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The Decline in Vitamin Research Funding: A Missed Opportunity?

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Abstract

Background: The National Nutrition Research Roadmap has called for support of greater collaborative, interdisciplinary research for multiple areas of nutrition research. However, a substantial reduction in federal funding makes responding to these calls challenging.

Objectives: The objectives of this study were to examine temporal trends in research funding and to discuss the potential consequences of these trends.

Methods: We searched the NIH RePORTER database to identify NIH research grants and USASpending to identify National Science Foundation and USDA research grants awarded from 1992 to 2015. We focused on those that pertained to vitamin research. For the years 2000 to 2015, we examined funding trends for different vitamins, including vitamins A, B (one-carbon B-vitamins were considered separately from other B-vitamins), C, D, E, and K.

Results: From 1992 to 2015, total federal research spending increased from ~$14 to $45 billion (2016 US dollars). Although vitamin research spending increased from ~$89 to $95 million, the proportion of grants awarded for vitamin research declined by more than two-thirds, from 0.65% in 1992 to 0.2% in 2015. Federal agencies awarded 6035 vitamin research grants over the time period, with vitamin A associated with the most research projects per year on average (n = 115) and vitamin K the fewest (n = 8). Vitamin D research projects were associated with the greatest average yearly project value ($34.8 million).

Conclusions: Vitamin research has faced a disproportionate decline in research funding from 1992 to 2015. Insufficient federal research funding streams risk stalling progress in vitamin research and leaving important advancements unrealized. *Curr Dev Nutr* 2017;1:e000430.

Introduction

Federal funding continues to be the principal source of financial support for academic research centers globally and is the backbone of biomedical research in the United States (1). However, federal funding agencies have faced substantial budget reductions in recent decades. Since the early 1990s, the share of the federal budget allocated to research funding has declined from >5% of the federal budget to ~3.8% (2). This sustained reduction in the proportion of the federal budget allocated to research funding threatens the sustainability of biomedical research and ultimately will slow the pace of innovation and scientific progress.

Although it is expected that federal research funding should track federally mandated research priorities, it is unclear how the overall reductions in federal research funding have varied across research disciplines. During an era in which the general public has

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Supplemental Table 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://cdn.nutrition.org.

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Abbreviations used: CVD, cardiovascular disease; NSF, National Science Foundation; RCT, randomized controlled trial.

unprecedented interest in nutrition guidance to improve quality of life and reduce the risk of specific chronic diseases, advancements in chronic disease prevention in the United States, including promotion of healthy eating patterns, have not kept pace with similar advancements in other affluent economies (3). Federal funding for chronic disease prevention currently focuses on the following: *1*) prevention across the life cycle, *2*) practical solutions to targeted interventions, and *3*) personalized solutions. One of the strategic priorities of the NIH is to accelerate the development of precise, individualized approaches to disease prevention (1). Similarly, the National Nutrition Research Roadmap 2016–2021, recently announced by the Interagency Committee on Human Nutrition Research, includes a call for the support of greater collaborative, interdisciplinary research for multiple areas of nutrition research, such as understanding the effects of individual variability on biological measures related to the epigenome, microbiome, metabolome, and proteome (4). However, the feasibility of responding to these federally issued calls for more interdisciplinary nutrition research concurrent to a period of perceived declines in federal funding is unclear.

Funding for nutrition research spans multiple federal agencies, but there is no universal tracking system of project funding across federal agencies in the United States. To address this challenging question, we chose to focus our study on trends in federal funding for vitamin research, which can span from fundamental science to the application of omics technology to understanding the individual response of vitamin precursors and metabolites in prevention of specific chronic disease processes. Our focus on vitamins complements the 2015 Dietary Guidelines for Americans Scientific Report, which identified multiple vitamins as nutrients that are underconsumed in the United States, relative to recommended intakes set by the Institute of Medicine (5). We had 2 study objectives: *1*) to compare how federal funding for vitamin research has changed over time relative to all federal research funding (2000–2015) and *2*) to examine how research funding for specific vitamin types has changed over time. The outcome of this analysis will provide insight into gaps between research funding and research priorities in vitamin research, and identify shifts in funding over time.

Methods

Data sources

We included research grants from the NIH, the National Science Foundation (NSF), and the USDA. For the USDA, we included only grants awarded by the Agricultural Research Services; the Cooperative State Research, Education, and Extension Service; and the National Institute of Food and Agriculture because we considered these divisions to be those most pertinent to vitamin funding.

We used NIH RePORTER to identify research grants awarded by the NIH and USASpending to identify grants awarded by the NSF and USDA. NIH RePORTER is an online database of NIH-funded research projects since 1992, and USASpending is an online database of federally funded research grants since 2000. Both databases contain information on each grant, including its project title and funding amount. We stratified the grants by year and recorded the number of projects and funding amounts (in 2016 US dollars) by vitamin type, which we determined by searching the project titles.

A study limitation is that we did not categorize identified research grants with regard to study type. In other words, we did not differentiate between grants in terms of their purpose (e.g., basic science, clinical trials, or meta-analysis). A second limitation is that we counted multiyear grants only in the year of the grant's origination and we did not divide the value of the grant across the grant's study period.

Search strategy

On 15 May 2016, we searched all project titles before 2016 to identify all vitamin A, B, C, D, E, and K grants with the use of the search terms shown in **Table 1**. We differentiated B-vitamins by those forms that contained one-carbon from those that did not, as described in Table 1.

Results

Federal research funding, 1992–2015

The proportion of federal research grant funding allotted to vitamins declined from 1992 to 2015 from ~0.6% to 0.2%. Total federal research spending (in 2016 US dollars), as reported by the NIH, NSF, and USDA, increased from ~$14 billion in 1992 to $45 billion in 2015; over the same time period, federal research spending (in 2016 US dollars) for vitamins increased from ~$89 million to $95 million

TABLE 1 Search terms used to identify vitamin research grants

Vitamin	Search terms
Vitamin A	vitamin a; carotene (all forms); carotenoids; isotretinoin; palmitate; retinal; retinoic acid; retinoid; retinol; retinyl acetate; retinyl palmitate; cryptoxanthin; lycopene; lutein; zeazanthin
Vitamin B (one-carbon forms)	adermin; antipernicious anemia; cobalamin; cyanocobalamin; folacin; folate; folic acid; folinic acid; hydroxocobalamin; lactoflavin; methylcobalamin; pteroyl-l-glutamate; pteroyl-l-glutamic acid; pyridoxal; pyridoxamine; pyridoxin; riboflavin; vitamin b2; vitamin b6; vitamin b9; vitamin b12
Vitamin B (non–one-carbon forms)	adenine; aneurin; antiberiberi factor; biotin; choline; coenzyme r; niacin; nicotinamide; nicotinic acid; pantothenate; pantothenic acid; thiamin; vitamin b1; vitamin b3; vitamin b4; vitamin b5; vitamin h
Vitamin C	vitamin c; ascorbate; ascorbic acid
Vitamin D	vitamin d; alfacalcidol; calcidiol; calcifediol; calcitriol; cholecalciferol; dehydrocholesterol; dihydroergocalciferol; ergocalciferol; hydroxycholecalciferol
Vitamin E	vitamin e; tocopherol; tocotrienol; vitamin e acetate; vitamin e succinate
Vitamin K	vitamin k; menadione; menaquinone; phylloquinone; phytomenadione; phytonadione

(**Figure 1**). Budget sequestration required the NIH to cut 5% from its 2013 budget. Thus, the total research dollars awarded in 2015 more closely resembled those awarded before the 2009 American Recovery and Reinvestment Act that aimed to stimulate economic growth after the Great Recession (6).

Research funding by vitamin type

In our analysis of funding by vitamin type, we limited the data set to the years 2000–2015 because reliable NSF and USDA funding data are unavailable before 2000. From 2000 to 2015, federal agencies awarded 1,732,197 research grants, of which 6035 (0.35%) pertained to vitamins. We found notable variations in the number and value of grants awarded by vitamin type (**Table 2**). Vitamin A was associated with, on average, the most research projects per year (n = 115); vitamin K was associated with the fewest (n = 8). Vitamin D projects were associated with the greatest average yearly project value ($34.8 million); vitamin K projects were associated with the lowest average yearly project value ($2.4 million).

The differences in funding trends by vitamin type were striking (**Figure 2**). Funding, as a percentage of the 2000 level, increased for only 2 vitamins—vitamin D and vitamin B (with the exception of one-carbon B-vitamins)—over the studied time period. Vitamin D funding peaked in 2013, at 326% of the federal funding awarded for vitamin D research in 2000 (**Supplemental Table 1**). Although funding for vitamin D research has since declined, its 2015 funding was still 268% of its 2000 level. Vitamin B (with the exception of one-carbon B-vitamins) peaked in 2006, at 269% of the 2000 budget, before falling to 176% of the 2000 budget in 2015 (Supplemental Table 1). In contrast to that for vitamin D and vitamin B (with the exception of one-carbon B-vitamins), federal funding for each other vitamin type was lower in 2015 than in 2000, with the greatest declines in vitamin A and vitamin E (26% and 35% of 2000 funding amounts, respectively). Funding for one-carbon B-vitamins was 42% of its 2000 level, but in absolute dollars was still 2-fold greater than funding for forms of non–one-carbon B-vitamins.

Discussion

Our data from 1992 to 2015 show that there has been a disproportionate reduction in federal funding allocated for vitamin research in the United States. Vitamin research has historically made significant contributions to the understanding of and improvement in nutrition at the population level through its impact on dietary guidance, vitamin fortification, and vitamin supplementation (7). Vitamin insufficiencies continue to be identified in national surveys both in the United States (3, 8) and globally (9). Federally issued nutrition research agendas continue to identify vitamin research as part of their roadmaps in the United States (4) and globally (10). Therefore, it is critical to address the impact of the consistent decline in federal funding for vitamin research relative to the potential benefits of sustained activity in this scientific discipline. First, we describe the impact of past federal funding for vitamins. We then discuss potential reasons for the overall decline in federal funding of vitamin research and finally address the consequences of continued reduction in funding.

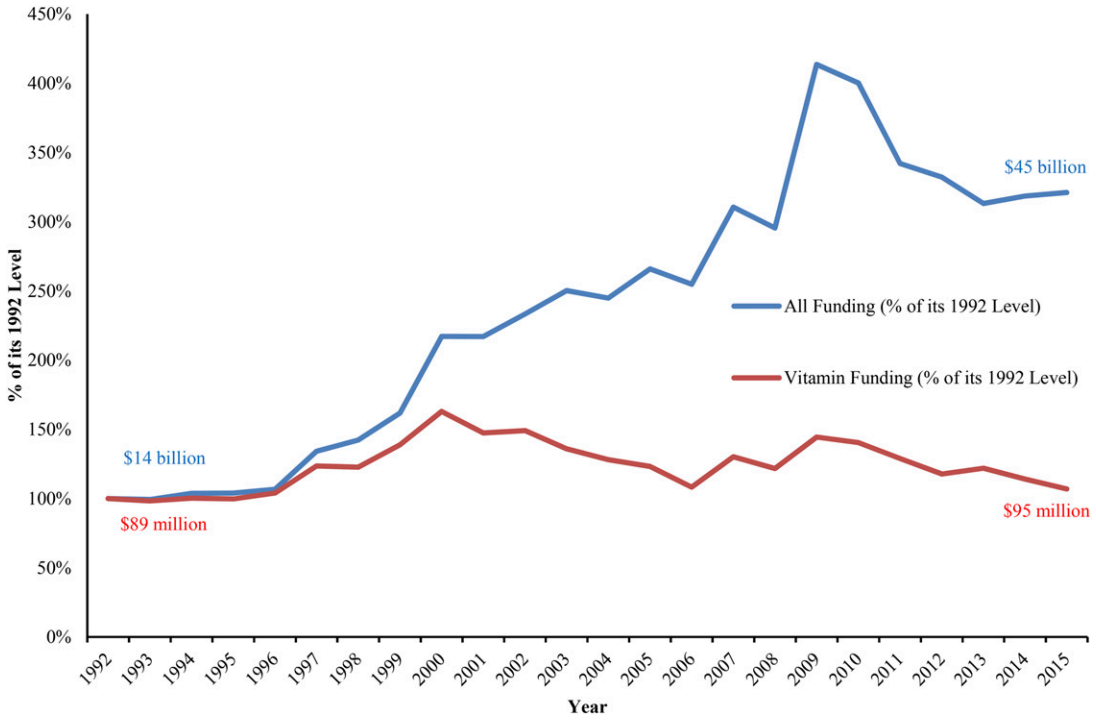

FIGURE 1 All federal research funding compared with vitamin federal funding (in 2016 US dollars) from 1992 to 2015 as a percentage of 1992 levels. NIH, NSF, and USDA federal funding data are shown (NSF and USDA funding data were unavailable for the years before 2000); NIH funding accounts for 96% of all funding after 2000. NSF, National Science Foundation.

TABLE 2 Number and total grant awards by vitamin type[1]

	Annual number of projects (2000–2015)	Total project value by award (2000–2015), $ (×100,000)
Vitamin A	115 ± 51	326 ± 130
Vitamin B (one-carbon)	74 ± 26	218 ± 51
Vitamin B (others)	27 ± 6	64 ± 19
Vitamin C	14 ± 5	37 ± 9
Vitamin D	101 ± 33	348 ± 160
Vitamin E	25 ± 12	96 ± 34
Vitamin K	8 ± 2	24 ± 6

[1] Values are means ± SDs.

Vitamin research breakthroughs

Vitamin research has had an enormous and positive impact on global population health (11). Vitamin research has allowed us to all but eradicate basic nutrition-related diseases as a direct result of vitamin deficiency—such as scurvy (vitamin C) (12), rickets (vitamin D) (13), pellagra (nicotinic acid) (14), xerophthalmia (vitamin A) (15), and beriberi (thiamine) (3) to name but a few—primarily through the addition of micronutrients to food or direct supplementation of malnourished populations. More recently, the discovery that consumption of the recommended amount of folate before and during early pregnancy can reduce the likelihood of neural tube defects led to the implementation of a federally mandated folic acid fortification program in the United States, which reduced the incidence of neural tube defects in newborns by almost 20% (16) and which has since been undertaken in nearly 80 other countries.

Beyond fortification, many vitamins are integral to the treatment of disease (17, 18), and the study of the biological properties of vitamins has led to the development of a number of pharmaceuticals. For instance, the study of vitamin K and its role in blood clotting led to the vitamin K antagonists [e.g., Coumadin (warfarin), Bristol-Myers Squibb] (19) that prevent clotting in patients with coagulation disorders. The study of the impact of folate on cell metabolism led to the first antibiotics (sulfa drugs) as well as the development of several chemotherapeutic agents that

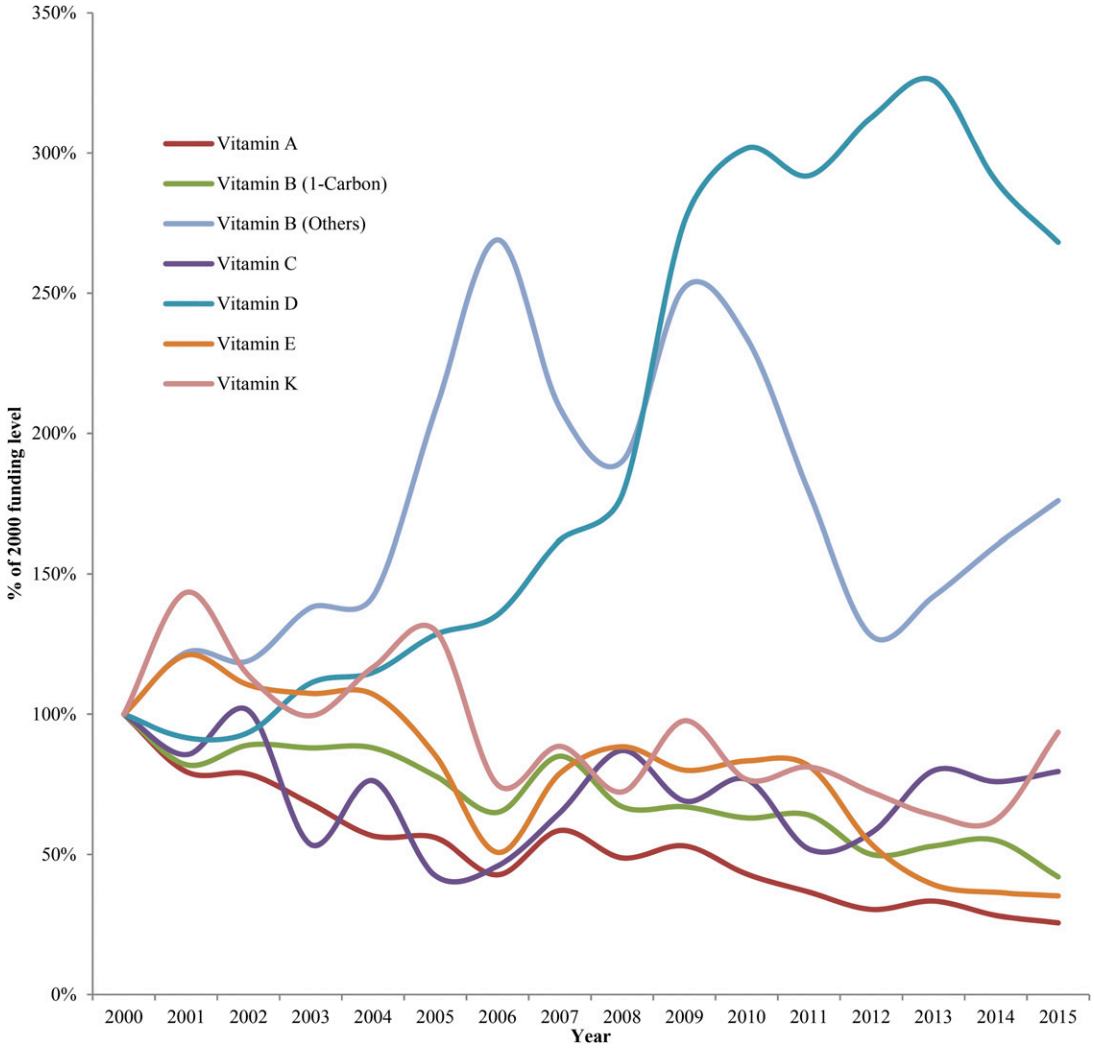

FIGURE 2 Vitamin funding as a percentage of the 2000 funding level.

remain important components of the current cancer treatment armamentarium (20, 21). Research continues to evaluate the role of folate in cancer, including whether upregulation of folate receptors on cancer cells can be used to target (22, 23) and locate (24) cancer cells in patients. There remains an unresolved controversy that continues to affect national nutrition policies worldwide as to whether adequate dietary folate consumption protects against common cancers, at what doses, and whether the excessive amounts consumed by many in the form of supplements can paradoxically enhance cancer risk (25–27).

There has been considerable recent progress in vitamin D research that coincides with a 300% increase in federal funding of vitamin D over the past decade. Current studies are examining the role of vitamin D on muscular function (28) and on left ventricular structure and function (29), and on reducing the conversion of prediabetic patients to diabetic patients (30). The optimal serum concentration of 25-hydroxyvitamin D, which is an accepted biomarker of vitamin D, is being studied along with the association of vitamin D deficiency with higher rates of hypertension (31–33), high LDL cholesterol (34), and reduced innate immune system function (35, 36) and executive cognitive function (37). Vitamin D is a useful case study given that there has been a surge of funding for this vitamin when funding for other vitamins is losing ground. Although beyond the scope of our analysis, it would be particularly useful to determine if the availability of a validated biomarker for vitamin D created the need for more federal funding or if the increased availability of funds for vitamin D research has driven more discovery.

Potential reasons for the decline in research funding

Vitamins were discovered more than a century ago (4), and in this era of rapid technological advancement and discovery, some may consider the influence of new vitamin research to be diminishing given the assumption that all of the vitamins have been discovered. Another possible contributing factor to the steady decline in federal vitamin funding is the growing uncertainty with regard to the health benefits of routine multivitamin supplementation in the general population (38). The effect of single-nutrient supplements on health outcomes has not always been beneficial (39), and there are inconsistent findings with regard to the role of vitamin supplements on reduction in the risk of chronic diseases, such as cardiovascular disease (CVD) and cancer (10). Defined as part of the Dietary Supplement Health and Education Act, a dietary supplement is intended to supplement the diet (40). Of concern is that ~35% of US adults consume dietary supplements on a regular basis (41) and that the segment of the population most likely to take dietary supplements already has a healthy diet—hence, are at risk of an excessive intake of single vitamins (42). For example, several groups have independently raised concerns, on the basis of clinical observations, that elevated concentrations of blood folate within commonly accepted ranges of normality place elderly individuals at a higher risk of the clinical manifestations of vitamin B-12 deficiency; similarly (43–45), there are concerns that excessive folate intake during pregnancy in the setting of marginal vitamin B-12 status may be transmitting a substantial risk of obesity and insulin resistance to offspring (46). Alternatively, there are those who express concern that individuals who do not consume a healthy diet will rely on dietary supplements to meet their nutritional needs (47). Although the study of routine vitamin supplementation is only a small part of vitamin research as a whole, the uncertainty surrounding it may have had a disproportionate influence on funders and led to hesitation in funding broader vitamin research.

However, the potential diminishing returns of further research and uncertainty surrounding multivitamins may actually necessitate more research. In contrast to the assumption of the diminishing returns of vitamin research, there are growing concerns that an appreciable number of North Americans do not meet the recommended intakes as suggested by the Institute of Medicine and that subgroups of the US adult population have increased needs for some vitamins, including but not limited to obese individuals, certain races/ethnicities, and older adults (5). There is also evidence that individuals of low socioeconomic status have not benefited from an overall improvement in dietary patterns observed among more affluent segments of the US adult population (48). However, the economic impact of inadequate vitamin status, be it due to increased needs and/or poor eating habits, has been poorly studied, with the exception of vitamin D (49).

With regard to questions surrounding vitamin supplementation, those conducting vitamin research in the community need to consider high supplement doses with the use of principles of drug regulation and respect the rule of "first, do no harm" (50) in their research. More importantly, vitamin research needs to find solutions through food and/or through combinations of vitamins as part of a healthy diet consistent with the Dietary Guidelines for Americans (5), and not in lieu of them.

Consequences of the current trend in vitamin funding and potential solutions

Despite great contributions from vitamin research, funding to support the field has persistently declined over recent decades. The shortfall in funding will undoubtedly affect our ability to leverage new technologies and study designs emerging for other areas of biomedical research as they applies to vitamin research. The impact that insufficient and inconsistent funding for vitamin research will have on the career development of young investigators pursuing research in this area will further delay research advances.

What is required is a fundamental change in our approaches to vitamin research, which, in turn, requires a more innovative and progressive perspective from federal funding agencies. Although traditionally study has focused on "parent vitamins," the science has evolved to the examination of the role of metabolites and biomarkers in health and disease. For example, niacin (51) and nicotinamide riboside have emerging roles in aging and survival, whereas the role of thiamine supplementation on heart failure reduction is also being studied (52). There is great potential for this research to be applied to tailor care to individual patients and prevention to high-risk groups (e.g., the elderly, cancer survivors, groups with metabolic disorders, or those suffering from particular diseases), consistent with current funding priorities for personalized medicine and prevention strategies (1). However, further advancements in conventional randomized clinical trial designs may be needed, because when testing the effects of specified

vitamin intake amounts, which are virtually always superimposed on extant intakes, there is no true placebo (53, 54) and perhaps depletion and repletion studies may be more appropriate to develop personalized nutrition protocols. We may also need to consider other preclinical models for the study of vitamins in the prevention of chronic disease, including the development of appropriate human in vitro model systems, including organoids, to minimize the use of animals, with reproducibility demonstrated in human trials.

This evolution in how we approach vitamin research in many ways mirrors the evolution of the science in other areas. In particular, pharmaceutical research has moved away from the focus of treating populations to a focus on individuals, with new treatments tailored to patients' individual characteristics. The advent of precision medicine (1) also provides an opportunity for researchers to advance our understanding of the relation between genetics, vitamins, and pharmaceuticals; and there are already a number of emerging and encouraging data showing the modification of the metabolic effect of vitamins by genotype. Individuals carrying the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) 677TT polymorphism, which is reported to be found in some populations, have a ≤32% higher risk of CVD and hypertension. A number of recent randomized controlled trials (RCTs) showed that riboflavin supplementation can significantly reduce systolic blood pressure by 5–13 mm Hg in these genetically at-risk adults (55).

There is a need to better understand the relation between vitamin requirements and eating patterns and human metabolic processes, particularly when choosing between low- and high-macronutrient (fat, protein, carbohydrate) diets. Even worse, if we do ignore progress in this field we might even draw the wrong conclusions. After encouraging data associating a lower risk of CVD with adequate vitamin E intake, a number of large-scale RCTs were initiated to investigate this finding. It was with surprise to many that the majority of the RCTs reported a null effect of vitamin E on CVD; however, they did not take genotype into account. In diabetic patients who carry the haptoglobin 2-2 genotype, which has inferior antioxidant properties, 400 mg vitamin E significantly reduced the 18-mo risk of cardiovascular events (56) and this effect was also shown for diabetic patients in the HOPE trial when genotype was taken into account (57). These examples show the importance of providing funds to investigate the role of vitamins applying current knowledge. An understanding of the contribution of proteins, genes, and metabolites to individual variation may facilitate the expansion from public health dietary guidelines to more evidence-based dietary guidance that is tailored to the individual and that accounts for eating patterns, disease status, disease risk, genetic profile, and patient behavior, particularly for those in specific risk groups. In this way, there is promise in leveraging "big data" analytics—the integration of large and diverse data sets toward answering wide-ranging research questions—to advance nutritional sciences and to develop and test predictive mathematical models of the effects of vitamin supplementation in different genetic, epigenetic, and macronutrient backgrounds. As reviewed elsewhere (58), the use of modeling for standardization of data and data interpretation, to fill in geographical gaps in the knowledge and for integrating multiple variables, is critical for moving nutrition research forward. Such research innovations have the potential to find clinically meaningful relations between individual variations, disease, and nutrition and vitamin consumption that can be tested to positively affect patient health.

The National Nutrition Research Roadmap 2016–2021 calls for support of collaborative, interdisciplinary research for understanding the short- and long-term effects of dietary and physical activity patterns on health across the life stages (4). If vitamin research is to fulfill its promise, a similar collaborative approach is required. Furthermore, to fully address research gaps and opportunities, better coordination between the federal funding agencies, academic researchers, and training programs is needed.

Conclusions

The study of vitamins has been fundamental to advancements in nutrition, medicine, and global public health. Current research holds promise for further progress in our understanding and treatment of a variety of diseases and high-risk subgroups. If we are to reap the benefits of this new frontier of vitamin research, it is vital for funding streams to keep pace with the evolving science and maintain relevance to the emerging needs of achieving optimal health and reducing morbidity in aging populations.

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