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Dietary Supplements: Baby and Bathwater

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Abstract

Inconsistent data regarding the health benefits of dietary supplements leave the public confused. Nutrient supplements may be viewed as the proverbial combination of baby and bathwater. It is as injurious to public health to discard the former as to embrace the latter. We need to distinguish between effective and ineffective supplementation. This paper explores the evidence base for micronutrient supplementation and aims to identify how the practice is best applied to advance public health. A key principle that must govern the contributions of supplements to public health is that they are meant to supplement the diet, not replace healthy eating. The best opportunity for supplements to influence wellness derives from careful consideration of what "nutrient gaps" need to be filled and who is likely to benefit. A conceptual framework we propose is to consider dietary supplementation along the continuum of health; individuals likely to benefit the most from supplementation are those in the middle of the continuum whose health and nutritional status is suboptimal. This proposed conceptual framework may serve as a model for finding answers to nutrient-chronic disease questions rather than providing answers itself. Nutrition scientists need to rethink the traditional single-nutrient approach to nutrition research and develop an interdisciplinary framework that considers the hierarchical etiology of complex health problems.

Keywords: Dietary supplements; Micronutrients; Health; Nutrient gaps

Dietary Supplements: Baby and Bathwater

Historically, supplements remediated nutrient deficiencies that have been irrefutably linked to certain medical conditions, such as vitamin D deficiency (rickets), the depletion of vitamin C (scurvy), and low vitamin A status (night blindness) [1]. The value of supplementation in this regard is uncontested; routine food fortification is testimony to the respect for targeted delivery of key nutrients by public health authorities including the World Health Organization, the Food Agriculture Organization of the United Nations, and the US Food and Drug Administration (FDA) [2]. However, data have been controversial regarding the benefits of dietary supplements in the prevention and/or treatment of chronic diseases such as cancer, cardiovascular diseases, and diabetes. Supplements have been investigated in many human studies in the same way as investigational new drugs (INDs), which impose numerous challenges in the study design itself including population relevance, no true placebo group, short duration of supplementation, and uncontrolled confounding factors at baseline and over the course of the study. Partly due to these methodological differences, conflicting findings, beneficial or ineffective or even harmful, have been repeatedly reported both in the scientific literature and the popular press. This supplement paradox leaves the public and even professionals confused: are supplements babies or bathwater?

Nutrient supplements as a whole category may be viewed as the proverbial combination of baby and bathwater. It is as injurious to public health to discard the former as to embrace the latter. Magical thinking about supplementation certainly needs to be discouraged. However, it is rather disappointing if our approach to clear out such dirty bathwater is to let the baby go down the drain as well. The right approach is an excess in neither direction – a thoughtful pursuit of the sweet spot in the middle where supplements are matched to nutrient gaps left by the diet [defined as dietary intake < the Estimated Average Requirement (EAR) or Adequate Intake (AI) values]. In this paper, we briefly review these competing forces, "baby" and "bathwater," and propose a balanced approach towards micronutrient supplementation: supplementing the diet, not replacing healthy eating.

Filling Nutrient Gaps The standard American diet (SAD) is low in vegetables, fruits, whole grains, and low-fat dairy products; at the same time it is high in refined grains, saturated fat, added sugars, and sodium [3]. According to the 2015 Dietary Guidelines Advisory Committee (DGAC) report, Americans aged ≥ 2 years have failed to meet the recommended intakes (EAR or AI levels) of 10 "shortfall nutrients" (vitamins A, C, D, E, folate, fiber, calcium, potassium, magnesium, and iron for adolescents and premenopausal women), and five are identified as "nutrients of public health concern" (vitamin D, fiber, calcium, potassium, and iron for premenopausal women and adolescents) due to consistent under-consumption across diverse demographic groups (ethnicity, age, and gender) and the associated health impact [3]. To achieve required nutrient intakes, the general advice from health professionals is to eat a healthy diet. Unfortunately, this dietary approach fails to correct inadequate dietary intake of nutrients among many Americans due to barriers like inadequate food access, food insecurity, and acculturation [4]. Such nutrient inadequacies in the diet may lead to an increased risk of nutritional deficiencies which are usually defined by biomarker cut points [4].

The role of supplements in filling nutrient gaps in the American diet has been recognized by the 2015 DGAC as "useful in providing one or more nutrients that otherwise may be consumed in less than

recommended amounts or that are of particular concern for specific population groups" [3]. According to the 2003-2006 National Health and Nutrition Examination Survey data (NHANES), compared to those who did not report taking any supplement in the past 30 days (nonusers), adults who reported supplement use (users) have significantly better total intakes (diet and supplement) and lower prevalence of inadequacy for micronutrients, including folate, vitamins A, C, D, E, K, B6, B12, calcium, iron, magnesium, zinc, phosphorus, copper, potassium, and selenium [5,6]. One limitation of these data we should bear in mind is that the data were collected by self-reported dietary recalls and they might be subject to potential under- or over-reporting bias. However, some nutrient requirements are still not being met even among supplement users, indicating a potential day-to-day non-compliance issue. For example, 40%, 13%, and 20% of users do not meet recommended intakes for vitamin D (among adults aged 19-30 years), vitamin E, and calcium/magnesium, respectively [5,6]. Nutrient inadequacies are even worse among nonusers, exemplified by 71% of 2192 female nonusers not meeting the recommended calcium intake (*versus* 24% for 2109 users) [5,6]. The association between dietary supplement use and a lower prevalence of micronutrient insufficiency is also reported among children, adolescents, and older adults; these groups are considered at higher risk and more vulnerable populations [7,8]. Interestingly, VMS users tend to eat a healthier diet and live a more positive lifestyle (i.e., more exercise, moderate alcohol use, and no smoking) than nonusers [4]. In our opinion, such evidence suggests that nonuse of supplements and risk for nutrient deficits may be correlated, indicating an obvious public health mandate: make better use of supplements where they are most needed and most apt to provide benefit. First and foremost is a healthy diet; filling nutrient gaps with the right supplementation is secondary. We also acknowledge a potential need of behavioral intervention in order to ensure satisfactory compliance of supplement use on a regular basis.

In the past, the recommended nutrient intakes primarily focused on preventing nutritional deficiencies; since 1994 the scope has expanded to optimizing health and avoiding excessive or inadequate nutrient intakes. That is, trying to find optimal personalized balance between over- and under-intakes [4]. Besides nutrient inadequacies, the NHANES data identify a small percentage of adult users whose total intakes of several minerals and vitamins exceed the recommended tolerable upper intake levels (ULs): 6-9% for calcium, magnesium, iron and zinc, and 0.7-7% for vitamins A,C,D,E,B6, and folic acid, compared to 0-0.5% of intakes above the ULs from foods alone [5,6]. In order to address potential over supplementation and safety concerns, ULs have been established by authorities in the U.S. and worldwide. The 2015 DGAC report specifies that dietary supplements containing the Recommended Dietary Allowance (RDA) level of nutrients are typically considered safe, provided that the total intake does not exceed ULs [3]. Consistent with the DGAC positioning, a recent meta-analysis examined the safety of the use of multivitamins/minerals (MVM), and concluded that long-term use of MVM (>10 years) can be safe if the doses are within the range of the Dietary Reference Intakes (DRIs) [9].

The dietary guidelines and recommendations put forth by scientific authorities and government agencies are to be used as a guide for generally healthy individuals to meet recommended dietary needs. However, at the individual level, we should not assume that "recommended" and "optimal" intakes are the same. Factors that influence "optimal" nutrient needs of an individual include inherent biological factors (i.e. age, gender), lifestyle (i.e., smoking status, physical activity levels, and dietary intake relative to recommendations), health conditions (i.e., morbidities and medications), socioeconomic status, and geographical location [10,11]. As an illustration, medical conditions and medications can alter nutritional needs. As an example, severe vitamin B6 deficiency is reported to be related to microcytic anemia, dermatitis, depression, and weakened immune function [4]. In some cases there is a direct relationship between increased nutrient needs and exercise. For instance, a training female athlete may require higher amounts of calcium to maintain bone health than her sedentary counterpart due to the possibility of lower circulating estrogen (important for bone mass maintenance in women) as a result of intense training [12]. The average requirement for iron is estimated by the Food and Nutrition Board to be 30% to 70% higher for individuals engaged in regular exercise [13]. Despite such recommendations, iron deficiency remains one of the most frequently reported nutrient deficiencies among athletes [12,14], indicating a potential need for behavioral intervention. Optimally meeting nutritional needs necessitates taking responsibility for one's nutritional status, modifying lifestyle choices as needed, and utilizing the available assessment tools to make personalized recommendations. "Natural" nutrient intake levels among our remote ancestors (also known as "hunter-gathers") appear to be a good inference that can help guide us in future research to define "optimal" nutrient needs [15].

Towards Better Health to optimize health, as reflected in the 1994 shift of the National Academy of Medicine (NAM) recommendations, diet is an essential lifestyle factor that contributes to overall wellness [4]. The established value of certain nutrients in addressing public health imperatives cannot be overlooked. An exemplary case is vitamin D in the prevention of low bone mass and associated complications (i.e., osteoporosis). Recently, vitamin D supplementation has been linked to reduced risks of falls, fractures, and mortality among the elderly. Meta-analyses of data from numerous trials further confirmed these benefits. For example, data from 5 double-blind randomized controlled trials (RCTs) comprised of 1237 institutionalized senior patients with low trauma showed that patients who took vitamin D had a 22% reduction in fall risk compared to patients receiving calcium or placebo (Odds Ratio [OR]: 0.78; 95% Confidence Interval [CI]: 0.64, 0.92) [16]. Another meta-analysis of 12 RCTs for nonvertebral fractures (42,279 subjects) and 8 RCTs for hip fractures (40,886 subjects) reported that vitamin D supplementation at a dose of >400 IU/day reduced the risks of nonvertebral and hip fractures among community-dwelling or institutionalized older adults (≥ 65 years) by 18% to 20% (for nonvertebral fractures, Relative Risk [RR]: 0.80; 95% CI: 0.72, 0.89; for hip fractures, RR: 0.82; 95% CI: 0.69, 0.97) [17]. Osteoporosis and falls are risk factors for fractures. Fractures, especially hip fractures, are linked to 8% to 36% excess mortality during the first year [18]. Pooled results from 18 RCTs (57,211 subjects) indicate a positive association between vitamin D supplementation and reduction in all-cause mortality (RR: 0.93; 95% CI: 0.87, 0.99) when vitamin D is administered orally or as a single injection at daily doses of 300 to 2000 IU over a duration of 6 months to 7 years [19]. Another recent meta-analysis involving 56 RCTs (RR: 0.97; 95% CI: 0.94, 0.99) confirms this association of vitamin D with reduced mortality [20]. Considering the number of Americans with osteoporosis (≥ 9.9 million) or low bone density (43.1 million) and the projected relevant health care cost ($ 25.3 billion by 2025) [21], vitamin D supplementation appears to be a promising nutrition-based approach to aid in the management of aging-associated disease burdens.

In order to distinguish between effective and ineffective or harmful supplementation, we should consider confounding factors including, but not limited to, population characteristics (i.e. age, gender, morbidities, and medications), lifestyle factors, clinical endpoints, and dosage for intervention when we design a study or interpret data. Inconsistent data in nutrition research are partly due to these methodological discrepancies across studies. As an example, daily supplementation of vitamin D and calcium is recommended by the U.S. Preventive Services Task Force (USPSTF) for the primary prevention of fractures and falls in "community-dwelling adults aged 65 years or older who are at increased risk for falls" (e.g. those diagnosed with osteoporosis or vitamin D deficiency) [22]. However, this effectiveness has not been confirmed in healthy asymptomatic younger adults without a history of fracture or vitamin D deficiency [22]. Besides population characteristics, clinical endpoints, dosage and lifestyle factors may confound or modify the effects of dietary supplementation. As an illustration, beta-carotene supplementation was reported in a meta-analysis of 9 RCTs to increase the incidence of lung cancer among smokers and asbestos workers compared to the placebo group, while no adverse effect was observed on the risk of other cancers including prostate, pancreatic, colorectal, breast, melanoma and non-melanoma skin cancer [23]. The deleterious effect of beta-carotene supplementation on lung cancer was reported at a dose of 20-30 mg/day while no increase in lung cancer incidence was observed at a lower dose level of 6-15 mg/day [23]. To this point, the European Food Safety Authority (EFSA) concluded supplemental beta-carotene below 15 mg per day does not pose adverse health concerns in the general population including heavy smokers, while the NAM considered the evidence to be insufficient to set a UL value for beta-carotene [24]. Additionally, increased risk of lung cancer with beta-carotene supplementation was observed only among smokers and asbestos workers [23]. Smoking and asbestos are two risk factors for lung cancer but unfortunately their causal influence on lung cancer was not teased out from beta-carotene supplementation in the analysis [23]. The World Cancer Research Fund (WCRF) noted "there was a marked interaction between beta-carotene, smoking and genotype" [25], which leads to another challenge we are facing in nutrition research: can the traditional single-nutrient approach address complex chronic morbidities when the etiology is hierarchical?

The traditional single-nutrient model assumes a simple cause-effect relationship between a particular nutrient and a specific disease. This approach has been successful in combating diseases of micronutrient deficiencies. However, such success stories have not been repeated in dealing with complex chronic morbidities (e.g., cancer and cardiovascular disease) [11]. In the arena of cancer prevention, supplements have been extensively investigated in epidemiological studies, clinical trials, systematic reviews, and meta-analyses, and a wide range of nutrients have been evaluated including antioxidants (i.e. vitamins C, E, beta-carotene), folic acid, vitamin D, calcium, selenium, and omega-3 fatty acids. The conclusion is that there is lack of consistent evidence supporting the use of dietary supplements for the prevention of cancers [26]. This conclusion is further agreed upon by scientific authorities including the National Institute of Health (NIH), the American Institute for Cancer Research, and the USPSTF [27-29]. Similarly, literature on the efficacy of antioxidants for the prevention of cardiovascular diseases is contradictory; therefore the American Heart Association (AHA) and the USPSTF do not recommend antioxidant supplementation to prevent CVD [27,30]. Obesity is another exemplary challenge in this regard. The causes of obesity involve both dual nutrition imbalance and many other multidimensional factors including lifestyle, genetic makeup, environment, and socioeconomic status [11]. The dual nutrition imbalance is also known as the double burden of "malnutrition," and it implies the co-existence of excessive caloric and insufficient micronutrient intakes (i.e., vitamins A, B, C, D, zinc, and selenium). Undoubtedly, dietary interventions are key to correct micronutrient deficits and energy surplus. However, an isolated factor (i.e., a single nutrient or a group of nutrients) can neither offset the deleterious impacts of all other causal components nor reverse the development of chronic health conditions. In other words, the traditional single-nutrient approach may not work when the etiology of health problems is hierarchical [11]. An alternative strategy to improve wellness is to adopt a holistic and multifaceted concept that matches proper supplementation to dietary nutrient gaps, lifestyle, host conditions, and at-risk population's in future investigational research.

A Balanced Approach to Dietary Supplementation

Calls for abandoning dietary supplements are no more valid, and comparably at odds with the evidence, as are aggressive marketing efforts touting overzealous benefits of supplements. Efforts should be directed at differentiating between nutrients known and not known to confer benefits. Severe deficiencies of essential nutrients usually are translated into measurable clinical conditions while marginal inadequacies may not have characteristic signs or symptoms [1]. However, suboptimal nutritional status may indicate suboptimal health, given the indispensable roles of essential nutrients in biochemical and physiological functions [31]. We propose a conceptual framework: in reference to 3 stages (primary, secondary, and tertiary) in preventive care, the opportunity for dietary supplementation towards wellness can be evaluated along the health continuum. As illustrated in Figure 1, health is a dynamic continuum from optimal to very ill. At extremes of the health continuum (completely healthy or extremely sick), either the healthy individual has received sufficient nutrients from the diet so there are no nutrient gaps to fill, or the very ill individual needs regular and intense medicinal care which is beyond the capacities of simply filling nutrient gaps. In the middle of the continuum, individuals with "suboptimal health" may have 1 or a few nutrient insufficiencies but are otherwise reasonably healthy or have not developed complicated clinical conditions. These at-risk groups may be those who benefit the most from supplementation of nutrients that have demonstrated roles in normal physiological or biochemical functions. That is, in the body of the metaphorical "health river," supplementation focuses more upstream by delaying the onset of disease, and medicine fulfills downstream efforts.

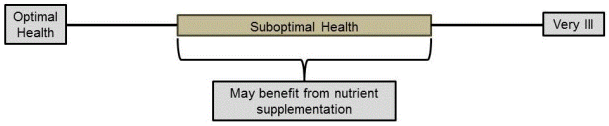

Figure 1: Continuous health spectrum.

Note: Dietary supplements are complementary to, not substitutes for, healthy eating and living.

In our opinion, the best opportunity for micronutrient supplements towards wellness derives from careful consideration of what "gaps" need to be filled.

A conceptual framework we propose is to consider dietary supplementation along the continuum of health: individuals likely to benefit the most from supplementation are those in the middle of the continuum whose health and nutritional status is suboptimal.

This proposed conceptual framework may serve as a model for finding answers to nutrient-chronic disease questions rather than providing answers itself.

In summary, we should not apply "one-size-fits-all" thinking to the whole supplement category. We need to distinguish between effective and ineffective supplementation. A key principle that must govern the contributions of dietary supplements to public health is that they are, indeed, supplements to, not substitutes for, healthy eating. This has 2 implications. First, it is misguided for supplements to be marketed by sellers or mistaken by buyers as a panacea or silver bullet for curing all that ails us. Their intended role is supportive of health, generally or specifically, in combination with fundamental diet and lifestyle elements. Second, in our opinion, the best opportunity for micronutrient supplements towards wellness derives from careful consideration of what "gaps" need to be filled. A conceptual framework we propose is to consider dietary supplementation along the continuum of health: individuals likely to benefit the most from supplementation are those in the middle of the continuum whose health and nutritional status is suboptimal. This proposed conceptual framework may serve as a model for finding answers to nutrient-chronic disease questions rather than providing answers itself. Integration of dietary supplementation safely and effectively into personalized nutrition demands a holistic and balanced view of wellness. We, as nutrition scientists, need to rethink the traditional single-nutrient approach to nutrition research as an interdisciplinary framework that considers the hierarchical etiology of complex health problems [11].

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All authors have contributed substantially to the concept, the drafting and revision of the manuscript. All authors have read and approved the manuscript.

Conflict of Interest

Dr. David Katz functions as an independent advisor to select supplement companies and chairs the scientific advisory board of the Nature's Bounty Co. Dr. Hua Kern is an employee of the Nature's Bounty Co.

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