

Dietary and Nutritional Influences on Allergy Prevention

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Abstract

Purpose of Review Nutritional status has a profound effect on immune function, and vitamin D, omega-3 fats, and other nutrients have long been suspected of influencing the development of the allergic march, and the incidence and severity of allergic conditions. This review provides an overview of research and opinion published during the past decade and summarizes clinically actionable information about dietary and nutritional influences on allergy prevention.

Recent Findings There is now enough evidence of effects of vitamin D, omega-3 fats, the Mediterranean diet, and antioxidants to recommend their use in routine clinical practice for prevention and treatment of allergic conditions.

Summary Uncertain areas remain, especially in methods to best identify persons with specific nutritional deficiencies, and in determining optimal target levels for all essential nutrients. The potential gain in individual quality of life, especially by asthma reduction, makes achieving good nutrition a key goal for every clinician.

Introduction

The immune system matures with antigen exposure, good nutrition, and the influence of a healthy microbiome. Disturbance in any of these is a potential reason to develop allergy, and an especially attractive

intervention is to influence maternal nutrition [1••]. It has recently been recognized that nutritional deficiencies still exist in the twenty-first century. For example, vitamin D deficiency is found in almost all populations [2]. As a

result, there are several questions clinicians must now consider. How does knowledge of possible nutrient deficiency in specific patients translate to treatment? How good is the evidence for preventing allergy with specific nutrients, and at what age(s) to intervene? Should some, or all, allergy patients be tested for nutritional status? And, if deficient, should pregnant mothers, children, or

other adults receive only nutritional information and diet recommendations, or, be given supplements?

This review surveys both research and expert opinion published during the past decade, to give clinicians both a condensed overview of the current evidence, and a summary of clinically actionable information. This topic is divided into nine sections based on nutrient types.

Antioxidants and flavonoids

Allergic animal models show definite effects of antioxidants. In mice, oxidants released by pollen exposure cause DNA damage, which then triggers allergic inflammation [3]. In rats, Chinese herb flavonoids reduce both immediate and delayed asthma symptoms and decrease allergic mediators [4]. Reviews of food antioxidants and their immunologic actions [5], flavonoid effects on allergies [6], and vitamin E effects on health [7] have been published.

In adults, antioxidant supplements of vitamins A, C, and E were linked, in a large aging study, to higher FEV1 levels in asthmatics [8]. A large birth cohort of children, whose total antioxidant capacity (TAC) was estimated from diets, was reevaluated in 10 years, and changes in allergic diseases evaluated [9]. TAC correlated inversely with both allergic sensitization and allergic asthma, implying that beginning an antioxidant-rich diet in childhood may prevent young adult asthma. One other, large, carefully controlled adult study did serum antioxidant testing 8 years prior to assessing new asthma cases, and found that normal alpha-tocopherol levels were associated with decreased asthma risk [10]. In a Korean birth cohort [11], more consumption of fruits and vegetables (higher TAC) in pregnancy was protective against infant respiratory infections, but protection level varied with genetic variation. The absorption of polyphenol antioxidants [12], and also proanthocyanidins acting as prebiotics (see below) [13], vary because of alterations in the gut microbiome. Finally, the specific form of an antioxidant may produce different responses in allergic patients, leading to inconsistent literature findings. This was found for vitamin E, which is protective against asthma as the alpha-tocopherol isoform, but increases asthma as the gamma isoform [14].

Diet type and individual food groups

A large number of studies have been done of Mediterranean (Med) diet health effects [15], and evidence is very strong that overall health and mortality is improved by adopting a Med diet. For children, evidence also suggests allergy protection from a Med diet and unfavorable outcomes from a Western diet [16]. The strongest evidence for an allergy-preventative effect of the Med diet is from a 2017 systematic review that found 12 of 15 studies in children protective, with overall high study quality [17•]. A 2016 review of reviews also found good-quality evidence for Med diet asthma benefits [18]. Japanese, vegetarian, and other diets for allergy prevention have shown no clear associations [1••], nor have specific foods, except for fish (see below), vegetables, fruit, sweetened

drinks, and meat. A 2014 systematic review showed that neither fruit nor vegetable consumption during pregnancy affected infant allergic outcomes, but both reduced childhood and adult asthma [19]. Dose-related higher fruit consumption also prevented new asthma and rhinitis over 4 years, in 520 primary school children [20]. Fruit protection was also seen in a review of reviews [19]. In contrast, the 2013 US Behavioral Risk Factor Surveillance System data found higher consumption of sugar-sweetened drinks correlated with increased adult asthma risk [21]. Artificial sweetener use in pregnancy is also associated with asthma and AR up to age 7 [22]. And, results from two prospective birth cohorts showed higher consumption of red or processed meat during pregnancy correlated with childhood wheezing in the first year of life [23]. A new trial of the Med diet in pregnancy is being planned [24].

Fish, fish oil, and omega-3 fatty acids

Observation studies have often suggested an allergy-preventative effect of fish or fish oil in maternal diets or during lactation [1••]. However, a 2017 meta-analysis found no evidence to support allergy prevention by maternal fish consumption, except in the subgroup of preschool children without a family history of asthma [25]. A second 2017 meta-analysis reviewed both prenatal and infant fish use and found significant reductions with infant fish use, in both eczema and allergic rhinitis (AR) [26]. A 2018 systematic review of breast milk fatty acid content and allergy outcomes found insufficient evidence for an effect [27]. However, the 2018 meta-analysis of Papamichael [28] shows fish consumed in early childhood both ameliorates asthma symptoms and reduces asthma incidence. Also, a large Icelandic birth cohort displayed dose-dependent decrease in food sensitization with fish oil supplementation between birth and age 2.5 years [29], and a large Swedish birth cohort showed AR protection at age 12 years, from eating fish at age 12 months [30].

Omega-3 fat supplementation studies are mostly positive. Adding omega-3 fats to infant formula significantly reduced allergy incidence and delayed allergy onset in 72 children by age 4 [31]. Two supplementation studies during pregnancy were also positive: when 533 mothers took 2.7 g of fish oil daily, asthma prescriptions for their children were significantly reduced 24 years later [32], and when another 736 mothers took 2.4 g of fish oil daily, their children had a 30% reduction in persistent wheezing or asthma and also reduced childhood respiratory infections [33]. These supplement doses are about 10–20 times the normal daily omega-3 intakes in Western countries, and supplementation effects were best in children of mothers with the lowest omega-3 blood levels. Protection was robust: the number to treat to prevent one asthma case was only 5.6 in the low omega-3 group and 14.6 overall [33]. On the other hand, a similar study in Australia of children from mothers supplemented with low dose, 900 mg, omega-3 fats, without determining maternal omega-3 status, showed no protection [34]. And an American study of 84 children of depressed mothers, supplemented during pregnancy with low dose, 1.1 to 1.3 g, omega-3 fats, without determining maternal omega-3 status, showed increased eczema but no other effects on allergies [35]. In contrast, drinking unprocessed farm milk, in 943 rural European children, significantly protected from allergies at age 6, due to substantially higher levels of omega-3 fats in farm milk, compared with commercial milk

[36]. Finally, a small, well-controlled study of adult asthmatics showed that 3 weeks of supplementation with fish oil, at doses of 3.2 to 6.1 g/day significantly reduced the fall in FEV1 from bronchial challenge, and also reduced exhaled nitric oxide levels by 25% [37]. Negative results in some omega-3 studies are believed to result from genetic differences in polyunsaturated fat metabolism, or because mothers and/or children were already omega-3 replete.

Minerals

Estimates of insufficient dietary magnesium (Mg) intake range as high as two thirds of people in Western nations [38]. Essential for many metabolic processes, Mg is useful for acute asthma treatment [39] and may also be useful as a part of asthma maintenance and preventive therapy, because cellular Mg levels are correlated with FEV1 and FVC, and low levels cause bronchospasm and asthma exacerbations [40].

There have been some studies of other minerals for allergy prevention. One hundred six Chinese adults with AR had higher copper (Cu) and lower zinc (Zn) and selenium (Se) levels than matched controls [41]. Low Se, correctable by supplements, was also found in asthmatic children [42]. In a large study, low Se in pregnancy, or in cord blood, was linked with wheezing at age 2 [43]. In over 2000 mother/child pairs, analysis of umbilical cord tissue for trace minerals showed correlations to childhood asthma only for low Se and iron (Fe) [44]. On follow-up [45], genetic analysis showed that at age 7, only those children with a homozygous SNP of the GPX4 Se-glutathione peroxidase gene and a Se-deficient mother had increased asthma risk. Infant food allergy patients have low Se and Zn intakes, and cellular and serum levels of Se-glutathione peroxidase and Zn-superoxide dismutase are correspondingly low, compared with healthy controls [46]. Low maternal Zn intake during pregnancy was also associated with recurrent wheezing at age 2 in 1290 infant/mother pairs [47] and with current or past asthma at age 5 in 1120 infant/mother pairs [48]. A linear relationship between higher maternal Cu and eczema, wheeze, and any allergy at age 1 was found for 300 mother/infant pairs [49]. Finally, low maternal Fe levels correlated with increased wheeze, decreased FEV1, and atopic sensitization at age 10 in 157 infant/mother pairs [50], and with childhood wheeze in a large mother/child study [44]. In the same study, manganese, lead, and mercury were not correlated with allergies [44]. Magnesium (Mg) is the only mineral for which there is enough current evidence to consider preventative or therapeutic use in asthma, but abnormal Cu/Zn balance, or low levels of Se, Fe, and manganese need further research.

Prebiotics

Microbiome assessment advances enabled studies linking food allergies, AR, eczema, and asthma to gut microbiome alterations [51, 52] that potentially can be prevented by use of probiotics [53] or other biome-altering treatments, such as prebiotics or antibiotic avoidance [54, 55]. A large study compared microbiome diversity and specific bacterial species with presence of AR, asthma, eczema, and allergy to specific foods, insects, and drugs. Low biodiversity and specific bacteria were correlated with allergies, with peanut allergy showing the

strongest results [56]. Probiotics are beyond the scope of this review; however, prebiotics [57, 58] are included.

Prebiotics quickly affect microbiome composition: a trial of prebiotic supplemented formula versus regular formula-fed and breast-fed infants showed that 6 weeks of prebiotics increased beneficial *Bifidobacteria* and reduced detrimental *Clostridia difficile* to breast-fed levels [59]. A cross-over study of adult asthmatics showed that 3 weeks of supplementation with galacto-oligosaccharides significantly reduced the fall in FEV1 from bronchial challenge [60]. Several animal models show suppression of AR, asthma, and food allergies from prebiotic use [61–64], and similar results were seen in two human in vitro food allergy studies [65, 66]. A 2017 systematic review of infant prebiotic use found a strong trend of improvement in eczema, asthma, and food allergy [67]. Based on these studies, the World Allergy Organization guidelines were updated in 2016 to recommend prebiotic supplementation for all not exclusively breastfed infants [68].

Peptides and amino acids

Some intriguing studies have evaluated the role of amino acids or peptides in allergy prevention. Molecular screening of multiple probiotic species identified a bacterial cell wall component, D-tryptophan, that increases gut microbiome diversity, increases regulatory T cells (Treg), decreases Th2 inflammation, and decreases asthma in mice [69], while 5-hydroxytryptophan also greatly inhibits asthmatic inflammation and impairs leukocyte recruitment [70]. In humans, a 6-month trial of L-isoleucine supplementation, at twice the recommended dietary allowance (RDA), produced visible eczema improvement, decreased SCORAD [71] scores in half, and reduced itching in all of 19 older children [72].

Peptides derived from allergenic proteins are currently under intensive investigation as preventive agents (reviewed in 2018) [73•]. For example, positive results for cow's milk allergy, in mice, were found with oral beta-lactoglobulin peptides adsorbed to poly(lactic-co-glycolic acid) nanoparticles [74]. Glycomacropeptide, a normal milk component, has oral antiallergic activity in animal models of asthma, anaphylaxis, and eczema, where it reduces mast cell activation and excess Th2 activity, and favors growth of beneficial gut bacteria [75]. N-acetylcysteine (NAC), an antioxidant peptide mucolytic, was evaluated in asthmatic adults and normal controls, assessed by methacholine challenge. During a crossover study of inhaled clean air, diesel exhaust in air, and diesel exhaust plus oral NAC treatment, NAC reduced baseline methacholine hyper-reactivity by 20% and prevented the 42% drop in FEV1 that was triggered in asthmatics by breathing diesel particles [76]. In 2018, a pilot study of grass buildup immunotherapy, using ryegrass pollen peptides, was successful [77]. NAC is currently the only peptide used therapeutically, but if the promise of tolerizing or immunizing peptides is realized, they could potentially reverse the worldwide increase of allergic diseases.

Fat-soluble vitamins

Vitamins A, E, D, and probably vitamin K are essential for immune function, and their individual dietary intakes can vary widely, so all are potentially

important in allergy prevention. Vitamin D is discussed separately below, and some studies of vitamin E were discussed above. In infant mice, development of allergic tolerance is delayed by maternal vitamin A deficiency, and the abnormal antigen transport across the gut barrier, and inefficient Th1 cell activation, is corrected by vitamin A [78]. A 2018 systematic review of vitamin A animal studies concluded that vitamin A stabilizes eosinophils and mast cells, induces tolerogenic dendritic cells, and upregulates Treg cells during allergic sensitization, which predicts a favorable effect in human allergy [79]. However, single high-dose vitamin A supplements, given to vitamin A-deficient infants during a vaccination program, were associated with increased allergy and wheeze later in childhood [80], while a large Danish aging study found only a weak relationship between low maternal vitamin A intake and AR [81].

Low maternal vitamin E does correlate with childhood AR [81]. But, much vitamin E literature is conflicting. In a thorough 2016 review, Strait and Camargo pointed out that animal studies and a few human intervention studies of vitamin E agree that the alpha-tocopherol isoform modulates the Th1/Th2 balance and decreases lung inflammation after challenge [82]. The gamma-tocopherol isoform has opposing effects [14], so older studies, where the proportions of vitamin E isoforms were not measured, are questionable. Alpha-tocopherol also regulates neonatal dendritic cells in an antiallergic direction [83]. A thorough study of 1748 children, whose mother's pregnancy vitamin D and vitamin E (alpha-tocopherol) levels were determined, showed low levels of both vitamins increased asthma risk over the children's first decade [84]. In adults, both allergic and not, use of vitamin A, C, and E supplements were linked to higher FEV1 levels [8]. Finally, in a review of reviews, vitamin E was found to be protective [19].

A possible enhancing effect of high vitamin K levels on asthma risk was identified in a Danish longitudinal study [81]. The only other information on vitamin K and allergy is a mouse model of allergic pulmonary Aspergillosis that found Gas6, a vitamin K-dependent gene, regulates the degree of allergic inflammation [85]. In their 2013 review, Han et al. felt that there was enough evidence for possible benefits of both vitamins D and E on asthma to warrant further research [86].

Water-soluble vitamins

Relatively few studies have been done of either vitamin C or the B vitamins as potential allergy preventative agents. Folic acid may be at supraphysiologic levels, due to availability of supplements and fortified foods, whereas other water-soluble vitamins may be deficient because of low fresh fruit and vegetable consumption and because of genetic variation in specific transporter genes [87]. Folate is capable of altering epigenetic gene expression by methylation, and in some animal studies, increases offspring allergies. A 2017 review of folate's effects on human allergies found mixed results [88]. A 2015 structured review found no risk of increased allergies from maternal folate supplementation during pregnancy, except for supplements early in pregnancy, which increased early childhood wheezing risk, and when mothers had the TT genotype of the MTHFR C677T polymorphism that impairs folate metabolism, where children had high risk of asthma [89]. A very large American cohort study found a

slightly increased risk of asthma at age 6 in children of mothers who had filled folate prescriptions during pregnancy [90]. Conversely, high folate levels in 858 American infants, whose mother's plasma levels were measured in the second and third trimesters, were correlated with decreased wheezing at age 3 [91]. Vitamins B6, B12, C, several amino acids, and choline also participate in methyl transfer pathways and could have effects like folate. Limited data shows that choline has an anti-inflammatory effect in both mice and humans [86], and vitamins B6 and B12 have not been studied.

Human vitamin C data is mixed, although animal models show decreased airway reactivity and decreased peribronchial inflammation with adequate vitamin C levels [86]. Vitamin C should have antiallergic activity, based on known immune functions of enhancing B and T cell differentiation and proliferation, and because adequate levels improve the response to the infections that often complicate asthma, AR, and eczema [92]. However, only one of three systematic reviews of human vitamin C studies, between 2009 and 2011, showed benefit in asthma [86]. In adults, both allergic and not, vitamin C supplement use correlates with higher FEV1 levels [8], and in both chronic obstructive pulmonary disease (COPD) patients and controls, increased vitamin C intake correlates with better lung function and lower risk of developing COPD [93]. In 300 pregnant women, vitamin C intake was inversely correlated with infant wheezing and food allergies [49]. A treatment trial of intravenous vitamin C in 71 allergic adults found that vitamin C deficiency was present and that supplementation improved allergic symptoms [94]. Vitamin C supplements, 500 mg daily, in pregnant women who could not stop smoking resulted in infants with markedly decreased abnormal DNA methylation, improved lung function, and decreased wheezing at 1 year, compared with no supplement [95, 96]. A 2014 review of reviews found that there was high-quality evidence for protective effects of vitamin C against asthma [19].

Vitamin D

In 2013, about 400 papers had been published about vitamin D and allergy [2], and in 2018, that number has more than doubled. Vitamin D has gene regulatory functions in every cell and affects immune system balance: antigen tolerance versus allergic inflammation and Th1-Th2 bias. In humans, low vitamin D correlates with increased risk for autoimmunity, infections, asthma, and food allergies, as well as major chronic diseases. Some reports indicate that vitamin D could help treat steroid-resistant asthma, prevent steroid-induced bone loss, improve immunotherapy results, decrease infections, and inhibit lung remodeling. However, there is lack of certainty because there have not been enough large vitamin D supplementation studies with pretreatment vitamin D level determinations. Also uncertain is the extent of vitamin D deficiency or insufficiency in various populations. Estimates range from as high as the majority of people in temperate zone nations to only about 25%, and because most people now live primarily indoors, even tropical areas have high deficiency rates [2]. The major transported vitamin D metabolite is calcidiol, 25-hydroxy vitamin D3, which is measured to assess vitamin D status. There is disagreement on optimal serum calcidiol levels, but frequently accepted values are < 30 nmol/L for deficiency and < 50–72.5 nmol/L for insufficiency. There are a number of

reports suggesting levels of 100 nmol/L or more may be better for optimal health, and reasons for this are discussed by Holick [97••].

A 2018 systematic review of vitamin D animal studies concluded that vitamin D stabilizes eosinophils and mast cells, induces tolerogenic dendritic cells, and upregulates Treg cells during allergic sensitization, all of which predict favorable effects in human allergy [79]. Another 2018 review of vitamin D in food allergy protection concluded that multiple immune pathways are affected by vitamin D levels and by an individual's genetics and microbiome [98]. In a mouse food allergy model, maternal and early life vitamin D deficiency increased symptoms, raised specific IgE, decreased Treg cells, decreased intestinal epithelial tight junctions, and induced intestinal barrier dysfunction [99]. Another mouse model of pollution-induced asthma found that adequate vitamin D levels (prenatal and postnatal) protected against asthma, but that vitamin D treatment after exposure had no benefit [100]. In human blood mononuclear cells, studied in vitro, from vitamin D insufficient (< 50 nmol/L) healthy adults before and after vitamin D supplementation, it was necessary to supplement calcidiol levels to > 100 nmol/L to achieve optimal innate immune function [101]. A well-controlled trial of vitamin D supplementation, 1000 IU, in children with AR improved symptoms and reduced exhaled nitric oxide concentrations [102], and, when 277 infants were randomized to 400 IU vitamin D vs placebo, they developed less recurrent wheezing by 1 year [103]. In a birth cohort study, persistent vitamin D deficiency over the first 5 years correlated with increased eosinophils, higher total IgE, and higher mite-specific IgE [104]. Finally, one of the most instructive reports of 2018 is a Turkish study of natural seasonal vitamin D variation in 30 7–17-year-old asthmatics studied every 3 months with asthma control tests (ACTs), lung function tests, and immune function tests [105•]. Vitamin D was lowest in winter and highest in summer, and high levels correlated well with ACT showing good control, high FEV1, and high Treg cell counts, and inversely correlated with high total IgE, high interleukin-4 levels, and poor bronchodilator responses.

In 2018, Abreo et al. reviewed 32 prior meta-analyses of major risk factors for childhood asthma and identified prenatal vitamin D status as the only nutritional risk with both substantial evidence and large impact [106••]. However, two other reviews in 2018 [107, 108] found insufficient evidence for a vitamin D effect on allergic diseases, although a strong reduction of respiratory infections and an improvement in lung function was identified. One cause of negative reviews has been small numbers of study enrollees, leading to nonsignificance. Recently, Wolsk, Chawes, and colleagues combined and reanalyzed two independent vitamin D supplementation trials with 2800–4400 IU during pregnancy, totaling 1287 mother/child pairs [109•]. The combined results were highly significant: an overall 26% asthma reduction and 46% reduction in children of mothers whose entry vitamin D level was < 75 nmol/L. There are four important points from this study. First, vitamin D supplementation protects better with lower maternal vitamin D levels but still has benefit for children whose mothers already have vitamin D levels far above the accepted minimum of 30 nmol/L. Second, the desirable level of vitamin D for asthma protection is not the same but is *much* higher than the level that adequately protects bone calcium levels. Third, the critical time for maximum vitamin D effects on embryos is not, as previously believed, the third trimester lung growth period, but at the earliest stage of first

trimester lung budding, and continues throughout pregnancy into infancy. In many earlier studies, supplements were not given until late in pregnancy or only in childhood, so prevention was not seen. Fourth, the optimum maternal blood level of vitamin D for fetal lung development appears to be much higher than previously thought, and could be as high as 100–150 nmol/L. Achieving this vitamin D level, in some mothers, will require higher daily supplement doses than these studies used. Finally, the asthma preventative effect of vitamin D is just one reason to supplement pregnant mothers, but there are other important reasons, such as prevention of preeclampsia, preterm labor, and other pregnancy complications, a topic recently reviewed [109•, 110]. The blood calcidiol levels required to prevent these pregnancy complications are similarly high, > 100 nmol/L [110].

Based on this current evidence, vitamin D supplementation of 4000 IU daily, or more, beginning prior to embryogenesis, and raising the mother's calcidiol level to at least 100 nmol/L, is desirable [110]. The Endocrine Society currently recommends up to 2000 IU vitamin D daily in pregnancy, up to 4000 IU for any adult, and up to 10,000 IU for correction of known deficiency, but this guideline is from 2011, before the research discussed above was reported [111]. Daily vitamin D supplements up to 10,000 IU have a wide safety margin, but because of substantial person-to-person variability in calcidiol levels produced by a given supplement dose, particularly in people with gastrointestinal inflammation or obesity, in order to achieve a specified vitamin D level, calcidiol levels must be measured during treatment [2]. A recent 1-year study of vitamin D supplementation with a target blood level of 100 nmol/L, at daily doses up to 15,000 IU in 3882 adults enrolled in a community-based wellness program, monitored for hypercalcemia and hypercalciuria, and found none [112]. Review of vitamin D toxicity studies in other mammals, and in accidental human overdoses, shows that calcidiol levels < 750 nmol/L do not cause toxicity [113], and < 250 nmol/L was suggested as a conservative upper dose range, to ensure a wide clinical safety margin.

Conclusion and clinical relevance

There is adequate evidence that essential nutrient deficiency in pregnancy and childhood can affect the probability of developing asthma and other allergic diseases, and also affects symptom severity. Because some nutrients, like folate, cause epigenetic modifications, and others, like vitamin D, have roles in early development, early nutrition has life-long consequences. In other cases, such as antioxidant vitamins and minerals, whether or not a particular nutrient intake is sufficient or not depends on the environmental load of pollutants and inflammatory burden to which each person is exposed. Our clinical goal should be to ensure both optimal nutrition for women at the start of pregnancy, and also optimal nutrition for all allergy patients throughout their lives (Table 1).

Unfortunately, we lack absolute proof of a protective effect of most nutrients, because of shortcomings in many studies. The clinician is thus in a dilemma between doing nothing because of insufficient evidence, and choosing to make diet recommendations or suggest supplements, when exact details are

Table 1. Nutrition in allergy prevention clinical goal and action plan

Clinical goal

Optimal nutrition for:

1. Women at the start of pregnancy
2. Allergy patients at any age

Clinical action plan

For every patient:

1. *Assess* nutrition by history and food diary
2. *Test* for nutritional deficiencies suggested by history
3. *Correct* deficiencies with diet changes and/or supplements to minimum of 100% of RDA intakes
4. *Confirm* nutrient repletion by interval repeat testing

uncertain, but the balance of evidence favors action (Table 2). The safest current strategy is to assess the nutritional status of each patient by history and food diary, to test for selected nutritional deficiencies suggested by history, and to correct identified deficiencies with diet changes and/or supplements. The conservative minimum target for nutritional remediation is ensuring intake of the nutrient RDA levels found in the list of dietary reference intakes produced every 5 years by the US Government [114], by the European Food Safety Authority [115], and in specialty society guidelines.

Mediterranean diet

The Med diet is recommended as one of three healthy eating patterns by the 2015 US Government dietary guidelines [116]. The Med diet is a good source of bioflavonoids, prebiotics, most antioxidants, and omega-3 fats, and the nutrient content meets all RDAs, except for vitamin D and calcium. Castiglione et al.

Table 2. Nutrients with balance of evidence favoring allergy prevention

1. Mediterranean diet
2. Antioxidants
 - Vitamin A
 - Vitamins B: especially folate, B12
 - Vitamin C
 - Vitamin E: alpha-tocopherol
 - Minerals: Fe, Mg, Zn, Cu, Se
3. Omega-3 fatty acids
4. Vitamin D

independently calculated Med diet nutrient content and found less vitamin D, vitamin E, folate, calcium, and potassium than in European RDAs [117]. Consequently, when the Med diet is recommended for allergy patients, supplements should also be advised.

Minerals

There are no guidelines, other than RDAs, for mineral supplementation. Most mineral deficiencies are identified only by specific tests. Deficient Fe intake occurs in developed nations at rates from 1 to 22% in different groups, more commonly in women [118]. Fe supplements are suggested for all infants [119], and anemia detection triggers Fe status review in others. Magnesium deficiency is almost universal [39], and because Mg repletion benefits asthma, Mg levels should be checked in all asthmatics. Deficient Zn intake occurs in 3–39% of adults, more often in men [118]. Selenium status varies widely, depending on diet choices and local soil levels [120]. When there is significant pollution exposure, or chemical sensitivity symptoms, or poor allergy control, it makes sense to assess Cu, Zn, and Se, in addition to Mg and antioxidant vitamins A, C, and E.

Fat-soluble vitamins

Except in pregnancy, most Americans are vitamin A replete [121]. The World Health Organization 2011 vitamin A guidelines address pregnancy [122]. Because high levels of vitamin A are teratogenic in early pregnancy, supplements are limited, even in known deficiency, to <25,000 IU single doses and <10,000 IU for daily supplements. Over 90% of Americans do not consume their RDA of vitamin E as the effective alpha-tocopherol isoform [123], which makes most allergy patients susceptible to oxidative injury and symptom worsening. Therefore, allergy patients should take an alpha-tocopherol supplement. There is insufficient information about vitamin K to recommend testing or treatment.

Water-soluble vitamins

Vitamin B deficiencies are not rare: a survey of UK women of reproductive age found deficiencies of B12 in >12% and folate in >6% [124]. The Society of Obstetricians and Gynaecologists of Canada 2015 guidelines [125] recommend a nonprescription multivitamin/multimineral containing 0.4–0.6 mg of folic acid for all women who could become pregnant, plus higher dose folate supplements for women with increased risks of having infants with neural tube defects. Folate testing guidelines for children, men, and women not of reproductive age are available [126]. Other adult vitamin B requirements can usually be met by a multivitamin supplement; however, some cases of vitamin B12 deficiency require high dose supplements [127]. Vitamin C deficiency occurs in >7% of US adults [128] and also occurs in children, especially when on allergy avoidance diets [129]. Higher doses of vitamin C than are found in multivitamins may be needed when antioxidant requirements are high.

Vitamin D

Vitamin D deficiency is very prevalent, reaching 80% in some populations [130]. Since 2011, the Endocrine Society has recommended calcidiol testing of anyone suspected of vitamin D deficiency [111]. In 2018, a consensus guideline by Italian pediatricians recommended vitamin D supplementation for all infants in the first year of life, independent of feeding method. After age 1, supplement when there are risk factors for vitamin D deficiency [131]. Also, in 2018, the Polish Society of Pediatric Endocrinology recommended vitamin D supplementation for all groups at risk of vitamin D deficiency, especially women planning pregnancy, pregnant and lactating women, and preterm babies [132]. Based on recent research, all allergy patients should have vitamin D levels determined, and be supplemented to levels above those necessary for bone health.

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Compliance with Ethical Standards

Conflict of Interest

Bruce R. Gordon declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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