PERSPECTIVE

Perspective: on Precision Nutrition Research in Heart, Lung, and Blood Diseases and Sleep Disorders

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ABSTRACT

The release of the 2020–2030 Strategic Plan for NIH Nutrition Research (SPNR) and its emphasis on precision nutrition has provided an opportunity to identify future nutrition research that addresses individual variability in response to diet and nutrition across the life span—including those relevant to the Strategic Vision of the National Heart, Lung, and Blood Institute (NHLBI). The SPNR and the NHLBI's Strategic Vision were developed with extensive input from the extramural research community, and both have 4 overarching strategic goals within which are embedded several objectives for research. For the SPNR, these include *1*) spur discovery science and normal biological functions (e.g., role of the microbiome in health and disease), *2*) population science to understand individual differences (e.g., biomarkers including 'omics that predict disease status), *3*) emerging scientific areas of investigation and their application (e.g., data science, artificial intelligence), and *4*) cross-cutting themes (e.g., training the scientific workforce and minority health and health disparities). These strategic goals and objectives serve as blueprints for research and training. Nutrition remains important in the prevention and treatment of heart, lung, blood, and sleep (HLBS) disorders and diseases, and the NHLBI has played a pivotal role in supporting nutrition research. In this paper, we report important gaps in the scientific literature related to precision nutrition in HLBS diseases. Research opportunities that could stimulate precision nutrition and their alignment with the SPNR and the NHLBI Strategic Vision Objectives are provided. These opportunities include *1*) exploring individual differences in response to varying dietary patterns and nutrients; *2*) investigating genetic/epigenetic, biological (e.g., microbiome, biomarkers), social, psychosocial, and environmental underpinnings of individual variability in diet; *3*) elucidating the role of circadian rhythm and chrononutrition; and *4*) applying implementation science research methods in precision nutrition interventions relevant to HLBS diseases. *Adv Nutr* 2022;13:1402–1414.

Statement of Significance: This paper highlights the need to stimulate research in precision nutrition as it relates to heart, lung, blood, and sleep (HLBS) diseases and conditions. It provides a synthesis of selected HLBS research examples that address individual variability and align with the 2020–2030 Strategic Plan for NIH Nutrition Research.

Keywords: National Heart, Lung, and Blood Institute (NHLBI), precision nutrition, cardiovascular nutrition, nutrition in lung diseases, nutrition in blood diseases, chrononutrition

Introduction

In 2020, the NIH unveiled the 2020–2030 Strategic Plan for NIH Nutrition Research (SPNR) that emphasizes cross-cutting and innovative opportunities to advance nutrition research across all NIH Institutes under the theme of precision nutrition (1). Precision nutrition embodies a complex array of factors, including genetics and epigenetics, dietary habits and eating patterns, circadian rhythms, health status, socioeconomic and psychosocial characteristics, food environments, physical activity, and the microbiome (1, 2). The SPNR identified 4 strategic goals that relate to precision nutrition, including *1*) discovery science and innovative foundational research, *2*) dietary patterns and behaviors for optimal health, *3*) nutrition across the life span, and *4*) reducing the burden of diseases in clinical settings. In addition, fundamental cross-cutting themes include research to address minority health and health disparities, the health of women, data science, artificial intelligence, and training

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of the scientific workforce. To leverage the SPNR, the National Heart, Lung, and Blood Institute (NHLBI) Nutrition Research Working Group initiated a process that included a portfolio analysis of NHLBI nutrition research, investment in extramural research, and mapping of the NHLBI Strategic Vision Objectives with awarded grants (2). Briefly, the findings, published in the *Journal of Nutrition*, revealed that from 2008–2019, approximately $2.13 billion were administered to 1,611 nutrition-related research projects, and 32% of newly funded grants focused on pathobiological mechanisms including novel diagnostic and therapeutic strategies and clinical and implementation science research. The findings also revealed significant alignment of the SPNR with the NHLBI Strategic Vision Objectives (3).

Although decades of nutrition research have led to new discoveries and emphasis on the importance of nutrition in preventing and treating chronic diseases—including cardiovascular, blood, and lung diseases and sleep disorders—the most recent data indicate diet-related risk factors contributed globally to 11 million deaths and 255 million disability-adjusted life-years (4, 5). High intake of sodium and low intake of whole grains, fruits, vegetables, and nutrient-dense foods have contributed significantly to noncommunicable disease morbidity and mortality, particularly cardiovascular diseases (CVDs), which remain the leading cause of death worldwide (4). Diet and nutrition are the fundamental causes of many chronic disease risk factors, such as hypertension, dyslipidemia, and inflammation (6, 7). The importance of nutrition for optimal immune response and prevention of infectious diseases and their effects on the gut microbiota is undisputed (8). Many nutrients, including vitamins C, E, and D and omega-3 fatty acids have anti-inflammatory and antioxidant properties that reduce oxidative stress at the cellular level and are implicated in chronic disease prevention (9). However, the extent to which precision nutrition could address the interrelations among the factors that contribute to nutrition-related diseases of the heart, lung, blood, and sleep (HLBS) is incompletely understood.

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Abbreviations used: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; *FAD*, fatty acid desaturase; HLBS, heart, lung, blood, and sleep; IDA, iron deficiency anemia; MIS-C, multisystem inflammatory syndrome in children; MTHFR, 5,10-methylenetetrahydrofolate reductase; NHLBI, National Heart, Lung, and Blood Institute; NRF-2, nuclear factor erythroid 2–related factor 2; SCD, sickle cell disease; SDOH, social determinants of health; SES, socioeconomic status; SNP, single nucleotide polymorphism; SPNR, 2020–2030 Strategic Plan for NIH Nutrition Research; tHcy, total homocysteine; TOPMed, NHLBI Trans-Omics for Precision Medicine; VDR, vitamin D receptor; VTE, venous thromboembolism.

Personalized nutrition advice based on gene–diet or gene–nutrient interactions has successfully been used to treat inborn errors of metabolism (e.g., phenylketonuria) in clinical settings for decades (10, 11). Recent discoveries suggest that personalized diets may be broadly applicable to the general population as gains in knowledge of, for example, biomarkers (e.g., 'omics) coupled with artificial intelligence tools are used to address lifestyle-related subclinical outcomes and clinical disease states. Differential responses to diet among populations suggest that specificity may be needed in future recommendations of the Dietary Guidelines for Americans to ensure optimal health outcomes. To that end, further research may develop approaches in certain populations where genetic and nutritional intake data could be interrogated for risk stratifications to refine nutrition recommendations, and potentially reduce health disparities and inequities.

In addition, an integrated approach to advancing our understanding of the role of nutrition in HLBS diseases and conditions could harness nutrition information across existing platforms to build the trajectory of evidence from basic to translational and implementation research. Knowledge derived from ancestry-based gene–diet interactions could be used to develop algorithms that could be integrated into clinical decision making for HLBS diet-related diseases. These algorithms would need to be tested in randomized controlled trials in order to become evidence based. This may equip clinicians with evidence-based recommendations for clinical applications and possibly lead to knowledge transfer to benefit the health of the public. The NHLBI Trans-Omics for Precision Medicine (TOPMed) database, which allows for an integration of whole-genomewide sequencing and other 'omics (e.g., epigenomics, metabolomics) data with molecular, imaging, behavioral, environmental, and clinical data from diverse populations, could be leveraged to better understand and inform individual- and population-level precision nutrition guidance (12). For efficiency, association studies could be conducted with TOPMed data on cloud-based platforms such as the NHLBI BioData Catalyst (13), which allows access to many studies with study participants from diverse ancestries. This flexible platform allows analytical activities to be collaborative, scalable, and reproducible and genomic and phenotypic data as well as dietary data to be pulled across multiple studies and analyzed using a variety of interactive tools. Finally, efficiency may require that these investigational pursuits are multidisciplinary in nature and involve training of diverse scientists from all career stages across the scientific spectrum and can leverage currently existing resources, such as cloud and cyber infrastructures for nutrition research.

This paper presents perspectives for nutrition research as they relate to HLBS diseases and conditions. It provides selected examples of individual variability of the risk factors to HLBS disease and circadian biology (e.g., chrononutrition), and highlights potential opportunities for future research in precision nutrition as related to HLBS. The objective is to provide information to research scientists and clinicians in

order to stimulate nutrition research discoveries, particularly as they relate to precision nutrition and HLBS diseases and conditions. Below, we reviewed the literature and identified selected HLBS research examples that address individual variability in nutrition.

Nutrition and Selected Examples of Research for Cardiovascular Health

Many studies have noted variability in the metabolism of various macronutrients and micronutrients relevant to cardiovascular health. For example, wide divergence exists in the fatty acid desaturase *(FAD)* gene locus in African-, European-, and American-Indian–ancestry populations, altering the efficiency of metabolism of n−6 and n−3 dietary 18C-PUFAs (14–16). For example, research suggests greater efficiency by Blacks compared with Whites (17). Contrastingly, studies by Harris et al., documented that Native Americans and certain European and Asian groups carry *FAD* gene profiles that support less-efficient conversion of 18C PUFAs into n–3 fatty acids, potentially conferring decreased ability to generate physiologically sufficient amounts of n–3 fatty acids (14, 15). Based on these findings, it can be postulated that, depending on the observed *FAD* gene cluster variation, exposure to higher intakes of n–6 fatty acids and arachidonic acids for certain subgroup of individuals may result in excessive generation of n–6 and n–6 proinflammatory metabolites (14). Therefore, individual-level variability in the metabolism of the dietary PUFAs may confer differences in the susceptibility of different populations to disease, suggesting the need for precision nutrition efforts.

Differences in vitamin D metabolism is yet another example in which genetic variants associated with blood concentrations of 25-hydroxyvitamin D have been found in many different genes, including,for example, cytochrome p450 family 27 subfamily B member 1 *(CYP27B1)*, and the vitamin D receptor (VDR) genes (18). The best studied examples are in the gc-globulin (*GC*) gene, which codes for the main carrier of vitamin D metabolites, the vitamin D-binding protein (19). These variations may have key implications for cardiovascular health because the active metabolite of vitamin D also binds to the VDR that regulates numerous genes involved in fundamental processes relevant to CVD (20). These include cell proliferation and differentiation, apoptosis, oxidative stress, membrane transport, matrix homeostasis, and cell adhesion. VDRs have been found in all the major cardiovascular cell types, including cardiomyocytes, arterial wall cells, and immune cells (20). Epidemiological evidence suggests that individuals with low blood concentrations of vitamin D have increased risks of heart disease, heart failure, stroke, hypertension, and diabetes, although a meta-analysis of supplementation trials with vitamin D has not shown definite benefit in reducing the risk of most CVDs in adults (21, 22). A recent systematic review for the US Preventive Services Task Force reported that, among asymptomatic, community-dwelling populations with low vitamin D concentrations, vitamin D has no effect on mortality or the incidence of fractures, falls, depression, diabetes, CVD, cancer, or adverse events (23). These differences in findings suggest a need for further investigation to examine, for example, individual differences in vitamin D metabolism with varying exposure levels.

Genetic polymorphisms have also been shown for proteins relevant in folate metabolism. Folate deficiency elevates plasma total homocysteine (tHcy), which is modestly associated with cardiovascular and cerebrovascular diseases (24). For example, serum folate and tHcy concentrations are influenced by not only folate intake but also genetic polymorphisms in 5,10-methylenetetrahydrofolate reductase (MTHFR) (24). This mutation results in the inability of the MTHFR enzyme to catalyze the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, leading to the increase in plasma tHcy concentrations in homozygous mutated subjects. Approximately 15% of the Japanese population may have this genotype (24). Future research may explore the interindividual variability in nutrient metabolism that influences CVD risks and ultimately contributes to precision nutrition approaches to prevent CVD and promote cardiovascular health.

Another important frontier for future studies includes the interindividual variability of the microbiome responses to diet. There is moderate to strong evidence that more plant sources of protein compared with the typical American diet, which is high in animal sources of protein, reduce CVD risk (25, 26). Plant-based proteins (e.g., nuts, legumes, beans) are associated with decreases in Bacteroides and increases in Bifidobacteria and Lactobacillus communities in both human and animal studies (27). Such diets are also high in fiber, and high fiber intake increases gut microbiota populations that generate SCFAs. Research is mixed on the role of SCFAs: some studies suggest beneficial effects in the gut (28), while others link SCFAs and dysbiosis to diseases such as chronic kidney disease, atherosclerosis, and hypertension (29). Carbohydrates, such as nondigestible sources (e.g., fiber, whole grains, and certain starches), are fermented in the gut and may release fatty acids and prebiotics that may increase bacterial biodiversity and phenotypic changes in the bacteria flora, leading to promotion of health-enhancing effects (30, 31). Conversely, in some, but not all, studies, animal proteins such as those in red meats and fish have opposite effects and have been linked with increases in trimethylamine N-oxide (TMAO), which increases CVD risk (27). There is also evidence from animal studies demonstrating that atherosclerotic plaques have microbiota communities from the gut or oral cavities (27), suggesting a link between CVD and bacterial pathogens. The mechanism by which microbial flora play a role in increasing CVD risk may include increases in adipose tissue inflammation, oxidative stress, and glucose intolerance (32). Overall, future nutrition research could include the elucidation of individual variability in microbiota and the role of nutrition in the microbiota and CVD pathophysiology in humans (33).

In addition to the genetic and biological underpinnings of variability in response to diet, there is also the need to explore

the social, psychosocial, and environmental influences of dietary choice and behavior. For example, certain communities have different availability and affordability of foods that are recommended to maintain cardiovascular health and prevent CVDs. This becomes increasingly relevant for minority populations that experience health disparities in heart disease and other CVD risk factors.

Nutrition and Selected Lung Diseases

The impact of nutrition deficiencies, supplementation, and dietary patterns on lung development (34) and lung diseases across the life span has been explored over the past 50 y. Macro- and micronutrients are important in lung development and may slow the progression of pulmonary disease. Precision nutrition interventions hold the promise of mitigating morbidity and improving pulmonary outcomes and health-related quality of life. We present some scientific advances on the role of nutrition in lung health and disease including infant lung development, asthma, chronic obstructive pulmonary disease (COPD), and acute respiratory distress syndrome (ARDS).

Appropriate maternal nutrition during pregnancy is critical for infant lung development and pulmonary outcomes. Low-birth-weight infants often have poor maximal lung function, which correlates with an increased risk of developing COPD in late adulthood (35–37). Adult-onset diseases such as pulmonary fibrosis and COPD could have their origins in early life (38). Targeted nutritional strategies, such as vitamin C in pregnant women who smoke (39), have been shown to improve airway function in infants at 3 mo of age. Vitamin D in premature African-American infants (12) decreased parent-reported wheeze at 1 y of age, suggesting that precision nutrition interventions could mitigate chronic lung diseases of prematurity (40). More research is needed to validate these observations.

Individual metabolic responses to specific dietary patterns and nutrients are unique and are influenced by genetics, race, gender, gut microbiome, health history, lifestyle habits, sleep, physical activity, and timing of meals, among others. Thus, the impact of maternal nutrition on infant lung development and pulmonary outcomes in later life must be studied in these contexts with a focus on precision nutrition. The field is largely unexplored. Some examples of research questions related to precision nutrition in lung disease include *1*) how individual factors, such as genetics and metabolomics, maternal smoking, and alcohol and fatty food consumption, affect the development of the lung, ventilatory control, and future pulmonary outcomes in the offspring, and *2*) how to standardize and dynamically measure and monitor nutrient intakes of pregnant and lactating mothers.

The NHANES has revealed an independent association of dietary fiber intake with self-reported asthma, respiratory symptoms, and inflammation. Those reporting high fiber intake have a lower prevalence of asthma and respiratory symptoms, especially in women and non-Hispanic White adults (41). Possible mechanisms include SCFAs and anti-inflammatory factors derived from the high-fiber diet. In addition, beneficial effects of the Dietary Approaches to Stop Hypertension (DASH) diet on asthma control were reported in a pilot randomized trial of 90 predominantly middle-aged women (42). A meta-analysis examining the impact of fish intake on childhood asthma suggests that the introduction of any type of fish early in life (6–9 mo) and regular consumption of fish (at least once a week) reduces asthma and wheezing in children up to 4.5 y of age (43). A randomized controlled trial revealed that a Mediterranean diet supplemented with 2 fatty fish meals per week ameliorated airway inflammation in childhood asthma (44). More research on individual variability in response to dietary anti-inflammatory factors (e.g., n–3 fatty acids) and other nutrients such as vitamin D is needed to better understand the role of diet in the development and treatment of lung diseases, including asthma, COPD, and ARDS.

Optimal nutrition is important for prevention and management of COPD. Western diets high in calories and processed foods were associated with a higher occurrence of severe respiratory symptoms in COPD compared with prudent diets composed of whole grains, fish, fruits and vegetables in the Atherosclerosis Risk in Communities (ARIC)) study (45, 46). The association of COPD with vitamin D deficiency was reported in NHANES (47). Low concentrations of 25-hydroxyvitamin D has also been suggested as a potential marker for COPD exacerbations and adverse outcomes (48). Furthermore, vitamin D supplementation in smokers with COPD was shown to be beneficial in decreasing progression of disease, suggesting a critical role of micronutrients in mitigating COPD (49, 50).

Nutritional aspects of ARDS and acute pulmonary disease continue to be areas of controversy where much remains to be elucidated. Any acute illness is associated with a catabolic state wherein the breakdown of fats, proteins, and complex molecules occurs faster than the synthesis of these same macromolecules. Nutritional support in this context could be both preventive in decreasing severity of disease and curative by its potential effects on the pathological trajectory of disease.

In critical lung disease, such as pneumonia, acute lung injury, or ARDS, the benefits of feeding the gut early, and not increasing food intake too quickly, are shown in several studies in adults and children (51, 40). The ongoing CALORIES trial, a phase III, open, multicenter, randomized controlled trial comparing the clinical and cost-effectiveness of early nutritional support in critically ill patients via parenteral versus enteral routes, has not yet convincingly shown that meeting targeted daily calorie goals necessarily improves outcomes in sepsis and ARDS, although enteral feeds have been shown to be of greater benefit than parenteral feeding (52). A retrospective analysis of calorie intake as a function of resting energy expenditure in critically ill patients suggested that feeding to achieve approximately 70% of calorie goals conferred a survival advantage, and that neither overfeeding nor underfeeding were beneficial to survival (53). A recent prospective trial of intensive versus

standard nutritional goals in 78 patients was terminated early as intensive nutrition (>75% of calorie goals) resulted in a trend towards higher mortality compared with standard nutrition strategies (75% of calorie goals) (54). An area of inquiry that is gathering momentum is the careful attention to carbohydrate load and its importance as a source of energy in the setting of likely impaired mitochondrial bioenergetics in acute lung injury. This could give rise to complex issues of increased carbon dioxide production, necessitating greater respiratory effort to eliminate the extra carbon dioxide. These and other metabolic considerations are likely to gain more importance in the future and necessitate a personalized approach to nutrition interventions. For example, one of the comorbidities during the current coronavirus disease 2019 (COVID-19) pandemic is obesity (55, 56). Obesity also plays a key role in the development of obstructive sleep apnea and obesity hypoventilation syndrome. Asthma is more common and often harder to treat in populations with obesity (57). The nutritional imperative to control obesity in the population may decrease morbidity from this pandemic in the short term and may improve societal pulmonary health for the future. The mechanistic links between obesity and respiratory diseases, as well as worse outcome as a result of COVID-19, need to be elucidated (58). The multisystem inflammatory syndrome in children (MIS-C) attributed to COVID-19 continues to perplex clinicians and investigators. Similar to COVID-19 in adults, obesity is a risk factor for increased severity of presentation and morbidity for children with MIS-C (59).

In summary, research on diet and nutrition in lung diseases is at a nascent stage. There are many research gaps that could be addressed by epidemiological studies, animal models, and novel 3-dimensional (3D) culture models to elucidate the influence of diet and nutrition on the impact of immunometabolism on the airway and lung microbiome in the pathobiology of lung disease. Well-designed randomized controlled clinical trials of dietary intervention to assess the efficacy of specific personalized nutritional approaches to the management of lung diseases are limited. Such trials may help identify novel nutrition strategies to treat and/or mitigate debilitating pulmonary diseases. Studies examining individual variability in response to various dietary interventions in lung diseases and conditions may further knowledge of nutrition in lung diseases and establish the foundation for precision nutrition interventions.

Nutrition and Selected Blood Diseases

Precision nutrition may have a significant role in blood conditions, such as in hemoglobinopathies [sickle cell disease (SCD), thalassemia], iron deficiency anemia (IDA), and venous thromboembolism (VTE), through a host of factors. This section will address multiple factors relevant to precision nutrition in blood diseases and conditions, including single nucleotide polymorphisms (SNPs), nutrition-related genes (i.e., VDR), epigenetic modifications, the interaction of diet and nutrients with gut microbiota (metagenomics), as well as environmental factors such as social determinants of health and culture. The selected blood conditions included in this review are not exhaustive of all blood conditions or diseases that are related to precision nutrition. However, they are illustrative of the role of nutrition in blood conditions and interconnections of preclinical, clinical, translation, and implementation stages of research.

The role of diet and nutrition in patients with SCD is limited (60) but available data provide a basis for understanding the importance of specific nutrients in the pathophysiology of SCD. A phase 1 study of broccoli sprouts concentrate to patients with SCD over 21 d showed a decreased level of dysregulation in the pathogenesis of SCD (61). Although no changes in hemoglobin F (*HgbF*) gene expression occurred during the study, there was an increase in mRNA levels of proteins, which are targets of nuclear factor erythroid 2–related factor 2 (NRF-2), the regulator of cellular resistance to oxidants. The study suggests that NRF-2 activation through sulforaphane-rich foods, such as broccoli sprouts, could regulate a pathophysiological pathway in SCD.

Vitamin D deficiency in pediatric and adult patients with SCD is associated with an increase in disease severity, specifically pain crises (62). Investigations on the role of VDR polymorphisms among this population are limited but provide intriguing results that suggest the SNPs may be involved in vaso-occlusive severity and specific VDR genotypes may be involved in reduced bone mineral density (63). Similar studies suggesting a role for VDR in reduced bone mineral density for individuals with thalassemia have been reported (64, 65).

The prevention and management of IDA are dependent on the regulation of iron metabolism and bioavailability of iron. The identification of genetic polymorphisms involved in iron bioavailability is an important aspect of precision nutrition and could play a significant role in targeting populations at risk for IDA for interventions. To date, genes that affect iron bioavailability include *TMPRSS6* mutations that increase systemic hepcidin concentrations in humans (66), mutations in the transferrin (*TF*) gene, the calcium channel gene (*CACNA2D3*), and the histone micro cluster gene (*HIST1H2BJ*) have been associated with low iron status in iron-deficient young women (67, 68).

An individual's microbiota may also have a role in IDA. A recent mouse study demonstrated that microbial colonization of the gut can impact the intestinal proteins that are involved in iron transport (69). Clinical studies supporting this finding suggest the consideration of the microbiome when planning for iron fortification. For example, Hoppe et al. (70) found that, after the addition of probiotics to an iron-fortified drink, iron absorption increased significantly in healthy menstruating women.

Choline supplementation may also be an important adjunct therapeutic nutrient when severe fetal IDA is present, as studies show the ability of choline supplementation to ameliorate neurological symptoms in the setting of iron deficiency (71, 72). Given this connection, interest for future studies may be the role of choline-deficient genes in the management of IDA.

Dietary intake influences thrombotic and fibrinolytic factors related to VTE, including factor VIIc, factor VIIIc, von Willebrand factor, and plasminogen activator inhibitor-1 (PAI-1), an inhibitor of fibrinolysis (73, 74). n–3 Fatty acid intake may be a protective nutrient for lowering the risk of initial and recurrent VTE (74–76), although fish intake alone may not explain this protection from VTE (77, 78). Studies evaluating the role of nutritional factors and dietary patterns on known genetic and epigenetic conditions associated with VTE risk are limited. To our knowledge, studies that specifically evaluated nutrition and VTE risk in the context of specific VTE-provoking factors, such as surgery, immobilization, and pregnancy, also need investigation.

Social determinants of health (SDOH) and lifestyle factors, including dietary intake, can influence blood conditions through their role in influencing genetic and epigenetic control mechanisms. Studies evaluating SDOH factors and neighborhood and socioeconomic status (SES) factors among individuals with blood conditions are scant but do show interesting results worthy of further exploration. For example, Isma et al. (79) found an association between lower income and education, single marital status, and an increased risk of VTE during a 13-y follow up of adults living in Sweden. Kort et al. (80) found that higher neighborhood SES was associated with a lower incidence of VTE over 4 y among individuals aged 15 y or older living in urban districts in the Netherlands. Food insecurity may also play a role in both IDA and SCD. Child-level food insecurity is an identified risk factor for IDA among children in the United States (81). and globally (82). Among individuals with SCD, studies show that food insecurity is associated with increased disease severity and reduction in quality of life (83–85).

In summary, preclinical and clinical research supports the intake of specific nutrients and dietary patterns in preventing and managing certain blood conditions. However, blood conditions can have significant underlying genetic factors. A significant gap in this area, particularly for VTE, is exploring differences in individual nutrition status and the role of nutrients in the setting of specific gene polymorphisms that confer an increased risk. Due to significant evidence on the role of SDOH, including neighborhood, SES, and food insecurity, on outcomes in blood conditions, future studies may include SDOH as contributing factors in both exposures and outcomes.

Nutrition, Sleep, and Circadian Biology

Feeding behavior and nutrient metabolism are regulated daily by a complex network of organ-specific circadian, or daily rhythms (86, 87). Circadian "clocks," the molecular circuitry that orchestrates biological function on a 24-h rhythm, are present in the brain and almost all the peripheral tissues and organs, creating a network of synchronized biological processes. These clocks act as nutrient sensors that drive the cell-signaling pathways underlying metabolic mechanisms that motivate feeding behaviors during specific times of the day. Cycles of feeding–fasting, including hormone regulation, appetite, and food seeking, are coordinated with other circadian-regulated behavioral cycles such as sleep and activity. Epidemiological and experimental studies show that dietary patterns and food choice, particularly those that are high in fat and carbohydrate intake, may lead to sleep and circadian clock disruption (88, 89). Conversely, staying up late due to work or social schedules can delay and shorten sleep duration, which has been shown to increase daily energy expenditure and presumably drives food intake to restore the energy imbalance, often towards calorie-dense choices later in the evening (91, 92). As a result, a new concept is emerging from the intersection of circadian biology and nutrition: When you eat is equally as important as what you eat, and there are individual differences related to the effects of timing of food intake and health outcomes.

Circadian clocks regulate metabolic and energetic processes at biologically appropriate times of the day. For example, glucose homeostasis and insulin release are governed by peripheral clocks in the liver and pancreas (93). During the night cycle, circadian clock transcription activity initiates a decrease in glucose production in the liver and an increase in glucose uptake through insulin secretion, lowering blood glucose concentrations during the rest phase. Similar to animal studies, human epidemiological and clinical studies have shown that variations in genes are central to the molecular regulation of circadian rhythms.

Environmental and behavioral cues have a robust influence on systemic misalignment, or the disruption of normal biological circadian function, which is associated with several chronic diseases (86, 87). The timing and nutrient composition of food itself serve as robust cues that reinforce the alignment of clocks associated with energy and metabolism and the larger circadian network. Macronutrients (e.g., fats and carbohydrates) can modulate circadian clock activity, suggesting that interventions that address healthful dietary patterns and changes in food choice may be effective in attenuating adverse health outcomes associated with circadian disruption (94). In cross-sectional studies, evening chronotypes (people who eat late at night) were associated with increased intake of calorie-dense foods and alcohol, and lower intake of fruits and vegetables (95). Global surveys show that wide regional variations in mealtime, energy intake, and nutrient composition reflect a critical role of sociocultural factors in determining dietary patterns and behaviors (96). An analysis of NHANES data found that mealtimes occurring later in the day have increased over the past 5 decades, presumably due to work schedules and other social factors (97, 98). Evidence from a number of clinical studies show that delaying the timing of food intake by a few hours in the evening has adverse effects on the circadian regulation of glucose homeostasis and energy metabolism, and may contribute to obesity and obesity-related disease (99–101).

One proposed mechanism by which short sleep duration influences food choice was presented in a recent study in sleep-deprived participants showing greater functional MRI

TABLE 1. Alignment between the NHLBI Strategic Vision Objectives and the Strategic Plan for NIH Nutrition Research.[1]

NHLBI Strategic Vision Objectives	Components of the SPNR
Objective 1: Normal biologic functions and resilience[2]	SG 1: Spur discovery and innovation through foundational research[2]
Objective 2: Pathobiology, onset, and progressions of HLBS disease[2]	SG 2: Investigate the role of dietary patterns and behavior for optimal health[2]
Objective 3: Differences in health among populations[3]	SG 3: Define the role of nutrition across the lifespan for healthy development and aging[3]
Objective 4: Individual differences in response to treatments[4]	SG 4: Reduce the burden of disease in clinical settings
Objective 5: Novel diagnostic and therapeutic strategies to prevent, treat, and cure HLBS diseases[3]	CC Theme 1: Minority health and health disparities[4]
Objective 6: Optimization of clinical and implementation science research[3]	CC Theme 2: Health of women[4]
Objective 7: Emerging opportunities in data sciences[5]	CC Theme 3: Rigor and reproducibility[5]
Objective 8: Further develop, diversify and sustain a scientific workforce[6]	CC Theme 4: Data science, systems science, and artificial intelligence[5]
	CC Theme 5: Training the scientific workforce[6]

[1]CC, cross-cutting; HLBS, heart, lung, blood, and sleep; NHLBI, National Heart, Lung, and Blood Institute; SG, strategic goal; SPNR, Strategic Plan for NIH Nutrition Research; SVO, Strategic Vision Objectives.
[2]Objectives 1 and 2 of NHLBI SVO align with SPNR SG 1 and SG 2, respectively.
[3]Objectives 3, 5, and 6 of the NHLBI SVO align SPNR SG 3 and SG 4, respectively.
[4]Objective 4 of NHLBI SVO aligns with SPNR CC Themes 1 and 2.
[5]Objective 7 of NHLBI SVO aligns with SPNR CC Themes 3 and 4.
[6]Objective 8 of NHLBI SVO aligns with SPNR CC Theme 5.

response to food odor in the part of the brain that encodes odor, thus modulating olfactory circuits toward energy-dense food options (102). These studies implicate irregular mealtimes, increased food intake, and lower-quality food, specifically later in the day, as possible contributors to obesity and obesity-related disease (100, 103).

Modifying the timing of food intake and nutrient composition throughout the day could be a cost-effective intervention to promote healthful dietary and sleep patterns while lowering the risk of adverse health outcomes (104, 105). Future research on best practices and standardized methodologies and assessments across populations is necessary to fully examine how chrononutrition impacts cardiometabolic health outcomes. It is important to define the bidirectional relation between circadian rhythms and dietary patterns (e.g., identifying metabolic biomarkers for circadian rhythms and circadian misalignment), and developing comprehensive methods and tools for evaluation of nutrient status and circadian alignment. Such information could be used in ecologically valid settings to produce personalized and sustainable interventions.

Strategic Alignments of the NHLBI Strategic Vision Objectives with the SPNR and Research Opportunities

Table 1 depicts the alignment of the SPNR and the NHLBI Strategic Vision Objectives. The table was developed with input from NHLBI staff who are members of the Nutrition Research Working Group and have expertise in nutrition. As shown, the NHLBI Strategic Vision Objectives 3 (Differences in health among populations), 4 (Individual differences in response to treatments), 5 (Novel diagnostic and therapeutic strategies), and 6 (Optimize clinical and implementation science research) align with the SPNR's Strategic Goals 3 (Define the Role of Nutrition Across the Lifespan for Healthy Development and Aging) and 4 (Reduce the Burden of Disease in Clinical Settings). Similarly, Objectives 1 and 2 of the NHLBI Strategic Vision align with SPNR Goals 1 and 2, and Objectives 4, 7, and 8 align with several of the cross-cutting themes of the SPNR. These associations demonstrate the synergy between the scientific objectives and goals of both visions and suggest the potential for precision nutrition in HLBS diseases and conditions.

Table 2 presents examples of potential research opportunities that are HLBS specific and their alignment with the NHLBI Strategic Objectives and with the SPNR Strategic Goals and cross-cutting themes. The opportunities are presented across the translational spectrum (from basic to implementation sciences) and represent research gaps and opportunities that were identified from our scientific review of the literature and could be stimulated in future scientific endeavors. Given the state of the science in nutrition and HLBS and emerging topics such as chrononutrition, these future research opportunities offer avenues to advancing knowledge in precision nutrition. The application of implementation science approaches to address research translation gaps will play a key role in maximizing the health impact of nutrition in the prevention and treatment of HLBS diseases and conditions, the elimination of health inequities, and facilitation of the uptake of evidence-based practice and research into regular use by practitioners and policymakers.

Limitations

Although the overall objectives of the NHLBI Strategic Vision Objectives align with those of the SPNR, the former did not explicitly address nutrition in its development. The

TABLE 2. Examples of potential research opportunities.[1]

Basic sciences	Epidemiology	Clinical trials	Translation/implementation
Nutrition and cardiovascular health and disease			
Studies that examine diet–microbiota interrelations and their role in the development and prevention of CVD (NHLBI SVO 1 and 2; SPNR SG1 and SG3)	Computational biology to identify gene–diet–health interrelations including ancestry-based differences and nutritional phenotypes (NHLBI SVO 1; SPNR SG 1)	Clinical trials that are informed by computational biology and systems science approaches in a diverse population (e.g., using nutrition and All of Us database). (NHLBI SVO 6; SPNR SG 4 and SPNR CC Theme DS, SS, AI)	Hybrid effectiveness-implementation science research to increase adherence to various dietary patterns and nutrients in the control of hypertension and other CVD risk factors (NHLBI SVO 7; SPNR SG 2, SG 4)
Research to understand metabolic flexibility, utilization of, and shifts in fuel substrate in heart failure subtypes with a focus on comorbidities and glucose-related metabolic disorders (NHLBI SVO 2; SPNR SG4)	Social determinants of health (SDOH) data to better characterize the context of environment and social experiences of health disparity populations (NHLBI SVO 3; SPNR CC Theme MHHD)	Clinical trials to understand how nutrition, medication or device affect fuel utility or fuel shifts in heart-failure patients (NHLBI SVO 6; SPNR SG 4)	Implementation science studies to translate evidence-based research into practice and engagement of the clinical workforce (NHLBI SVO 7; SPNR SG 2, SG 4)
Studies that identify novel biomarkers of CVD and biomarkers of nutritional status (e.g., nutrigenomics and metabolomics) (NHLBI SVO 5; SPNR SG1)	Understand the relations among ultra-processed foods, food quality, and CVD risk (NHLBI SVO 5; SPNR SG 1; SPNR CC Theme: MHHD)	Trials to study the effects of diet among populations taking statins and other lipid-lowering drugs and ensure diversity of study populations in such trials (NHLBI SVO 6; SPNR SG 4; SPNR CC Theme: MHHD)	Uniform definitions of food-group–based intervention diets within the research community to stimulate cross-study comparisons (NHLBI SVO 3; SPNR SG 2)
Studies to understand the role of macro- and micronutrients and their effects on fuel energetics and nutritional status in heart-failure patients (NHLBI SVO 2; SPNR SG 1, 2, 3)	Knowledge of the associations among vascular dementia and CVD risk factors and diet quality (NHLBI SVO 2; SPNR SG 1, 2, 3)	Clinical trials comparing CVD impacts of different diets (e.g., plant protein vs. animal protein diets, vegetarian diets, ultra-processed diet, etc.) (NHLBI SVO 6; SPNR SG 2, 3)	Shared database of foods used in interventions for clinician access to ensure accuracy of information transferred to consumers/patients (NHLBI SVO 6; SPNR SG 4)
Nutrition in lung diseases			
In vitro studies and animal models to understand micro and macronutrients in Lung development. Examples include: mechanisms of the antiviral and anti-inflammatory effects of micronutrients (e.g., vitamin D and zinc) in the lung; the role of macro- and micronutrients in the development of lung diseases; identify novel biomarkers including "omics" (metabolomics, proteomics, etc.) for nutrition assessment in lung diseases (NHLBI SVO 1; SPNR SG 1, 2, 3)	Studies on the prevalence of nutrition supplements (e.g., over-the-counter) use in lung diseases (NHLBI SVO 3; SPNR SG 2, 3) Secondary data analysis (e.g., data mining of existing discovery studies) to understand the relations among nutritional status, dietary measures, and pulmonary diseases (NHLBI SVO 2; SPNR SG 2, 3)	Studies on maternal nutrition supplementation and its impact on lung development and long-term pulmonary health (NHLBI SVO 1, 2, and 6; SPNR SG 2, 3) Trials on anti-inflammatory effects of omega-3 fatty acids and effects on progression of pulmonary disease and asthma (NHLBI SVO 2 and 6; SPNR SG 1 and SG 2) Large-scale validating clinical trials on role of vitamin D and zinc in respiratory infections (NHLBI SVO 2 and 6; SPNR SG 1, 2)	Implementation science research to understand the acceptability and adherence to high, low, and normal doses of vitamin D and other nutrients (e.g., zinc) in improving respiratory outcomes of COVID-19 (NHLBI SVO 6; SPNR SG 1, 2)
Studies that examine the role of diet and nutritional status in lung development and regeneration after injury and the progression of lung diseases (e.g., COPD) (NHLBI SVO 1 and 2; SPNR SG 1, 2, 4)	Research to understand the relation between nutrients, vitamin D, and COVID-19 effects in the lung (NHLBI SVO 1 and 2; SPNR SG 1, 2)	Nutrition interventions to mitigate pulmonary morbidity and progression of in lung diseases (NHLBI SVO 6; SPNR SG 4)	Studies that evaluate analytical tools to study pulmonary effects of nutritional status in nonsmokers with COPD (NHLBI SVO 2; SPNR SG 2)

(*Continued*)

TABLE 2. (*Continued*)

Basic sciences	Epidemiology	Clinical trials	Translation/implementation
Studies on the role of nutrition in sarcopenia and cachexia in pulmonary disease (e.g., COPD, ARDS) (NHLBI SVO 2; SPNR SG 1, 2, 4)	Secondary data analysis of clinical trials to understand the associations of nutritional status and dietary intake in lung diseases (NHLBI SVO 2; SPNR SG 2, 3)	Studies that test the effects of diet nutrients in prevention/mitigation and treatment of COVID-19–related pulmonary complications, e.g., vitamin D supplementation (NHLBI SVO 2; SPNR SG 1, 2, 4)	Implementation science research to understand precision nutrition interventions addressing the relation between obesity and asthma/COPD (NHLBI SVO 6; SPNR SG 4)
Nutrition and selected blood diseases			
Studies that improve understanding of nutritional regulation of epigenetic factors (NHLBI SVO 1, SPNR SG 1)	Studies that examine the relations among various dietary patterns and microbiome and its metabolites in cohort studies (NHLBI SVO 3 and SPNR SG 2)	Clinical trials that are informed by systems science approaches and computational biology (NHLBI SVO 3, 4, 6, 7; SPNR SG 3, 4 and SPNR CC Theme: DS, SS, AI)	Studies that evaluate the effectiveness of various dietary patterns on gut microbiome modulation and examine adherence, acceptance, and feasibility (NHLBI SVO 3, 4, 6; SPNR SG 3, 4, and SPNR CC Theme: MHHD, HW, RR)
Studies that identify novel epigenetic biomarkers linked to nutritional status (NHLBI SVO 1 and 2, SPNR SG 1)	Research that includes social determinants of health (SDOH) indicators in cohort studies to better characterize the context of environment and social experiences (NHLBI SVO 3, SPNR SG 2, 3, and SPNR CC Theme: MHHD, HW)	Clinical trials comparing impacts of different diets (e.g., plant protein vs. animal protein diets, vegetarian diets, ultra-processed diet, etc.) on symptoms and disease severity (NHLBI SVO 3, 4, 6; SPNR SG 3, 4 and SPNR CC Theme: MHHD)	Studies that translate evidence-based research into practice and engagement the clinical workforce on blood diseases (NHLBI SVO 6, 8; SPNR SG 3, 4, and SPNR CC Theme: MHHD, HW, TSW)
	Association of neighborhood- or individual-level SES and dietary patterns with blood conditions (NHLBI SVO 3, SPNR SG 2, 3, and SPNR CC Theme: MHHD, HW)	Clinical investigation and application of nutrient-regulated epigenetic markers (NHLBI SVO 3, 4, 6; SPNR SG 3, 4, and SPNR CC Theme: MHHD, HW, RR)	Utilization of the understanding of environmental factors, such as SDOH, on nutrition and dietary intake (NHLBI SVO 6, 8; SPNR SG 2, 3, 4, and SPNR CC Theme: MHHD, HW, TSW)
Nutrition, sleep, and circadian biology			
Circadian 'omics studies to promote the identification of biological pathways linking environmental/behavioral cues to circadian metabolic control (NHLBI SVO 1, SPNR SG 1)	Observational and clinical studies examining the bidirectional relation between circadian rhythms and dietary patterns, particularly across special populations (e.g., shift workers) (NHLBI SVO 1, 2, 3; SPNR SG 2, 3; SPNR CC Theme: MHHD, HW)	Longitudinal therapeutic intervention strategies to evaluate the beneficial effects of meal timing on health outcomes to inform future clinical practice and public health campaigns (NHLBI SVO 3, 4, 5, 6; SPNR SG 3, 4, and SPNR CC Theme: MHHD, HW, TSW)	Personalized or tailored approaches that consider the physiological, sociocultural, environmental contexts that contribute to dietary health disparities and poorer health outcomes (NHLBI SVO 3, 4, 6; SPNR SG 3, 4, and SPNR CC Theme: MHHD, HW, TSW)
Translational roles and interrelations of central or peripheral clock genes, master regulators (e.g., KLF15) and pathways upon heart, lung, and blood organ health, disease, metabolism, and eating behaviors (NHLBI SVO 1 and 2; SPNR SG 1)	—	—	The development and evaluation of accurate and objective measures and assessments for chronotype and dietary/nutrition status including simple screening tools that could be used easily in clinical and public settings (NHLBI SVO 3, 7; SPNR SG 3, 4, and SPNR CC Theme: MHHD, HW, TSW)

(*Continued*)

TABLE 2. (*Continued*)

Basic sciences	Epidemiology	Clinical trials	Translation/implementation
Development of biomarkers of insufficient sleep and circadian rhythm disruption to optimize diagnostic and intervention timing and improve cardiometabolic outcomes (NHLBI SVO 1, 3, 4, SPNR SG 1)	—	—	Tools/methods for evaluation of tailored and community-based interventions in ecologically valid settings (NHLBI SVO 3, 6, 7; SPNR SG 3, 4, and SPNR CC Theme: MHHD, HW, TSW)

[1]AI, artificial intelligence; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; DS, data science; HLBS, heart, lung, blood, and sleep; HW, health of women; KLF15, Kruppel-like factor 15; MHHD, minority health and health disparities; NHLBI, National Heart, Lung, and Blood Institute; RR, rigor and reproducibility; SPNR CC Theme, Strategic Plan for NIH Nutrition Research Cross-Cutting Theme; SPNR SG, Strategic Plan for NIH Nutrition Research Strategic Goal; SS, systems science; SVO, Strategic Vision Objective; TSW, training the scientific workforce.

NHLBI Strategic Vision Objectives focused primarily on HLBS disease prevention and treatment but also on cross-cutting themes (e.g., training the workforce, addressing minority health). There were also knowledge gaps in the role of nutrition, particularly in diseases of the lung, sleep, and blood but also of the cardiovascular system that were not a focus of the NHLBI Strategic Vision. While expertise of the extramural community involved in the development of the strategic vision and SPNR varied, the timing of release did not enable collaboration between the SPNR extramural staff with those of the NHLBI extramural staff. (Note, the NHLBI released its Strategic Vision objectives in 2016 and the Office of Nutrition Research released the SPNR in 2020.) Additionally, a limited number of SPNR extramural staff participated in both the development of the SPNR and the NHLBI Strategic Vision Objectives. Despite these differences, similarities exist in both the SPNR and the NHLBI Strategic Vision Objectives: both integrated input from the extramural community and both addressed unique cross-cutting themes.

Discussion

This paper provides perspectives and examples of potential research opportunities to advance knowledge about the role of nutrition in HLBS diseases and conditions and suggests the promise of an integrated and transformative nutrition research approach that addresses fundamental discoveries and implementation science across HLBS. Nutrition research is nascent in diseases of the lung and blood and disorders of sleep and is ripe for future study. Investigations spanning the spectrum of basic, epidemiologic, clinical trial, and implementation science research and addressing precision nutrition approaches could benefit public health. Advances in "Big Data" analytics have the potential to stimulate research that addresses diet and nutrition and their relations in various aspects of the objectives of the SPNR and the NHLBI Strategic Vision. A holistic approach to precision nutrition in the prevention, treatment, and management of HLBS diseases and conditions could harmonize data from various sources, including those from the NHLBI TOPMed program and biodata Catalyst. Data (13) on genetics (e.g., polygenic risk scores), immunologic, behavioral, environmental, metabolomic, psychological factors, health status (e.g., related to HLBS), and dietary patterns may be combined through machine-learning algorithms to identify phenotypes and to stimulate specific dietary and lifestyle strategies for management of HLBS diseases and conditions. An integrated approach to nutrition in HLBS diseases and conditions may advance the nutrition field to understand the role of macro- and micronutrients in normal biological processes. Understanding the role of diet and nutrition in preventive treatment and management of HLBS diseases and conditions also has the potential to stimulate translational and implementation science research. The development of the scientific workforce in nutrition is yet another avenue to stimulate future research and develop precision nutrition approaches to enhance population health. Training in nutrition research, data analytics, and precision

nutrition are needed and could provide knowledge that can be translated into clinical practice by both nutritionists and clinicians. Overall, precision nutrition research in HLBS diseases and conditions has the potential to improve the health of the nation.

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