fiber intake is associated with chronic kidney disease (CKD) progression and cardiovascular risk, but not protein nutritional status, in adults with CKD, Asia Pac, J. Clin. Nutr. 26 (4) (2017) 598–605, https://doi.org/10.6133/apjcn.072016.08.
[85] S.K. Gill, M. Rossi, B. Bajka, K. Whelan, Dietary fibre in gastrointestinal health and disease, Nat. Rev. Gastroenterol. Hepatol. 18 (2) (2021) 101–116, https://doi.org/10.1038/s41575-020-00375-4.
[86] C.R. McGill, V.L. Fulgoni 3rd, L. Devareddy, Ten-year trends in fiber and whole grain intakes and food sources for the United States population: National Health and Nutrition Examination Survey 2001-2010, Nutrients 7 (2) (2015) 1119–1130, https://doi.org/10.3390/nu7021119.
[87] K. Harris, F. Overcash, D. Belobrajdic, J. Slavin, Perspective: utilizing high amylose wheat flour to increase dietary fiber intake of children and adolescents: a health by stealth approach, Front. Public Health 10 (2022), 817967, https://doi.org/10.3389/fpubh.2022.817967.
[88] P.S. Baenziger, K. Frels, S. Greenspan, J. Jones, A. Lovegrove, D. Rose, et al., A stealth health approach to dietary fibre, Nat. Food 4 (1) (2023) 5–6, https://doi.org/10.1038/s43016-022-00674-w.
[89] Y.E. Tuncil, R.D. Thakkar, S. Arioglu-Tuncil, B.R. Hamaker, S.R. Lindemann, Fecal microbiota responses to bran particles are specific to cereal type and in vitro digestion methods that mimic upper gastrointestinal tract passage, J. Agric. Food Chem. 66 (47) (2018) 12580–12593, https://doi.org/10.1021/acs.jafc.8b03469.
[90] Y.E. Tuncil, R.D. Thakkar, S. Arioglu-Tuncil, B.R. Hamaker, S.R. Lindemann, Subtle variations in dietary-fiber fine structure differentially influence the composition and metabolic function of gut microbiota, mSphere 5 (3) (2020), e00180, https://doi.org/10.1128/mSphere.00180-20, 20.
[91] Y.E. Tuncil, R.D. Thakkar, A.D.R. Marcia, B.R. Hamaker, S.R. Lindemann, Divergent short-chain fatty acid production and succession of colonic microbiota arise in fermentation of variously-sized wheat bran fractions, Sci. Rep. 8 (1) (2018), 16655, https://doi.org/10.1038/s41598-018-34912-8.
[92] S.R. Lindemann, A piece of the pie: engineering microbiomes by exploiting division of labor in complex polysaccharide consumption, Curr. Opin. Chem. Eng. 30 (2020) 96–102, https://doi.org/10.1016/j.coche.2020.08.004.
[93] A.D. Romero Marcia, T. Yao, M.H. Chen, R.E. Oles, S.R. Lindemann, Fine carbohydrate structure of dietary resistant glucans governs the structure and function of human gut microbiota, Nutrients 13 (9) (2021) 2924, https://doi.org/10.3390/nu13092924.
[94] T. Yao, M.H. Chen, S.R. Lindemann, Structurally complex carbohydrates maintain diversity in gut-derived microbial consortia under high dilution pressure, FEMS Microbiol. Ecol. 96 (9) (2020), fiaa158, https://doi.org/10.1093/femsec/fiaa158.
[95] R.D. Thakkar, Y.E. Tuncil, B.R. Hamaker, S.R. Lindemann, Maize bran particle size governs the community composition and metabolic output of human gut microbiota in in vitro fermentations, Front. Microbiol. 11 (2020) 1009, https://doi.org/10.3389/fmicb.2020.01009.
[96] K. De Paepe, J. Verspreet, M.N. Rezaei, S.H. Martinez, F. Meysman, D. Van de Walle, et al., Modification of wheat bran particle size and tissue composition affects colonisation and metabolism by human faecal microbiota, Food Funct 10 (1) (2019) 379–396, https://doi.org/10.1039/c8fo01272e.
[97] H. Yao, B.A. Williams, D. Mikkelsen, B.M. Flanagan, M.J. Gidley, Composition and functional profiles of human faecal microbiota fermenting plant-based food particles are related to water-holding capacity more than particle size, Food Hydrocoll 141 (2023), 108714, https://doi.org/10.1016/j.foodhyd.2023.108714.
[98] T.M. Cantu-Jungles, B.R. Hamaker, New view on dietary fiber selection for predictable shifts in gut microbiota, MBio 11 (1) (2020), e02179, https://doi.org/10.1128/mBio.02179-19, 19.
[99] T.M. Cantu-Jungles, A.C. Ruthes, M. El-Hindawy, R.B. Moreno, X. Zhang, L.M.C. Cordeiro, et al., In vitro fermentation of Cookeina speciosa glucans stimulates the growth of the butyrogenic Clostridium cluster XIVa in a targeted way, Carbohydr, Polym 183 (2018) 219–229, https://doi.org/10.1016/j.carbpol.2017.12.020.
[100] T. Yao, D.G. Deemer, M.H. Chen, B.L. Reuhs, B.R. Hamaker, S.R. Lindemann, Subtle differences in fine polysaccharide structures govern selection and succession of human gut microbiota, BioRxiv, 2022, https://doi.org/10.1101/2022.10.04.510853 [Preprint].