

Effects of antioxidant supplements and nutrients on patients with asthma and allergies

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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Activity Objectives

1. To discuss the role of exogenous and endogenous antioxidants in asthmatic patients.
2. To discuss the nutrients and supplements involved in the antioxidant pathways.

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Asthma and allergic diseases have become a worldwide public health concern because of their increased prevalence. Despite decades of research on risk factors, the causes of these disorders are poorly understood. They are thought to develop through complex interactions between genetic and environmental factors. Because pulmonary and systemic oxidative stress increase inflammatory responses relevant to asthma and allergy, dietary or vitamin supplementation with antioxidants (a broad and varied category) has been proposed as an approach to reducing asthma incidence or morbidity. Meta-analyses of observational epidemiologic studies of variable methodological quality suggest associations of relatively low dietary intake of antioxidants and higher asthma and allergy prevalence. However, there have been few longitudinal studies of maternal or child dietary or vitamin/supplement antioxidant intake and asthma/allergy development. Moreover, there are no clinical trial data to support the use of dietary antioxidants or supplements to

prevent asthma or allergy. A few small clinical trials suggest that specific antioxidants from diet or vitamin supplements might improve asthma control or lung function in asthmatic children or adults. Studies suggest that responses to antioxidants might be modified by life stage, genetic susceptibility, and environmental sources of oxidative stress. Large trials of antioxidant vitamin supplementation to prevent cancer suggest an increase in overall mortality with antioxidant vitamin supplementation, at least in populations with sufficient dietary antioxidant intake. This cautionary experience suggests that future trials to assess whether antioxidants reduce asthma incidence or improve asthma control should focus on supplementation of dietary sources of antioxidants. The potential benefits and risks of trials of vitamin supplements might be considered in special situations in which vulnerable populations have marked deficiency in dietary antioxidants, poor access to dietary antioxidants, and high exposure to environmental sources of oxidants. (*J Allergy Clin Immunol* 2014;133:1237-44.)

Key words: Antioxidants, asthma, diet

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Asthma, allergic rhinitis, atopic dermatitis, and food allergies are caused by excessive and inappropriate immune responses to environmental antigens, which lead to inflammation. Asthma and

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Abbreviations used

C-ACT:	Childhood Asthma Control Test
CAT:	Catalase
GST:	Glutathione-S-transferase
GSTM1:	Glutathione-S-transferase Mu1
GSTP1:	Glutathione-S-transferase Pi1
GSTT1:	Glutathione-S-transferase theta1
HMOX1:	Heme oxygenase 1
Nrf2:	Nuclear erythroid 2 p45-related factor 2
SOD:	Superoxide dismutase

different allergic diseases often develop in the same person or in different persons within the same family.¹ The prevalence of asthma and allergic diseases has increased rapidly over recent decades in many countries, especially among young persons.^{2,3} This increase most likely results from changes in lifestyle and environmental exposures.^{3,4} Changes in exposure to antioxidants could play an important role. Some researchers have proposed that the increased prevalence of allergic diseases is a consequence of decreasing intake of antioxidants as people adopt Western diets characterized by a reduced amount of fresh fruits and vegetables. Others have suggested that it is linked to the increased antioxidant intake consumption of processed and antioxidant enriched foods.^{5,6}

Epidemiologic studies have produced conflicting results. Low intake of antioxidants has been associated with the diagnosis of asthma and asthma-related disorders, such as wheezing, airway reactivity, and reduced ventilatory function.² However, some studies reported no association between antioxidants and allergy,^{7,8} whereas others reported potential adverse effects.^{9,10} We review the roles of antioxidant intake and supplementation on asthma and allergic diseases, discussing the mechanisms by which endogenous (produced by the body's enzymes) and exogenous (diet-derived) antioxidants might contribute to pathogenesis. We also review the epidemiologic evidence for associations between antioxidants and asthma and allergy from studies of diet alone, supplement intake, and genetic susceptibility, including interactions between genotype and diet. Epidemiologic studies were identified through a PubMed search from 2000 through 2013 on diet, antioxidants, asthma, and allergic disease. A complementary search was conducted on antioxidant genes and asthma. We report findings from recent systematic reviews and meta-analyses, as well as from most recent original research studies, covering different populations with various study designs.

MECHANISMS OF ACTION

Reactive species and antioxidants play an essential role in the immune system. An imbalance between pro-oxidant and antioxidant defenses is known as oxidative stress, which can cause dysfunction in cell signaling and arachidonic acid metabolism (Fig 1) and increase airway and systemic inflammation. Although oxidative stress might increase inflammation related to either T_H1 or T_H2 cytokine production, in some cases it might increase skewing toward a T_H2 phenotype,¹¹ which is associated with the development of allergic diseases.^{10,12,13}

Oxidative stress

Oxidative stress occurs continually to kill some infecting microorganisms and prevent T cells from becoming

overactivated.¹⁴ Mitochondrial respiration, peroxisomes, and inflammatory cells are endogenous sources of reactive species. Enzymes associated with arachidonic acid metabolism, such as COX (which is responsible for the formation of prostaglandins and thromboxane) and cytochrome P450 (which catalyzes oxidation of organic substances), are another important source of reactive species.¹⁵ Environmental exposures to ozone and xenobiotics provide sources of additional exogenous oxidants. Oxidative stress stimulates inflammatory responses that can lead to allergic disorders, such as asthma, allergic rhinitis, atopic dermatitis, and food allergies.¹ Asthmatic patients are exposed to additional endogenous oxidative stress¹⁶; their antioxidant system can be overwhelmed in comparison with that of healthy subjects.¹⁷ Sources of increased oxidative stress in asthmatic patients include inhaled oxidants and reactive species generated by the inflammatory, immune, and structural cells of the airways. Despite the potential protective actions of antioxidants, Murr et al¹⁰ have suggested that "too much" intake of antioxidants could increase susceptibility to allergic disease and asthma by downregulating the T_H1-type immune response, thereby increasing the T_H2-type cell response and immunoglobulin production.¹⁰

Antioxidants

Antioxidants are molecules that are stable enough to eliminate oxidants or prevent their conversion to more toxic compounds by neutralizing free radicals and thereby delaying or inhibiting cellular damage. They are the first line of defense against reactive species, acting at different levels in the oxidation process by scavenging initiating radicals, binding metal ions, or removing damaged molecules. At a low level of oxidative stress, healthy lung tissues have enough antioxidants to prevent accumulation of reactive species. Antioxidant enzymes, such as catalases (encoded by *CAT*), the glutathione-S-transferase (GST) enzymes (encoded by a supergene family located on at least 7 chromosomes), heme oxygenase 1 (encoded by *HMOX1*), and superoxide dismutase (*SOD*) are produced by cells in the human immune system. Vitamin C, vitamin E, flavonoids, and carotenoids are diet-derived antioxidants.

Antioxidant molecules are present to varying degrees in intracellular and extracellular spaces and are unevenly distributed in tissues. For example, concentrations of glutathione in the epithelial lining fluid of the respiratory tract exceed those of plasma levels by 100-fold,¹⁶ whereas vitamins C and E are present in similar concentrations as those found in blood plasma.⁵ Antioxidants can also interact with each other; for example, a group of SODs reduces O₂⁻ to H₂O₂, which is then converted to H₂O through oxidation of glutathione (Fig 2).¹⁸ Fluid in the lining of the lungs contains a broad spectrum of antioxidants,¹⁹ yet little is known about the mechanisms by which these enzymes or those from lung cells or tissues interact with exogenous and endogenous oxidants in this organ.²⁰

Endogenous antioxidants. Most of the antioxidant capacity of cells comes from enzymes produced by the cells themselves.²¹ In a hierarchic model a low level of oxidative stress leads to the activation of the transcription factor nuclear erythroid 2 p45-related factor 2 (Nrf2), which encodes more than 200 genes that control antioxidant, anti-inflammatory, cytoprotective, and detoxification activities. These include *SOD*, *CAT*, *HMOX1*, and GSTs, which encode the essential first-line enzymes with antioxidant activities in the lungs.²² Briefly, *SOD* encodes a set of

Reactive species		Antioxidants	
Endogenous	Exogenous	Endogenous	Exogenous
<ul style="list-style-type: none"> Mitochondrial respiration Inflammatory cells Peroxisomes Arachidonic acid metabolism 	<ul style="list-style-type: none"> Ozone Cigarette smoking Others xenobiotics 	<ul style="list-style-type: none"> Nrf2 Superoxide dismutase (SOD) Catalase (CAT) Heme oxygenase-1 (HMOX1) Glutathione Other detoxifying enzymes 	<ul style="list-style-type: none"> Vitamin C Vitamin E Carotenoids Selenium

FIG 1. Oxidative stress: endogenous and exogenous oxidants and antioxidants.

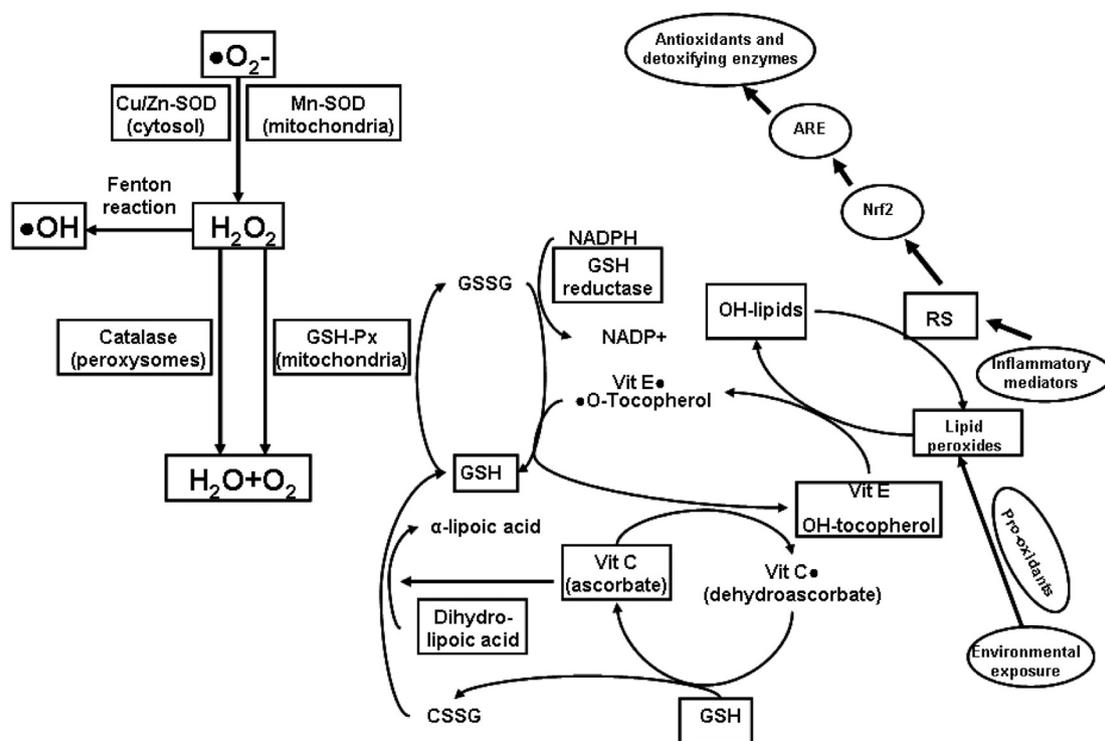


FIG 2. Endogenous and exogenous antioxidant defenses in the organism. Reactive species (RS) and inflammatory mediators activate the transcription factor Nrf2, which leads to release of antioxidants and detoxifying enzymes. Interactions among antioxidant molecules are essential in the defense response. Vitamin C contributes to the regeneration of oxidized tocopherol, allowing it to regain its function as an antioxidant. Vitamins C and E help to regenerate glutathione disulfide to glutathione. SOD reduces O_2^- to H_2O_2 , which is then converted to H_2O through oxidation of glutathione. ARE, Antioxidant responsive element; GSSG, glutathione disulfide. Adapted from Lazo-de-la-Vega-Monroy and Fernández-Mejía.¹⁸

ubiquitous enzymes that convert O_2^- to H_2O_2 . H_2O_2 can still react with other reactive species, and therefore it requires degradation by either glutathione peroxidase or CAT enzymes. H_2O_2 is degraded by reduction, during which 2 glutathione molecules are oxidized to glutathione disulfide. Regeneration of glutathione by glutathione reductase requires nicotinamide adenine dinucleotide phosphate (NADPH), which is oxidized to NADP+. CAT is mainly located in peroxisomes and detoxifies the H_2O_2 that diffuses from the mitochondria to the cytosol, converting it to water and molecular oxygen. HMOX1 generates antioxidants through degradation of heme molecules. The glutathione system is required to reduce hydrogen peroxide, complementing catalase,

and eliminate additional varieties of toxic peroxides.^{23,24} Reactive species, together with inflammatory mediators, activate different transcription factors, such as Nrf2 (Fig 2). Polymorphisms in *SOD*, *CAT*, *HMOX1*, and *GST* genes have been associated with diverse asthma-related phenotypes.²⁵⁻²⁷

Exogenous antioxidants. Diet-derived antioxidants protect against lipid peroxidation.¹⁷ Vitamin C appears to be the most abundant antioxidant in the extracellular fluid that lines the lung. It is a water-soluble vitamin that contributes to antioxidant activity through several mechanisms, including scavenging oxygen free radicals and suppressing macrophage secretion of superoxide anions.²⁸ Vitamin C acts on airways by affecting prostaglandins

(arachidonic acid metabolites). It cannot be synthesized by human tissues and must be obtained from the diet. Cherries, lemons, kiwifruit, broccoli, and cabbage are some dietary sources of vitamin C. Epidemiologic studies have reported a protective effect of this vitamin on lung function.^{29,30}

Vitamin E is a collective name for a set of 8 vitamins with antioxidant properties. They are present in foods, although in variable amounts. Of these, α -tocopherol and γ -tocopherol are the most abundant natural forms of vitamin E; they have opposing regulatory functions during inflammation. Whereas α -tocopherol is anti-inflammatory, γ -tocopherol has inflammatory properties.³¹

α -Tocopherol has been the most studied and is perhaps the most important lipid-soluble antioxidant. It is important in defense against oxidant-induced membrane injury in human tissue in that it disrupts the chain reaction of lipid peroxidation.²⁴ Vitamin C contributes to the regeneration of membrane-bound oxidized α -tocopherol, allowing it to function as an antioxidant (Fig 2). Sources of α -tocopherol include green vegetables and seed oils, such as olive and sunflower oil. α -Tocopherol has been reported to have beneficial effects on lung function, wheezing, and adult-onset asthma in Finland and Italy. However, dietary supplementation with α -tocopherol had no effect on FEV₁, asthma symptoms, or bronchodilator use in English adults with mild-to-moderate asthma.³² γ -Tocopherol has been shown to have inflammatory activities and increases airway hyperreactivity during eosinophilic allergic lung inflammation in mice.³² In accordance, countries with the highest prevalence of asthma tend to have higher plasma levels of γ -tocopherol.³¹ Canola and soy oils are sources of γ -tocopherol. Cook-Mills et al³² suggest that the γ -tocopherol in soy oil opposes the benefits of α -tocopherol.

β -Carotene is a red-orange pigment that can be transformed in vitamin A and is abundant in plants and fruits. β -Carotene accumulates in tissue membranes, scavenges superoxide anion, and reacts directly with peroxy free radicals, serving as a lipid-soluble antioxidant. It is mainly found in carrots, cabbage, mangoes, and peaches.³³ Dietary carotenoids have been associated with improved lung function³⁰ and lower asthma prevalence.

Selenium is a mineral mainly found in seafood, meat, nuts, and wheat depending on selenium soil content. It is incorporated into glutathione peroxidase, which protects cells against oxidative damage by preventing lipid peroxidation and the subsequent instability of cell membranes. Vitamins C and E increase selenium absorption. Increased serum levels of selenium have been associated with reduced prevalence of asthma³⁴ and increased lung function.³⁵

EPIDEMIOLOGIC STUDIES

Epidemiologic studies have associated exogenous sources of antioxidants with asthma-related phenotypes and allergic diseases. Most of these studies have reported beneficial results after antioxidant use, whereas others suggested no effect or even an adverse effect.

Association between asthma or allergy and dietary antioxidants

Consumption of fruits and vegetables was associated with reduced prevalence of asthma in a cohort study of women in France.³⁶ A cross-sectional study found reduced respiratory symptoms in children in rural Crete with a traditional

Mediterranean diet rich in fruits, vegetables, and nuts.³⁷ Low intake of vitamin C was associated with deficits in lung function³⁰ in Los Angeles.

In 2009, after a careful assessment of the quality of methodologies, Allen et al³⁸ selected 37 studies for meta-analysis; these were conducted from 1985 to 2007 in adults or children living in different countries. Case-control and cross-sectional designs were used most often; only 2 studies used a cohort design, and there were no clinical trials. Sample sizes ranged from 16 cases and 18 control subjects³⁹ to 77,866 women in a cohort study.⁴⁰ The exposures analyzed included dietary intake of vitamins A, C, and E (measured by using a food frequency questionnaires) or levels of antioxidants in body fluids. Health outcomes included asthma, asthma severity, wheezing, or airway reactivity.

Study results evaluating associations of levels of antioxidants or diverse combinations of dietary antioxidants with asthma outcomes were not entirely consistent in their findings. Nevertheless, the meta-analysis found a significant association between low dietary intake of vitamins A and C and higher rates of asthma and wheezing. Dietary intake of vitamin A was 182 μ g/d less in persons with versus those without asthma. Persons in the lowest quartile of dietary intake of vitamin C had a 12% increase in asthma risk. Vitamin E levels were not associated with asthma, but patients with severe asthma had lower levels than those with mild asthma (a mean reduction of 1.2 μ g/d).³⁸

There has been much interest in the association between antioxidant levels in pregnant women and allergic diseases in their children. In 2011, Nurmatov et al⁴¹ conducted a systematic review of the role of diet in preventing asthma and atopic disease, evaluating studies that included children. They included 21 cohorts, 15 case-control studies, and 26 cross-sectional studies but no randomized controlled trials. Sample sizes, study populations, and strategies of diet assessment were diverse. Although findings were inconsistent among studies, a meta-analysis showed that diets high in vitamin E during pregnancy reduced the risk for wheezing in children by 32%. Adherence to a Mediterranean diet during pregnancy reduced the risk for persistent wheeze in children by 78% and atopy by 45%. Most studies assessing the effect of fruits and vegetables found them to protect against asthma and allergy. However, no associations were found for any outcomes in relation to vitamin C and selenium.⁴¹

Patelarou et al⁴ conducted a systematic review of antioxidant levels in pregnant women and allergy in their infants; they included only 18 studies that assessed the dietary exposure to antioxidants in pregnant women, infants, or both by using biochemical indicators. The authors reviewed outcomes of asthma, wheezing, allergic rhinitis, and eczema in 9 case-control, 5 prospective cohort, and 4 cross-sectional studies. Once again, the study populations and sample sizes were diverse. Nevertheless, most of the selected studies reported that antioxidant status during pregnancy and children's consumption of antioxidants protect against the development of allergic disease.

Few population-based randomized controlled trials have been conducted. Hemilä et al⁴² supplemented the diets of 7- to 10-year-old children with 200 mg/d vitamin C for 6 weeks. They used the Childhood Asthma Control Test (C-ACT) scoring system (range, 0-27 points; <20 points indicates uncontrolled asthma) and FEV₁ to measure the severity of asthma symptoms. Among younger

children with baseline scores of 18 to 19, the vitamin C increased C-ACT scores by 4.2 points, whereas among children 8.3 to 10 years old with baseline C-ACT scores of 14 to 15 points, vitamin C increased the C-ACT score by only 1.3 points. Their findings indicated that the effects of vitamin C on C-ACT scores varied with age and baseline C-ACT scores, whereas the effects of vitamin C on FEV₁ levels varied with age and exposure to dampness.⁴²

In 2012, Wood et al,⁴³ through a randomized controlled trial, investigated the effects of a high-antioxidant diet in asthmatic adults. Participants were randomly assigned to either a high- or low-antioxidant diet based on fruits and vegetables consumed for 14 days. Persons on the low-antioxidant diet were then randomly assigned to groups that were or were not given tomato extract in their diet (45 mg of lycopene per day). It was found that the low-antioxidant group was more than 2.26-fold as likely to have exacerbations of asthma at any time compared with the high-antioxidant group. No differences in airway or systematic inflammation were observed in relation to tomato extract intake.

Clark et al⁴⁴ conducted a randomized controlled trial in which 43 women with a history of asthma were randomly assigned to a group given a diet enriched in vitamin E (for an intake of 15 mg/d) or a control group from 12 through 20 weeks of gestation. The enriched diet increased mean intake levels of vitamin E from 7.13 to 17.4 mg/d. Although the association between this increase and asthma symptoms was not assessed, this study showed that dietary interventions based on food exchange can increase antioxidant intake.

Studies on the effects of antioxidants in children exposed to high levels of air pollution have also been conducted. Romieu et al⁴⁵ performed a double-blind trial among 158 asthmatic children randomly assigned to groups given placebo or antioxidant supplements (50 mg/d vitamin E and 250 mg/d vitamin C). Children were exposed to environmental ozone and followed for 12 weeks, undergoing spirometric tests twice each week. The antioxidant supplements reduced the harmful effects of ozone exposure in the small airways. In children with moderate-to-severe asthma, environmental ozone levels 1 day before spirometric testing were inversely associated with lung function. For each increase of 10 ppb of ozone exposure, forced expiratory flow from 25% to 75% of vital capacity decreased by 13.3 mL/s, FEV₁ decreased by 4.59 mL/s, and peak expiratory flow decreased by 15.0 mL/s in the placebo group, whereas no association was observed in the supplement group.

Compared with studies of asthma, there have been few studies of associations between diet and atopic dermatitis, allergic rhinitis, or IgE levels. Sausenthaler et al⁴⁶ described a protective role of vitamin E during the development of allergic sensitization in adults 29 to 54 years old. Increased β -carotene intake was associated with a reduced risk of allergic sensitization and lower IgE levels in children. In contrast, vitamin E was associated with increased risk of allergic sensitization in children 5 years old.³ Rosenlund et al⁴⁷ reported an inverse association between intake of β -carotene and rhinitis, whereas magnesium consumption was found to protect against atopic sensitization in Swedish children. However, after exclusion of children who avoided certain fruits and vegetables because of allergic symptoms, the association became nonsignificant.

Fogarty et al⁷ found an association between high concentrations of vitamin E intake with lower serum IgE concentrations and lower frequency of allergen sensitization. Nevertheless, there

was no effect of vitamin C intake on IgE concentrations. In a randomized controlled trial including 300 adults, no effect of vitamin C on clinical asthma control was found after 16 weeks.⁸

Association between asthma or allergy and antioxidant enzymes

Because reactive species are involved in the etiology of asthma, researchers have investigated associations between genes that encode antioxidant enzymes (and the transcription factors that regulate them) and asthma or some allergic diseases. Genes that encode GSTs (eg, glutathione-S-transferase Mu1 [*GSTM1*], glutathione-S-transferase Pi1 [*GSTP1*], and glutathione-S-transferase theta1 [*GSTT1*]), as well as *CAT*, *SOD*, and *HMOX1*, encode enzymes that defend against oxidants,⁴⁸ although association studies have provided controversial results. A case-control study found that polymorphisms in the GST genes were not associated with asthma in Italian adults.⁴⁹ Minelli et al⁵⁰ conducted a systematic review and meta-analysis of case-control, cohort, cross-sectional, and family studies to examine associations among asthma, wheezing, and bronchial hyperresponsiveness and polymorphisms in *GSTM1*, *GSTT1*, and *GSTP1*. They observed large amounts of heterogeneity among studies and did not find that any single GST gene affected risk for asthma symptoms. They proposed that research focus on interactions between genes and between genes and environmental factors.

In contrast, a meta-analysis of 26 case-control studies encompassing 3000 cases and control subjects associated deletions in *GSTM1* and *GSTT1* with an increased risk of asthma. The study found that the diverse genetic backgrounds among ethnic groups could account for the observed heterogeneity among studies. Lack of the *GSTM1* gene was associated with asthma in Europe, Africa, and Latin America, whereas lack of *GSTT1* was found to significantly increase the risk for asthma in Asian and Russian populations.²⁶

Islam et al²⁷ demonstrated the important role of ethnicity in genetic susceptibility to asthma and allergic diseases. They found that Hispanic children with a common variant in *CAT* had an increased risk of asthma. However, *HMOX1* short alleles reduced the risk of new-onset asthma among non-Hispanic subjects exposed to low concentrations of ozone.

Interactions between antioxidant enzymes and diet-derived antioxidants

On the basis of the hypothesis that dietary intake of antioxidants and endogenous antioxidant capacity are involved in the susceptibility of asthmatic children to oxidative stress, Romieu et al⁵¹ studied the effects of antioxidant supplementation on ozone-related decreases in lung function based on *GSTM1* genotype. Children lacking the *GSTM1* gene (*GSTM1*-null genotype) receiving placebo had significant reductions in forced expiratory flow from 25% to 75% of vital capacity after exposure to ozone (2.9% of change per 50 ppb of ozone), whereas *GSTM1*-positive children did not. Conversely, the effects of antioxidants were stronger in children with the *GSTM1*-null genotype. In an extension of this study, Moreno-Macias et al⁵² reported that the effects of ozone in children with persistent asthma with 4 to 6 risk alleles in 3 antioxidant genes (*GSTM1*, *GSTP1*, and NAD[P]H dehydrogenase, quinone 1 [*NQO1*]) and low dietary intake of vitamin C (30-105 mg/d) were more pronounced (97.2 mL/s per 60 ppb of ozone) than in children with high levels of vitamin C intake

(>105 mg/d). The authors concluded that asthmatic children with compromised antioxidant defense systems caused by genetic susceptibility and deficiencies in antioxidant intake might be at increased risk for the adverse effects of ozone on pulmonary function.

Epigenetics

Epidemiologic studies have assessed the association between variants in multiple genes that regulate the immune system and asthma risk.⁵³ Oxidative stress activates expression of genes that regulate the inflammatory response; epigenetic studies are now being used to investigate this process during the development of asthma and allergy.⁵⁴ Perea et al⁵⁵ associated exposure to polycyclic aromatic hydrocarbon with methylation of the *ACSL3* gene and asthma risk in children. Yamamoto et al⁵⁶ examined microRNA profiles in peripheral blood samples from patients with mild asthma exposed to controlled diesel exhaust with and without antioxidant supplementation. Systemic levels of microRNAs with known biologic functions were significantly altered by acute and moderate exposure to diesel exhaust. Increased levels of some microRNAs were associated with levels of a systemic marker of oxidative stress; these increases were reduced with antioxidant supplementation.⁵⁶ The main characteristics of selected epidemiologic studies are summarized in [Table E1](#) in this article's Online Repository at www.jacionline.org.

METHODOLOGICAL ISSUES

Conflicting results from epidemiologic studies could be caused by differences in study design, assessment of exposure, sample size, or statistical analysis. Cross-sectional studies aim to identify risk factors for prevalent disorders. However, they cannot provide information on temporal relationships between factors, such as antioxidant intake and allergic disease. For example, subjects can alter their diets or environmental exposure because of their symptoms or for other reasons that would alter the level of any association with time but cannot be assessed under the cross-sectional design. It is also difficult to interpret cross-sectional data because factors such as past dietary intake and exposures are not taken into account. Interpretation of case-control studies is similarly limited by the lack of information on temporal relationships between exposures and disorders. In addition, results can be biased, such as by recall of certain exposures in specific groups.

Cohort studies have many advantages but can be flawed by lack of follow-up of all participants. Few cohort studies have investigated associations between antioxidant levels or exposure and asthma or allergy; most studies had cross-sectional or case-control designs.^{3,47} Although prospective studies are more likely to provide information on true causal relationships, they are usually conducted in clinical settings with a small number of subjects. This limits application of findings to larger populations and reduces their power. Therefore it is a great challenge to determine the effects of genetic and environmental factors (especially small effects) and their interactions on the development of any disease.

There are many limitations to interpreting results from dietary assessments. Study participants complete various versions of food frequency questionnaires, answering questions on intake of 10 to 20 to more than 150⁵ food groups, as well as portion sizes. Assessments of nutrient intake based on food frequency questionnaires provide limited information on true

intake; results are compromised by factors such as incomplete food nutrient databases, variations in the nutrient composition of foods, methods of preparation, and individual eating habits.¹⁰ Measurement errors in dietary assessments can lead to underestimations of the relationships between dietary factors and allergic diseases.²⁸

Although biomarkers are more precise, they reflect recent intake and do not provide adequate information on long-term intake, which is most likely to affect the development of asthma and allergic diseases. Additionally, levels of nutrient and inflammatory biomarkers are likely to vary among tissues; levels measured in blood might not reflect those of other tissues, such as the fluid in the epithelial lining of the lung. Ngoc et al¹² showed that analyses of immune responses in peripheral blood provide limited information about what is happening in the entire immune system. Known doses are given to subjects in randomized controlled trials of antioxidant supplementation. However, it is a challenge to establish compliance with the supplementation, which must be monitored with blood biomarkers.

Even though the studies included in the systematic reviews we have discussed were carefully selected, the authors reported that the body of evidence was weak based on methodological factors. Most of the studies reported unadjusted results; potential confounders, such as socioeconomic status, body mass index, consumption of other nutrients, and environmental exposure, were not considered. Unadjusted results can provide spurious associations or mask true relations. In addition, differences in timing and concentration of antioxidants can affect the development of allergic diseases, depending on the characteristics of the study population. Adults and children are exposed to different environmental factors and have different metabolisms. Genetic and cultural diversity can also cause differences in development of asthma and allergic diseases.

Assessment of gene-environment interactions and epigenetic studies could contribute to a better understanding of the cause of these complex disorders. Observational and randomized trials are needed to assess the effect of complex interactions taking into account disease dynamics,⁵⁷ considering factors such as genetic susceptibility and environmental exposure to identify any effects of antioxidants. New strategies, such as toxicogenomic and nutrigenomic studies, will open new lines of research. As Shachar and Karin⁵⁸ stated, the functions of proinflammatory and anti-inflammatory cytokines could depend on factors such as their local concentration, disease stage, and combination with other cytokines. The effects of antioxidants are also likely to depend on these types of factors, as well as the oxidative potential of the environmental and genetic variations. Studies suggest that responses to antioxidants might be modified by life stage, genetic susceptibility, and environmental sources of oxidative stress. Large trials of antioxidant vitamin supplementation to prevent cancer suggest an increase in overall mortality with antioxidant vitamin supplementation, at least in populations with sufficient dietary antioxidant intake.^{59,60} This cautionary experience suggests that future trials to assess whether antioxidants reduce asthma incidence or improve asthma control should focus on supplementation of dietary sources of antioxidants. The potential benefits and risks of trials of vitamin supplements might be considered in special situations in which vulnerable populations have marked deficiency in dietary antioxidants, poor access to dietary antioxidants, and high exposure to environmental sources of oxidative stress.

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Concepts and therapeutic implications

- Dietary or vitamin supplementation with antioxidants (a broad and varied category) has been proposed as an approach to reducing asthma incidence or morbidity.
- Meta-analyses of observational epidemiologic studies of variable methodological quality suggest associations of relatively low dietary intake of antioxidants and higher asthma and allergy prevalence.
- The origins of asthma and allergy might be in fetal life or early childhood, but there have been few longitudinal observational studies of maternal or early childhood dietary or vitamin supplement antioxidant intake and asthma/allergy development.
- Large trials of antioxidant vitamin supplementation to prevent cancer suggest an increase in overall mortality with antioxidant vitamin supplementation, at least in populations with sufficient dietary antioxidant intake. This cautionary experience suggests that future trials to assess whether antioxidants reduce asthma incidence or improve asthma control should focus on supplementation of dietary sources of antioxidants.
- A few small clinical trials suggest that specific antioxidants from diet or vitamin supplements might improve asthma control or lung function in asthmatic children or adults.
- Responses to antioxidants might be modified by life stage, genetic susceptibility, and environmental sources of oxidative stress.
- The potential benefits and risks of trials of vitamin supplements might be considered in special situations in which vulnerable populations have marked deficiency in dietary antioxidants, poor access to dietary antioxidants, or high exposure to environmental sources of oxidants (eg, air pollution).
- As McKeever and Britton⁶¹ stated, “The therapeutic implication of a healthy diet consists in taking advantage of the amount of natural nutrients in particular foods and the combination and interaction among nutrients in different foods. The best way to deliver a suitably comprehensive and synergistic range of nutrients is to supplement the diet with fresh fruits and vegetables.”

What is known?

- The prevalence of asthma and allergic diseases has increased over recent decades.^{2,3}
- Pulmonary and systemic oxidative stress increase inflammatory responses relevant to the development and control of asthma and allergy.¹
- The fluid that lines the lungs contains a broad spectrum of low-molecular-weight antioxidants, such as reduced glutathione, vitamins C and E, and uric acid levels, as well as small concentrations of antioxidant enzymes, such as catalase and SOD.²⁰
- There are marked differences in the concentration of antioxidants in the upper and lower respiratory tracts.³³

- Combinations of genetic and environmental factors determine the features of allergic diseases in each patient.¹³

What is still unknown?

- The exact mechanisms by which exogenous and endogenous oxidants interact with molecules in the cells, tissues, and epithelial lining fluid of the lung²¹
- The protective roles of different types of antioxidants on the blood-gas barrier and the factors they regulate⁵
- The extent to which levels of antioxidants in peripheral blood act as oxidants in the lungs
- The long-term effects of dietary or vitamin sources of antioxidants on asthma and allergy development or control
- Differences in the effects of specific antioxidants on the development or control of asthma or allergy
- How antioxidants in the diet or dietary supplements might be used to either control or prevent asthma or allergies

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