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Diet and asthma: an update

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Abstract

Purpose of review—Our objective is to provide an overview and discussion of recent experimental studies, epidemiologic studies, and clinical trials of diet and asthma. We focus on dietary sources and vitamins with antioxidant properties (vitamins (A, C, and E), folate, and omega-3 and omega-6 polyunsaturated fatty acids (n-3 and n-6 PUFAs).

Recent findings—Current evidence does not support the use of vitamin A, vitamin C, vitamin E or PUFAs for the prevention or treatment of asthma or allergies. Current guidelines for prenatal use of folate to prevent neural tube defects should be followed, as there is no evidence of major effects of this practice on asthma or allergies. Consumption of a balanced diet that is rich in sources of antioxidants (e.g. fruits and vegetables) may be beneficial in the primary prevention of asthma.

Summary—None of the vitamins or nutrients examined is consistently associated with asthma or allergies. In some cases, further studies of the effects of a vitamin or nutrient on specific asthma phenotypes (e.g. vitamin C to prevent viral-induced exacerbations) are warranted. Clinical trials of "whole diet" interventions to prevent asthma are advisable on the basis of existing evidence.

Keywords

asthma; diet; vitamin A; vitamin C; vitamin E; folate; omega-3 polyunsaturated fatty acids

INTRODUCTION

Asthma is a complex and heterogeneous syndrome, likely affected by multiple genetic and environmental or lifestyle factors, including dietary intake. Over the last few decades, changes in dietary patterns may have contributed to the worldwide "asthma epidemic".

Current evidence suggests that a "Mediterranean diet" (rich in fruits and vegetables, and low in refined grains and saturated fat) protects against the development of asthma or asthma

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symptoms, but that a “Western” diet (low in fruits and vegetables, and high in refined grains and saturated fat) increases the risk of asthma (1, 2). Consistent with mediation of the detrimental effects of a “Western” diet through increased systemic inflammation, a `dietary inflammatory index' (DII) was recently associated with asthma, reduced lung function and increased IL-6 plasma level in a case-control study of adults(3). Moreover, murine models have demonstrated that a high-fat diet leads to airway hyper-reactivity (AHR) through a pro-inflammatory cytokine (interleukin (IL)-17A)(4), and that a low-fiber diet worsens allergic airway inflammation (5).

In this review, we examine recent findings for asthma and dietary factors not covered elsewhere in this issue: diet-derived antioxidants, vitamins with antioxidant properties (vitamin A, C, and E), nutrients acting as methyl donors (folate), and essential fatty acids (omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs)).

Diet-derived antioxidants

An imbalance between reactive oxygen species (ROS) and antioxidants results in oxidative stress, which may exacerbate asthma by increasing airway and systematic inflammation, down-regulating T-helper (Th)1 immune responses, and increasing Th2 (pro-allergic) immune responses (6).

Findings from a recent meta-analysis of observational studies suggest that dietary intake of vitamins with antioxidant properties protect against asthma or wheeze (a key asthma symptom) in childhood or adulthood (7). In a combined meta-analysis of 18 to 23 studies including children and adults, a high dietary intake of fruits and a high dietary intake of vegetables were significantly associated with 16% and 12% reductions in the risk of asthma, respectively. In a meta-analysis of 4 studies with available data, high intake of both fruits and vegetables was associated with a 36% reduction in the risk of asthma (7).

Vitamin A

Provitamin A carotenoids and retinol are two major dietary sources of vitamin A. Orange-yellow fruits and vegetables are abundant in carotenoids (α-carotene, β-carotene, and β-cryptoxanthins), with whole milk, liver, eggs and fortified foods serving as major sources for retinol.

In murine models, pre-natal deficiency of vitamin A or retinoic acid (a bioactive metabolite of vitamin A) leads to abnormal accumulation of airway smooth muscle and AHR in adulthood (8), and fenretinide (a semisynthetic analog of vitamin A) inhibits expression of IL-1β and IL-6 (9). Moreover, treatment of sensitized mice with fenretinide (60mg/kg/day) prevents ovalbumin (OVA)-induced changes in arachidonic acid metabolism, oxidative stress, AHR and inflammation in the lungs(10). Consistent with potential anti-inflammatory effects of vitamin A or vitamin A sources, increased levels of carotenoids (11) or β-carotene (12) in serum have been associated with reduced levels of markers of systemic inflammation (such as C-reactive protein (CRP) and IL-6) in humans.

In spite of experimental evidence for airway inflammation and human findings for systemic inflammation, recent studies fail to resolve prior conflicting and insufficient evidence of an

effect of vitamin A on asthma in children or adults (1). In the Danish National Birth Cohort study of 44,594 mother-child pairs, there was no association between maternal intake of vitamin A and E during pregnancy and asthma or allergic rhinitis during the first 7 year of life (13). Of note, this study was limited by non-measurement of serum vitamin A, and maternal dietary intake was assessed by a one-time self-report dietary food frequency questionnaire (FFQ) in the second trimester of pregnancy. In a randomized controlled trial of vitamin A supplementation in early life to prevent childhood atopy, there was no significant effect up to age 7 years (14). However, this trial only included 274 children (and thus had limited statistical power) and employed a non-sustained intervention (1–2 doses of vitamin A).

Vitamin C

Vitamin C (ascorbic acid), a potent water-soluble antioxidant found in various fruits and vegetables, has known anti-inflammatory properties and thus is of interest in asthma. In a mouse model, intranasal treatment with vitamin C (alone or in combination with choline chloride (ChCl) and selenium) decreased oxidative stress, AHR, airway inflammation, IL-4 and IL-5, IgE, and NF-κB. Moreover, vitamin C reduced serum levels of IL-10 (an immune-regulatory cytokine that attenuates Th2 responses). In this model, the combination of vitamin C with both ChCl and selenium had the strongest effect against allergic airway disease (15).

Recent studies of vitamin C have focused on potential benefits in subjects with established asthma. A systematic review of three studies (including two randomized controlled trials) in 79 subjects with asthma found suggestive but inconclusive evidence for protective effects of vitamin C against disease exacerbations or AHR induced by a common cold (16). Similarly, a Cochrane review of 11 randomized controlled trials including 419 children and adults with asthma concluded that there is insufficient evidence to recommend vitamin C as a therapeutic agent in asthma (17). Although there was suggestive evidence of beneficial effects of vitamin C in exercise-induced bronchoconstriction, this was inconclusive due to small sample size.

In the only recent study of preventive effects of vitamin C against the development of asthma, vitamin C supplementation (500 mg/d) in 179 pregnant smokers led to improved pulmonary function and decreased risk of wheeze in their newborns, up to age 1 year (18). Given that most wheezing in early life is transient, it is unclear whether these findings are due to anti-viral effects or truly protective effects of vitamin C against asthma.

Vitamin E

Vitamin E, a potent antioxidant with lipo-peroxyl radical scavenging activities, refers to a group of lipid-soluble compounds that occur naturally in eight chemical forms (α, β, γ, and δ-tocopherol and α, β, γ, and δ-tocotrienol). Dietary sources of vitamin E include nuts, seeds, green vegetables, and vegetable oils (19).

Experimental evidence supports anti-inflammatory and antioxidant effects of vitamin E on airway inflammation or injury. In an OVA-sensitized rat model, single-walled carbon nanotubes (SWCNTs) induced exacerbations of allergic airway inflammation. Such

exacerbations were prevented by oral administration of vitamin E (100 mg/kg), an effect attributed to reduction of reactive oxygen species in lung tissue, down-regulated Th2 responses, and reduced production of IgG (20). In a separate rat model of endotoxin-induced lung injury, treatment with γ-tocopherol was shown to inhibit neutrophil-mediated lung injury and to induce expression of the regulatory cytokines IL-10 and IFN-γ (21).

Results of two large prospective cohort studies provide conflicting inconclusive evidence for a protective effect of vitamin E against the development of asthma or atopy in childhood. A birth cohort study of 1,924 British mother-child pairs showed that each standard deviation in maternal plasma α-tocopherol level at 11 weeks of gestation was associated with 48% reduced odds of medication use for asthma in 1,748 children followed to age 10 years (95% confidence interval [CI] for odds ratio [OR]=0.31 to 0.87) (22). Moreover, maternal intake of vitamin E during pregnancy was associated with 11% reduced odds of asthma in 934 children in whom questionnaire data was available at age 10 years (95% CI for OR=0.81 to 0.99). In contrast to findings from the birth cohort study, a multicenter European study found that serum concentration of α-tocopherol or γ-tocopherol at age 1 year was not significantly associated with asthma, wheeze or atopy by age 6 years (23). Conflicting findings from these two observational studies may be due to different degrees of selection bias due to differential loss of follow-up or, alternatively, to age-dependent immune modulatory effects of vitamin E (pre- vs. post-natal) (22) (23). A recent Cochrane review of five randomized controlled trials further suggests that additional high-quality research is needed to determine whether vitamin E protects against asthma, asthma morbidity or exercise-induced bronchoconstriction (24).

Conflicting findings for vitamin E and asthma may partly be due to opposing effects of the vitamin isoforms, as α- and γ-tocopherol seem to have anti- and pro-inflammatory properties, respectively (25). In support of this hypothesis, a nested case-control study of Chinese women (aged 40 to 70 years) found that a twofold increase of plasma α-tocopherol at baseline was associated with 48% decreased odds of asthma after 8 years of follow up (26). In contrast, there was no significant association between γ-tocopherol and incident asthma. Thus, it would be advisable to measure and analyze vitamin E isoforms separately in future studies of asthma.

Folate

Diet may cause asthma or allergies by affecting DNA methylation and, ultimately, expression of disease-susceptibility genes (27). DNA methylation is catalyzed by enzymes that transfer methyl groups from the methylating agent S-adenosylmethionone (SAM) to cytosine. Folate, vitamin B_{12} and choline are major dietary sources of methyl donors, which are essential to form SAM from homocysteine (28).

Because prenatal folic acid is broadly used, some questioned whether this practice is related to the “asthma epidemic”. This concern was heightened by murine models showing that high intake of methyl donors (including but not limited to folate) worsen allergic airway inflammation(29). However, the prevalence of asthma increased well before the widespread use of folate supplementation during pregnancy in industrialized countries, and a comprehensive review of observational studies published up to early 2013 concluded that

there is no evidence of a moderate or strong effect of prenatal folate on asthma(30). More recent systematic reviews or meta-analyses generally agree with this conclusion (31, 32), and a database-driven study yielded results that must be deemed inconclusive due to methodological shortcomings (33). Because of proven benefits of folate supplementation during pregnancy in preventing neural tube defects and the aggregate evidence of multiple observational studies of asthma, there is no justification for a randomized controlled trial of prenatal folate and asthma.

Little is known about the effects of folate (if any) on morbidity in subjects with established asthma or on asthma or atopy in adults (30). A recent study of adults with (n=35) and without (n=47) sensitization to mouse (nested within a cohort of laboratory workers) found that subjects who had serum folate levels in the highest tertile had 5.6-fold higher odds of mouse allergy than those whose serum folate levels were in the lowest tertile (95% CI for OR=1.8 to 31.3)(34). Longitudinal studies of adequate sample size are needed to examine whether folate affects atopy or asthma in adults, as well as disease morbidity in subjects with asthma.

Omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs)

Lipid-related mediators play various regulatory roles in chronic inflammation. Most lipid-related mediators of inflammation are metabolites derived from omega-3 (n-3) or omega-6 (n-6) polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA, 20:5n-3), docosahexaenoic acid (DHA, 22:6n-3), arachidonic acid (AA, 20:4n-6), and linoleic acid (LA, 18:2n-6) (35). Oily fish consumption and fish oil supplementation are the major dietary sources of n-3 PUFAs, and vegetable oils are the major dietary source of n-6 PUFAs.

N-3 PUFAs may be beneficial in preventing or treating chronic inflammatory diseases such as those of the cardiovascular system (36). Given this observation and potential effects of n-3PUFAs against allergic airway inflammation (37), there has been significant interest in studying whether n-3 or n-6 PUFAs influence the pathogenesis of asthma. To date, however, murine models have yielded conflicting results for fish oil supplementation and airway inflammation.

In OVA-sensitized rats with allergic airway inflammation, fish oil supplementation with 60 mg of EPA and 48 mg of DHA decreased nitrite concentration in bronchoalveolar lavage (BAL) and lipid hydroperoxide concentration in lung tissue, while also increasing glutathione peroxidase activity and superoxide dismutase activity in BAL. However, there was no effect on the bioactivity of a pro-inflammatory mediator (platelet-activating factor) in lung tissue (38). Further suggesting complex and divergent effects of the components of fish oil supplements on allergic airway inflammation, an experiment in OVA-sensitized mice showed that high dietary intake of DHA for 6 weeks leads to significantly increased eosinophils and IL-6 in BAL, and a trend for increased levels of IL-4 and IL-13 in BAL. In this model, mice fed both DHA and EPA had the lowest airway resistance, while those fed only DHA had the highest airway resistance (39).

Similar to rodent models, findings from human studies of PUFAs of fish oil supplementation have been inconsistent. In a systematic review and meta-analysis of observational studies,

fish consumption in early life was associated with a decreased incidence of asthma between ages 1 to 4 years (relative risk [RR] =0.76, 95% CI=0.61 to 0.94), and a high concentration of fatty acids in maternal expressed breast milk was associated with decreased risk of asthma between ages 4 and 7 years (RR=0.71, 95% CI=0.52 to 0.96). In contrast, dietary intake of fish or n-3 PUFAs was not significantly associated with incident asthma (40). Findings from the studies in children have to be cautiously interpreted due to inability to confidently diagnose asthma before age 6 years. In fact, two separate birth cohort studies showed no link between maternal dietary intake of n-3 or n-6 PUFAs (or their ratio) and wheeze or allergic disease before age 2.5 years (41, 42), and a third independent birth cohort study found no significant association between n-3 or n-6 PUFAs in cord blood and asthma, allergic rhinitis or eczema up to age 10 years (43). Findings from three recent randomized controlled trials provide further negative or inconclusive evidence for beneficial effects of n-3 PUFAs (as both EPA and DHA, or as DHA only) on the prevention (through prenatal administration) (44, 45) or treatment(46) of asthma or allergies in early childhood (up to age 3 years) (44, 45) or adulthood (46). Thus, it is not surprising that two recent systematic reviews concluded that there is insufficient evidence to recommend supplementation with fish oil or any fatty acid (including arachidonic acid) for the prevention or treatment of asthma or allergies (47, 48). Nonetheless, one of these reviews recommended additional well-designed randomized controlled trials of n-3 PUFAs to treat exercise-induced asthma, given suggestive but inconclusive evidence for beneficial effects on this particular asthma phenotype (48).

Conclusions and Future Directions

A summary of the current evidence and future directions for research on selected dietary nutrients and asthma is shown in Table 1. On the basis of current evidence, one cannot recommend use of vitamin A, vitamin C, vitamin E or PUFAs for the prevention or treatment of asthma or allergies. Moreover, there is no basis to change current guidelines for prenatal use of folate to prevent neural tube defects. Questions to be addressed in future research studies include whether vitamin C or PUFAs play a role in specific asthma phenotypes (e.g. does vitamin C prevents viral-induced exacerbations?, do certain PUFAs help exercise-induced asthma), whether vitamin C helps ameliorate detrimental effects of environmental tobacco smoke, or whether folate affects morbidity in subjects with pre-existing asthma. Yet another complex and insufficiently studied question is whether particular isoforms or components of vitamin E and PUFAs have different effects when used alone or in combination (with themselves or other vitamins and nutrients).

A fundamental question moving forward is whether intervening on diet as a whole is more advisable or cost-effective than supplementing individual nutrients or vitamins (6). First, nutrients or vitamins may have stronger beneficial effects on asthma when acting additively or synergistically. Thus, a combination of dietary factors could be more effective. Moreover, whereas dietary habits reflect overall nutritional patterns throughout lifetime, supplementation of individual nutrients or vitamins may be delivered inconsistently or too late to be effective. Second, antioxidant vitamin supplementation has not been shown to be beneficial (and in some cases may be detrimental) in preventing other diseases such as cancer, particularly in individuals with normal levels of the nutrient or vitamin that is being

supplemented. Third, individual components of a vitamin or nutrient (e.g. vitamin E or PUFAs) may have opposing effects on inflammation or asthma (see above). Findings from several studies support this “whole-diet” approach, including a recent report of an inverse association between dietary total antioxidant capacity (TAC) and current asthma in Spanish children ages 9 to 12 years (1, 49).

On the other hand, interventions targeting a specific vitamin or nutrient are or may be justifiable in the following situations: 1) the study population has deficient levels and poor access to relevant dietary sources (e.g. fruits and vegetables), 2) the study population is at risk for asthma morbidity due to environmental sources of oxidative stress (e.g. traffic-related air pollution), and 3) when diet is a poor source of the vitamin or nutrient of interest (e.g. vitamin D). Moreover, it should be noted that a “whole-diet” approach could not have sustained major beneficial effects without sound and long-term public health policies to promote and facilitate access to a healthy diet to underserved or vulnerable populations (50, 51).

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KEY POINTS

- The use of vitamin A, vitamin C, vitamin E or PUFAs is not recommended for the prevention or treatment of asthma or allergies.
- Current evidence strongly suggests that prenatal use of folate has no major effects on the risk of asthma or allergies in childhood.
- Studying the effects of a “healthy” diet (e.g. Mediterranean) on asthma or allergies should take precedence over examining individual vitamins or nutrients, except in special situations in which dietary sources are not accessible or unlikely to ensure an adequate nutritional status.

Table 1

Summary of current evidence and future directions for research on selected dietary nutrients and asthma

Nutrient	Dietary source	Potential mechanisms of action	Quality of Evidence	Future Directions
Diet-derived antioxidants (vitamins A, C and E)	Fruits, vegetables	Down-regulation of oxidative stress, airway inflammation, and Th2 (allergic) immune responses	Insufficient for causality, sufficient to justify a clinical trial	Clinical trials of a “healthy diet” or an “antioxidant rich” diet to investigate potential benefit
Folate	Dark leafy vegetables, fortified cereals and bread	DNA methylation of genes influencing Th1/Th2 immune responses	Sufficient to exclude a moderate or strong effect of prenatal folate on asthma	Continue current recommendations for prenatal folate supplementation
			Insufficient to exclude an effect of folate status on asthma morbidity	Longitudinal observational studies of folate status and asthma morbidity or allergic sensitization
Omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs)	Oily fish, fish oil supplement, vegetable oils	Up-regulation of anti-inflammatory pathways or down-regulation of pro-inflammatory pathways	Sufficient to exclude major effects of supplementation with exogenous n-3 PUFAs on asthma Insufficient to determine beneficial effects on certain asthma phenotypes	Observational studies of endogenous PUFAs Clinical trials of n-3 or n-6 PUFAs to treat certain asthma phenotypes (e.g. exercise-induced asthma)