INTRODUCTION

In recent studies, dietary factors have been implicated in the cause and prevention of important diseases. Nutritional factors could significantly modify host response to environmental toxicants. An adequate diet may be able to inhibit, arrest, or even reverse the chain of events in toxicity (1), while a deficient diet could increase a person’s susceptibility to adverse environmental exposures, such as allergens, environmental tobacco smoke, infectious agents, and air pollution (2). Several dietary factors have been implicated in the genesis of obstructive lung diseases, mainly because of the potential role of dietary factors in inflammatory reactions (1) and in the activities of airway smooth muscle and enzymatic reactions that affect neuromuscular transmission (3). These factors include a deficiency of antioxidant vitamins, a lower consumption of ω-3 fatty acids, and a higher consumption of ω-6 oils, processed foods, and salt (4).

In this paper, we examine the relation between dietary factors and most prevalent obstructive lung diseases, including asthma and chronic obstructive pulmonary disease (COPD). We limit our review to nutrients that have recently been implicated in the genesis or severity of obstructive lung diseases; we do not address the issues of food allergy, breastfeeding, or body mass index (a combination of caloric intake and energy expenditure). First, we review the mechanisms by which specific dietary factors may affect respiratory health. Second, we review the epidemiologic evidence for a link between diet and obstructive lung diseases.

Epidemiologic studies were identified through a MEDLINE search (US National Library of Medicine) on dietary factors and obstructive lung diseases. Studies were classified by health outcome, nutrient, and study design. The evidence is discussed in light of some of the criteria proposed by Hill (5) for evaluating causal relations, including biologic plausibility, temporality, and consistency of the association.

MECHANISM OF ACTION

Role of oxidants and antioxidants

Normally, the lung exists in an oxygen-rich environment balanced between the toxicity of oxidants (generated through normal cellular function or exposure to prooxidants) and the protective activities of several intracellular and extracellular antioxidant defense systems. A tight control of redox balance is critically important for the maintenance of normal pulmonary cellular function (6). Disequilibrium, either through an increase in oxidant stress or a compromise of antioxidant resources, can initiate a series of pathophysiologic events in the lung that culminates in cellular death and pulmonary dysfunction (7). A shift of the oxidant/antioxidant balance in favor of oxidants has been termed “oxidative stress” (8). Researchers have hypothesized that a diet low in antioxidants such as β-carotene and vitamins C and E may reduce natural defenses and increase susceptibility to oxidant attack and airway inflammation (7).

Cigarette smoke and atmospheric pollutants such as ozone and nitrogen oxide are rich in free radicals, and exposure to them can induce oxidant-mediated lung injury by direct tissue oxidation, as well as through endogenous oxidizing agents and proteolytic enzymes released after recruitment and activation of neutrophils during the inflammatory response (9). Inhaled oxidants also amplify the effect of neutrophil proteases by oxidative deactivation of α-1-proteinase inhibitor (6, 10).

The antioxidant defenses of the lung have recently been reviewed (7, 10–13). Antioxidants are the first line of defense against oxygen free radicals, which are capable of damaging cellular components and contributing to inflammation. Briefly, the major antioxidant system available to cells during oxidative stress is that of free-radical-scavenging agents. These agents are present to varying degrees in the intracellular and extracellular spaces, and they function by either eliminating oxidants or preventing their conversion to more toxic compounds (8). Antioxidants may act at different levels in the oxidation process—for example, by scavenging initiating radicals, binding metal ions; by scavenging peroxyl radicals; or by removing oxidatively damaged biomolecules (8). Antioxidant defenses in the lung are provided by endogenous enzyme systems and nonenzymatic antioxidant compounds. The major enzymatic antioxidants are superoxide dismutase,
which degrades superoxide anion, and catalase and the glutathione redox system, which inactivates hydrogen peroxide (11). Nonenzymatic antioxidants such as vitamin E (α-tocopherol), vitamin C (ascorbic acid), and β-carotene (a precursor of vitamin A), ubiquinone, flavonoids, and selenium are present in foods and are considered dietary antioxidants (8).

Vitamin E, a lipid-soluble vitamin, represents the body’s principal defense against oxidant-induced membrane injury in human tissue, via its role in breaking the lipid peroxidation chain reaction (14). Vitamin C, a water-soluble vitamin, contributes to antioxidant activity through several mechanisms, including scavenging the superoxide radical \( \text{O}_2^- \). Vitamin C acts on airways by affecting arachidonic acid metabolites, particularly prostaglandins. An antagonist effect of vitamin C on prostaglandin \( \text{F}_2\alpha \)-induced bronchoconstriction has been shown in animals (3). Vitamin C appears to be the most abundant antioxidant substance in the extracellular fluid lining of the lung (15), and it also contributes to the regeneration of membrane-bound oxidized vitamin E, allowing it to function again as a chain-breaking antioxidant (16). In addition, vitamin C plays a role in immune function and is transported into neutrophils and lymphocytes (12). β-Carotene, a precursor to vitamin A, accumulates in tissue membranes, scavenges superoxide anion, and reacts directly with peroxyl free radicals, thereby serving as a lipid-soluble antioxidant (8). Thus, dietary intake of these vitamins may play a role in host defense against oxidative lung damage. Flavonoids such as quercetin are scavengers of superoxide anion; they exhibit singlet oxygen-quenching properties, scavenge lipid peroxyl radicals, and can act as chelators of iron ions (8). Selenium is incorporated into the antioxidant enzyme glutathione peroxidase, which reduces hydrogen peroxide and other organic peroxides, thereby preventing lipid peroxidation and subsequent instability of cell membranes (3). Selenium also has an overlapping function with vitamin E (17) (see table 1).

Antioxidant intake may act primarily on the evolution of asthma, modulating the impact of oxidants on the lung, decreasing inflammation of the airway. Infection and inhaled pollutants activate leukocytes to produce oxidants. Eosinophils, alveolar macrophages, and neutrophils from asthmatic patients produce more reactive oxygen species than do those from normal subjects. Reactive oxygen species directly contract airway smooth muscle preparation (18) and can stimulate histamine release from mast cells (15). A number of antioxidant disturbances have also been observed in COPD patients, and the involvement of oxidative stress in COPD has been indicated through higher hydrogen peroxide exhalation, an increase in lipid peroxidation products, and DNA damage. Cigarette smoke, a major risk factor for COPD, is a significant source of oxidants; smokers have been found to have decreased levels of plasma ascorbate, β-carotene, and vitamin E (11). In addition, the coexistence of airway inflammation and parenchymal inflammation is observed in most patients with COPD. Therefore, antioxidant intake could modulate the lung damage induced by oxidative stress (11).

Fresh fruits and vegetables contain considerable amounts of vitamin C (e.g., broccoli, spinach, tomatoes, and citrus fruits) and carotenoids (e.g., carrots, tomatoes, grapefruit, beans, broccoli, oranges, and mangoes) (19). The main carotenoids serving as provitamin A, α- and β-carotene and cryptoxanthin, may be transformed into vitamin A. The richest sources of vitamin E in the human diet are oil products such as mayonnaise, vegetable and seed oils (corn, safflower, and soybean), butter, and eggs. Flavonoids are mainly found in fruits and vegetables (apples, lemons, oranges, potatoes, and cauliflower) and tea (8). Selenium is found in grain, meat, seafood, and certain vegetables. The current Recommended Dietary Allowance requirements are 60 mg/day for vitamin C (100 mg/day for smokers), 800–1,000 retinol equivalents per day (1 retinol equivalent = 6 μg of β-carotene) for vitamin A, 8–10 mg/day for α-tocopherol, and 55–70 μg/day for selenium (20).

Role of \( \omega-3 \) and \( \omega-6 \) fatty acids

Patterns of consumption of \( \omega-3 \) and \( \omega-6 \) fatty acids have been related to the development of airway inflammation. In brief, \( \omega-3 \) polyunsaturated fatty acids (n-3 PUFA), which are stored in cell membranes, have an important role in controlling inflammation (4) but are easily replaced by \( \omega-6 \) polyunsaturated fatty acids (n-6 PUFA), which facilitate the development of inflammation. The most abundant n-6 PUFA in the Western diet, linoleic acid (18:2n-6), is converted to arachidonic acid, a progenitor of both prostaglandin \( \text{E}_2 \) and leukotriene \( \text{B}_4 \) via cyclooxygenase and 5-lipoxygenase enzymatic pathways, respectively. Both prostaglandin \( \text{E}_2 \) and leukotriene \( \text{B}_4 \) have proinflammatory biologic actions.

In contrast, \( \alpha \)-linolenic acid (18:3n-3) n-3 PUFA is converted to eicosapentaenoic acid (20:5n-3), which can inhibit arachidonic acid metabolism competitively via the enzymatic pathways and thereby suppress production of the n-6 eicosanoid inflammatory mediators. Eicosapentaenoic acid is a potential cyclooxygenase substrate for the synthesis of prostaglandin \( \text{E}_3 \) and a 5-lipoxygenase substrate for the synthesis of leukotriene \( \text{B}_4 \). Both prostaglandin \( \text{E}_3 \) and leukotriene \( \text{B}_4 \) have little inflammatory activity in comparison with prostaglandin \( \text{E}_2 \) and leukotriene \( \text{B}_4 \). Thus, increasing dietary n-3 PUFA can shift the balance of the eicosanoids produced to a less inflammatory mixture (21). Prostaglandin \( \text{E}_2 \) acts on T lymphocytes to reduce the formation of interferon-γ without affecting the formation of interleukin-4. This may lead to the development of allergic sensitization, since interleukin-4 promotes the synthesis of immunoglobulin E, whereas interferon-γ has the opposite effect (22). Leukotriene \( \text{B}_4 \) increases postcapillary vascular permeability, is a potent stimulator of airway smooth muscle cells, and mediates pulmonary asthma through involvement in vasoconstriction and mucus secretion. n-3 PUFA may also suppress the production of tumor necrosis factor-α and interleukin-1β; however, the mechanism for this suppression remains unknown (21).

The competitive interactions between n-6 PUFA and n-3 PUFA determine the cellular content of arachidonic acid and eicosapentaenoic acid. A higher concentration of eicosapentaenoic acid occurs in diets low in linoleic acid. In the Western diet, 20- to 25-fold more n-6 PUFA than n-3 PUFA
TABLE 1. Proposed mechanisms and dietary sources of putative protective nutrients in environmental lung disease

<table>
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<th>Nutrient</th>
<th>Mechanisms</th>
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| Vitamin C (ascorbic acid)| • Water-soluble antioxidant  
• Scavenges $O_2^-$  
• Regenerates oxidized vitamin E  
• Present in neutrophils and lymphocytes | • Fruits: papaya, cantaloupe, citrus fruits, strawberries  
• Vegetables: cauliflower, broccoli, brussels sprouts, kale, sweet peppers | • Humans are unable to synthesize vitamin C.                                    |
| Vitamin E ($\alpha$-tocopherol) | • Lipid-soluble antioxidant  
• Reacts with peroxyl free radicals to terminate membrane lipid peroxidation | • Vegetable and seed oils  
• Eggs  
• Green vegetables | • Level of vitamin E in food best correlates with the level of unsaturated fat. |
| $\beta$-carotene, lycopene, and other carotenoids | • Lipid-soluble antioxidants  
• React with peroxyl free radicals, decreasing lipid peroxidation  
• Scavenge $O_2^-$  
• Growth regulation of malignant cells (via vitamin A effects) | • Red, orange, and yellow fruits and vegetables: sweet potatoes, carrots, winter squash  
• Green vegetables | • Antioxidant activity of carotenoids may be more important in environmental lung disease than the provitamin A effects. |
| n-3 fatty acids | • Decreased leukotriene synthesis  
• Inhibition of prostaglandin $E_2$ synthesis  
• Growth regulation of malignant cells | • Fish oils  
• Fish and shellfish  
• Soy and canola oil  
• Leafy vegetables | • Ratio of n-3:n-6 fatty acids in diet may be more important than absolute consumption levels. |
| Magnesium | • Cofactor in enzyme activation reactions requiring adenosine triphosphate  
• Bronchodilator of airway smooth muscle  
• Inhibits cholinergic neuromuscular transmission  
• Stabilizes mast cells and T lymphocytes | • Nuts, legumes  
• Cereal grains  
• Corn, peas, carrots, parsley, spinach, lima beans  
• Brown rice  
• Seafood | |
| Selenium | • Cofactor for glutathione peroxidase, which reduces lipid and hydrogen peroxides  
• Detoxification of heavy metals  
• Plays a role in DNA repair | • Animal products, especially organ meats  
• Seafood | • Foods grown in selenium-poor soils may contribute to selenium deficiency in humans.  
• Vitamins C, E, and A enhance selenium absorption.  
• Mercury and other heavy metals inhibit selenium absorption. |

are consumed (21). Therefore, changes in dietary patterns in the developed countries could partly explain the increase in the prevalence of asthma. n-3 PUFA are found in high quantities in fish oil (very long chain $\omega$-3 fatty acids) and in monounsaturated oils such as canola and flaxseed oils, whereas n-6 PUFA are found in polyunsaturated fats, such as soybean, corn, safflower, and sunflower oils (21).

Role of electrolytes

Certain electrolytes have also been implicated in the development of airway diseases.

Sodium is important in many aspects of the regulation of smooth muscle tone; in vitro sensitization of airway smooth muscle cells has been shown to lead to increased sodium influx of the cells, with the subsequent stimulation of Na⁺,K⁺-adenosinetriphosphatase, resulting in the sustained hyperpolarization of the airway smooth muscle cells. The contractile response of airway smooth muscle cells to specific antigen has been demonstrated to be dependent on the level of hyperpolarization resulting from sodium influx (3). Therefore, a diet with a high salt content could predispose people toward the development of airway disease, particularly airway hyperreactivity. Dietary sodium intake could act by changing the levels of endogenous steroid or catecholamine release (23). A sex difference in the importance of salt intake is plausible, because animal and skeletal studies show sex differences in sodium metabolism that may influence muscle tone (24).
Magnesium may also influence airway disease, because it is involved in maintaining electric potential across cell membranes and may therefore have a direct action on bronchial smooth muscle, producing airway dilatation (3). Magnesium is an essential cofactor for enzymes that require adenosine triphosphate, and it is involved in the synthesis and replication of RNA and DNA. Magnesium has been shown to relax airway smooth muscle in vitro, to bronchodilate asthmatic airways in vivo, to inhibit cholinergic neuromuscular transmission, to stabilize mast cells and T lymphocytes, and to stimulate the generation of nitric oxide and prostacyclin (25). A diet low in magnesium could therefore be a risk factor for airway diseases. Magnesium in the diet is obtained principally from cereals, nuts, green vegetables, and dairy products (17).

**EPIDEMIOLOGIC STUDIES**

**Methodological issues**

**Study design.** Two major types of studies have been used to investigate the impact of diet on obstructive lung diseases: experimental studies, in which patients were randomly assigned to receive diet supplement or placebo, and cross-sectional studies, in which dietary intake was assessed simultaneously with airway responsiveness, change in lung functions, or respiratory symptoms. Although the experimental study design is more likely to provide information on a true causal relation, the existing studies were conducted in clinical settings on small numbers of patients, which limits the application of the results to larger populations. They usually focused on acute outcomes such as bronchoconstriction and were aimed at determining the potential for nutritional therapy in the management of obstructive lung disease, particularly asthma. In contrast, most of the epidemiologic data from free-living populations are based on cross-sectional studies of adults or children that evaluated dietary factors among people with and without disease at a single point in time. These studies aimed at determining risk factors for prevalent obstructive lung diseases; however, because of their cross-sectional nature, they cannot provide information on the temporal relation between dietary intake and lung diseases. For instance, there is a possibility that subjects with prevalent symptoms may alter their diet as a result of their symptoms, thus altering the nature of the association. In addition, there is uncertainty about the biologically relevant exposure window(s), and dietary agents might plausibly act at different stages of the disease process. It is likely that, as in other chronic diseases, nutrient intake several years prior to diagnosis may be the most relevant in relation to the development of obstructive lung diseases. In addition, the difficulty of reconstructing past dietary intake renders difficult the interpretation of cross-sectional data.

There have been few cohort studies that have enrolled persons initially free of disease and evaluated the incidence of lung disease over time. Because the estimation of dietary intake precedes the diagnosis of obstructive lung disease, results from these studies provide a correct temporal relation. However, a cohort study is costly and time-consuming to carry out. It is also difficult to assess long-term dietary intake in these studies because of changes in nutrient status during the long follow-up periods needed, particularly for COPD; and lack of knowledge on the relevant window of susceptibility may lead to misclassification of the exposure of interest. However, the cohort design is the only observational design that provides the elements needed to establish a causal relation between diet and obstructive lung diseases.

**Assessment of dietary intake.** Different methods have been used for dietary assessment across studies, including measurement of biomarkers of intake and administration of dietary questionnaires such as 24-hour recalls, food frequency questionnaires, and diet histories. Biochemical indicators of dietary intake include serum vitamin C levels and urinary sodium and potassium excretion. These biomarkers reflect recent intake (26) and therefore will not provide adequate information on long-term intake, the most relevant risk factor for chronic disease. In addition, some factors, such as exposure to tobacco smoke, will decrease serum levels of vitamin C (11, 19) and therefore provide erroneous information on dietary intake. Similarly, assessment of nutrient intake based on 24-hour dietary recalls provides a poor measurement of usual intake because of potentially wide variation from day to day, particularly for micronutrients such as electrolytes and vitamins, and it has been noted to be more variable than use of semiquantitative food frequency questionnaires, which gather data on average dietary intake over a period of several months or years (27). While the use of a food frequency questionnaire provides better assessment of food intake, it still results in random error in the measurement of dietary intakes and thus may lead to underestimation of the relation between dietary factors and lung disease (28).

For some nutrients, such as vitamin E and selenium, relying on dietary assessment methods to classify individuals is problematic, since accurate data on food content are limited. Selenium content will vary according to the origin of the food. Additionally, intake of fats from oils, which are rich in vitamin E, is difficult to discern in quantity (29). Finally, because few studies consider more than one nutrient in their analyses, a protective or adverse effect attributed to one nutrient or micronutrient, such as vitamin C, may actually reflect the effect of another, correlated dietary constituent or an interaction between dietary constituents. It is particularly difficult to exclude the possibility that another component of certain fruits or vegetables may have a true protective effect (27). These issues are particularly relevant when considering the endpoints used in different studies. While the use of an indicator of short-term intake may be adequate for an acute outcome such as bronchoconstriction, it is not adequate for a chronic outcome such as decrement in lung function.

**Epidemiologic studies of diet and airflow limitation**

Obstructive lung diseases such as asthma and COPD have in common airway narrowing, with a consequent increase in the work of breathing. Intraluminal airway obstruction has multiple causes. Airway smooth muscle contraction, a classic mechanism in asthma, is the most commonly considered cause of airway narrowing. Infiltration with inflammatory
cells, scarring edema, and intraluminal narrowing by secretion are also causes of airway obstruction (30). Snider et al. (31) have proposed a Venn diagram for depicting the syndrome of airway obstruction and the interrelation between asthma and COPD. Asthma could be defined as a disease whose hallmark is reversible airway obstruction, with the possible development of unremitting airway obstruction, while COPD involves chronic bronchitis and/or emphysema with or without airway obstruction (figure 1). An asthmatic person exposed to chronic irritation may also have a chronic productive cough and features of both asthma and chronic bronchitis. Subjects with chronic bronchitis and emphysema can develop increased reactivity of the airways that might be reversible (31). However, the evolution of COPD is characterized by a slowly progressive and irreversible decrease in forced expiratory volume in 1 second (FEV₁) (11).

This interrelation between these obstructive diseases is reflected in the epidemiologic literature by the fact that studies address health outcomes ranging from airway hyperresponsiveness (airway hyperreactivity) to change in lung function, respiratory symptoms, or reported diseases. Outcomes such as airway hyperreactivity and wheezing are acute in nature but reflect a chronic status of airway hyperreactivity or asthma. Other outcomes, such as lowered lung function, reflect a status of persistent obstructive lung disease. There is no ideal way to summarize epidemiologic data given the interrelations between chronic airflow limitations; therefore, we decided to focus on 1) asthma-like symptoms, including airway hyperreactivity and wheezing, and 2) COPD-type change in lung function and chronic respiratory symptoms—acknowledging that there is no clear-cut division between these pathologies and that some studies have addressed various health outcomes.

**Airway hyperresponsiveness, wheezing, and asthma.** Airway hyperresponsiveness is an abnormality in the airways that allows them to narrow too easily and too much. It is often associated with asthma, although airway hyperreactivity may occur in asymptomatic subjects. Asthma has been defined as a chronic inflammatory disorder of the airway in which many cells, especially mast cells, eosinophils, and T lymphocytes, play a role. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible, either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli (32). Because of the components of airway constriction and inflammation involved in asthma, several nutritional factors that may act on muscle constriction or inflammatory response have been hypothesized to act on this disease. In addition, the large increase in the prevalence of asthma observed in most developed countries (4, 33) in recent years has pointed toward environmental factors being responsible for part of this increase—particularly changes in diet, such as decreased consumption of fresh fruits and vegetables and unprocessed food (4, 34–36).

**Sodium.** The development of airway diseases has been related to sodium intake. On the basis of an ecologic comparison between regional differences in mortality in England and Wales and corresponding regional differences in salt intake, Burney (37) suggested that a high intake of dietary sodium might be related to asthma. Further epidemiologic studies have led to diverse results. Among eight cross-sectional studies, four reported positive associations between sodium intake and airway hyperreactivity (38–41), while four concluded that there was no relation (23, 42–44). In one British study of adult males, a significant association was observed between salt excretion and airway hyperreactivity (38). In another study, a small association between dietary sodium intake and airway hyperreactivity was observed in only one of three study samples of adult males (41). In two other studies conducted among male children (39) or among healthy adults without known airway hyperreactivity (40), salt intake was positively associated with self-reported wheezing (41).

However, other studies have failed to find a causal association between sodium intake and airway hyperreactivity. Data from the First National Health and Nutrition Examination Survey (NHANES I), which included 9,074 subjects aged ≥30 years, suggested a positive association between the ratio of dietary sodium to dietary potassium (but not dietary sodium alone) and self-reported wheezing (42); after adjustment for potentially confounding factors, including other nutrients, this association lost its significance. In a study of males in the United States, researchers found a relation between potassium excretion and airway hyperreactivity but no relation between sodium excretion and airway hyperreactivity (43). In the United Kingdom, in a population-based sample of 1,702 adults aged 18–70 years, researchers found no associa—

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**FIGURE 1.** Venn diagram showing subsets of patients with chronic bronchitis, emphysema, and asthma in three overlapping circles. Chronic obstructive pulmonary disease (COPD) is characterized by the presence of chronic bronchitis or emphysema that may lead to airway obstruction and airway hyperreactivity. Asthma patients have completely reversible airway obstruction without symptoms of chronic bronchitis or emphysema. (Adapted from Snider et al. (31)).
They also observed a reduction in self-reported wheezing in the previous months (odds ratio = 0.85, 95 percent CI: 0.76, 0.95). Data were adjusted for potential confounders such as age, sex, height, atopy, smoking, caloric intake, and vitamin C intake. The dose-response characteristics of this association suggest that FEV₁ increases in approximately linear relation to magnesium intake up to the level of 400 mg/day. Britton et al. suggested that, in previous studies, magnesium could have confounded the association between sodium or potassium and airway hyperreactivity and asthma. In a case-control study conducted in Scotland, decreasing intake of magnesium was also related to an increased risk of airway hyperreactivity (49).

Experimental studies have not confirmed the association between magnesium intake and airway hyperreactivity and pulmonary functions. Magnesium infusion among patients with acute asthma exacerbation has produced either a transient improvement in FEV₁ (50) or no improvement (51). In a randomized trial among 17 stable asthmatic patients, Hill et al. (52) reported no significant improvement in airway hyperreactivity or FEV₁ during a 3-week magnesium supplementation period, although high magnesium intake was associated with improvement in symptom scores. Some authors have also measured serum and intracellular magnesium levels (erythrocytes and mononuclear leukocytes). Because magnesium is largely intracellular, it is thought that magnesium levels in erythrocytes and leukocytes are more accurate measures of magnesium status than serum levels. In a study by De Valk et al. (53), no significant difference was found between asthmatic patients and nonasthmatic controls in either extracellular or intracellular magnesium levels.

On the basis of experimental data, there is no clear evidence that magnesium intake may have an impact on the genesis or evolution of chronic asthma. Although magnesium intake was found to have a beneficial effect on the lung in two studies conducted in free-living populations (25, 49), diet was evaluated retrospectively in those studies. In addition, the association between magnesium and respiratory outcomes might be confounded by intake of other micronutrients that may be correlated with magnesium intake, such as calcium, potassium, or selenium.

Antioxidants. Some researchers have hypothesized that a deficiency in dietary antioxidants could contribute to asthma, because 1) the US diet has grown deficient in foods containing antioxidants (34) while the asthma rate has increased and 2) there is increasing evidence for a role of antioxidants in lung defense mechanisms. In a recent review, Hatch (15) suggested that oxidant exposure, particularly in infancy, could be a causative factor for asthma. Oxidants could increase susceptibility to infections that in turn cause lung injury. This injury or inflammation could further be an underlying cause of asthma (15).

Experimental studies have also produced conflicting results. Burney et al. (45) reported a greater bronchial response to histamine among asthma patients taking a sodium supplement as compared with those taking a placebo. These results were observed only among men, and no significant change in FEV₁ was seen in either group during the study. Similarly, Carey et al. (46) reported an increase in airway hyperreactivity and respiratory symptoms among asthmatic patients receiving a sodium supplement as compared with those receiving placebo. In addition, a decrease in FEV₁ was observed in the supplement-taking group. Medici et al. (47) observed a decrease in FEV₁ and peak expiratory flow rate among asthmatic patients receiving sodium supplements but no change in airway hyperreactivity. Another experimental study (48) failed to find an effect of dietary sodium levels on bronchial responsiveness. Although these studies suggested that increased sodium intake may adversely affect the bronchopulmonary system in small groups of asthmatic patients, the fact that the increase in airway hyperreactivity was found only among males raises some concern about the pathogenesis of this effect, which may or may not involve the airway smooth muscles. In addition, these studies provided little support for the adoption of a low-salt diet by patients with asthma (3). On the basis of experimental data, an increase in salt consumption could be associated with an increase in airway hyperreactivity among asthmatic individuals, but there is no evidence of an impact of sodium intake on the increase in asthma incidence.

Magnesium. Few epidemiologic studies have investigated the impact of magnesium intake on airway reactivity (table 2). In a cross-sectional UK study of 2,633 adults aged 18-70 years, Britton et al. (25) reported that a 100-mg/day higher magnesium intake (assessed by semiquantitative food frequency questionnaire) was associated with both a reduction in airway hyperreactivity (odds ratio = 0.82, 95 percent confidence interval (CI): 0.72, 0.93) and a higher FEV₁. They also observed a reduction in self-reported wheezing in the previous months (odds ratio = 0.85, 95 percent CI: 0.76, 0.95). Data were adjusted for potential confounders such as age, sex, height, atopy, smoking, caloric intake, and vitamin C intake. The dose-response characteristics of this association suggest that FEV₁ increases in approximately linear relation to magnesium intake up to the level of 400 mg/day. Britton et al. suggested that, in previous studies, magnesium could have confounded the association between sodium or potassium and airway hyperreactivity and asthma. In a case-control study conducted in Scotland, decreasing intake of magnesium was also related to an increased risk of airway hyperreactivity (49).
<table>
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<tr>
<th>Nutrient(s) and study</th>
<th>Design</th>
<th>Population</th>
<th>Outcome(s)</th>
<th>Factor(s)</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>Burney et al., 1986 (38)</td>
<td>Cross-sectional, population-based</td>
<td>138 men aged 18-64 years, England</td>
<td>bronchial reactivity (PD20)* (methacholine challenge)</td>
<td>Sodium (24-hour urinary excretion)</td>
<td>10-fold difference in PD20 over the 95% range of sodium excretion</td>
</tr>
<tr>
<td>Tribe et al., 1984 (40)</td>
<td>Cross-sectional</td>
<td>59 young men aged 18-35 years, England</td>
<td>bronchial reactivity (PD20) (methacholine challenge)</td>
<td>Sodium and potassium (24-hour urinary excretion)</td>
<td>PD20 increase with urinary sodium excretion and decrease with urinary potassium excretion</td>
<td>Adjusted for body size, skin sensitivity, serum immunoglobulin E, symptoms, and creatinine levels</td>
</tr>
<tr>
<td>Pistelli et al., 1993 (39)</td>
<td>Cross-sectional, population-based</td>
<td>2,593 schoolchildren aged 9-16 years, Italy</td>
<td>wheezing (yes/no)</td>
<td>sodium (urinary excretion); salt intake (personal and familial)</td>
<td>Wheezing apart from colds and sodium intake: OR = 2.71 (95% CI: 1.44, 5.10) among boys</td>
<td>Adjusted for age, father's education, parental smoking, familial asthma, and atopy</td>
</tr>
<tr>
<td>Devereux et al., 1995 (41)</td>
<td>Cross-sectional</td>
<td>234 shipyard workers aged 16-27 years</td>
<td>bronchial reactivity (methacholine challenge)</td>
<td>Sodium (24-hour urinary excretion)</td>
<td>No association between sodium excretion and PD20 in shipyard workers or rural residents</td>
<td>Positive association between urban dwellers and sodium excretion</td>
</tr>
<tr>
<td>Schwartz and Weiss, 1990 (42)</td>
<td>Cross-sectional, population-based</td>
<td>NHANES III (9,074 adults aged 30 years, United States)</td>
<td>wheezing and bronchitis</td>
<td>Sodium, potassium, fish, serum vitamin C, and serum zinc/copper ratio (24-hour recall)</td>
<td>Wheezing—serum vitamin C (change of 12 mg/liter: OR = 0.71 (95% CI: 0.58, 0.88); niacin intake (change of 22.8 mg/day): OR = 0.74 (95% CI: 0.59, 0.93); serum zinc/copper ratio (change of 0.4): OR = 0.70 (95% CI: 0.58, 0.94)</td>
<td>Adjusted for age, sex, race, smoking, total caloric intake, and intake of other nutrients</td>
</tr>
<tr>
<td>Britton et al., 1994 (23)</td>
<td>Cross-sectional, population-based</td>
<td>1,762 adults aged 18-70 years, England</td>
<td>bronchial reactivity (PD20) (methacholine challenge)</td>
<td>Sodium (24-hour urinary excretion)</td>
<td>No relation between PD20 and sodium and potassium excretion</td>
<td>Adjusted for age, sex, smoking, atopy, and creatinine levels</td>
</tr>
<tr>
<td>Sparrow et al., 1991 (43)</td>
<td>Cross-sectional, population-based</td>
<td>273 males aged 44-62 years Participants in the Normative Aging Study, United States</td>
<td>bronchial reactivity (methacholine challenge)</td>
<td>Sodium and potassium (24-hour urinary excretion)</td>
<td>Significant dose-response relation between bronchial responsiveness and potassium excretion</td>
<td>Adjusted for age, percentage of predicted FEV1, smoking, skin test reactivity, and creatinine sodium, and potassium levels</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Cross-sectional, population-based</td>
<td>2,415 adults aged 18–70 years, England</td>
<td>Bronchial reactivity (methacholine challenge), wheezing</td>
<td>Magnesium (FFQ)</td>
<td>Increase of 100 mg/day in dietary magnesium was associated with a reduction in hyper-bronchial reactivity (OR = 0.82, 95% CI: 0.72, 0.93)</td>
<td>Adjusted for age, sex, smoking, atopy, and caloric intake</td>
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<td>Britton et al., 1994 (25)</td>
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<td>Reduction in self-reported wheezing in the past 12 months (OR = 0.85, 95% CI: 0.76, 0.95)</td>
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**Antioxidants (vitamin C, vitamin E, carotenoids)**

Schwartz and Weiss, 1990 (42)

Cross-sectional, population-based

NHANES II (9,074 adults aged ≥30 years, United States)

Wheezing

Serum vitamin C

Serum vitamin C (change of 12 mg/liter: OR = 0.71 (95% CI: 0.58, 0.88))

Adjusted for age, sex, race, smoking, total caloric intake, and intake of other nutrients

Soutar et al., 1997 (49)

Cross-sectional, population-based

52 subjects with seasonal symptoms and 38 controls

29 reactors and 58 non-reactors

Selected from 2,000 individuals, Scotland

Seasonal allergic symptoms, bronchial reactivity (methacholine challenge)

Retinol, vitamin C, vitamin E, magnesium, zinc, and selenium (FFQ)

Increase in symptoms was associated with lower zinc intake (OR = 4.70, 95% CI: 1.33, 16.53 (lowest tertile vs. highest tertile))

No impact of antioxidant intake on allergic symptoms

Increase in bronchial reactivity was associated with lower intake of vitamin C (OR = 7.13, 95% CI: 1.91, 26.71 (lowest tertile vs. highest tertile)) and manganese (OR = 8.14, 95% CI: 2.11, 31.39 (lowest tertile vs. highest tertile))

Bodner et al., 1999 (61)

Nested case-control study

94 cases and 203 controls aged 39–45 years

Onset of adult asthma

Vitamin C, vitamin E, retinol, and β-carotene (FFQ)

Plasma levels of ascorbate, α-tocopherol, retinol, and β-carotene

Higher intake of vitamin E was related to lower risk of adult onset of asthma (OR = 4.02 (95% CI: 1.30, 12.42) for lowest tertile vs. highest tertile))

Higher plasma levels of ascorbate (OR = 0.98 per unit) and α-tocopherol:triglyceride ratio (OR = 0.34 per log unit) were related to lower risk

Adjusted for smoking, socio-economic status, atopy, family history of atopic disease, and total energy intake

Table continues
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<tr>
<th>Nutrient(s) and study</th>
<th>Design</th>
<th>Population</th>
<th>Outcome(s)</th>
<th>Factor(s)</th>
<th>Results</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Troisi et al., 1995 (62)</td>
<td>Cohort study—10-year follow-up of the Nurses’ Health Study</td>
<td>77,866 nurses aged 34–68 years, United States</td>
<td>Onset of adult asthma (n = 1,446 incident cases during follow-up time)</td>
<td>Vitamin C, vitamin E, vitamin A, and carotenoids (FFQ)</td>
<td>Lower incidence of asthma in highest quintile of vitamin E intake (vs. lowest quintile) (OR = 0.53, 95% CI: 0.33, 0.86)</td>
<td>Adjusted for age, smoking, body mass index, area of residence, number of physician visits, total caloric intake, and intakes of vitamin C and carotene</td>
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<tr>
<td>Cook et al., 1997 (63)</td>
<td>Cross-sectional, school-children</td>
<td>2,650 children aged 8–11 years from 10 towns in England and Wales</td>
<td>FEV₁ and wheezing</td>
<td>Fresh fruits and vegetables (FFQ)</td>
<td>Plasma vitamin C level</td>
<td>Adjusted for social class and passive smoking</td>
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<tr>
<td>Forastiere et al., 2000 (64)</td>
<td>Cross-sectional, school-children</td>
<td>18,737 children aged 6–7 years, Italy</td>
<td>Wheezing, coughing, shortness of breath, noncoryzal rhinitis</td>
<td>Frequency of consumption of citrus/kiwi fruits</td>
<td>Reduction in reported wheezing symptoms (OR = 0.68, 95% CI: 0.55, 0.78) for eating 5–7 times per week vs. less than once per week</td>
<td>Adjusted for sex, study area, paternal education, household crowding, passive smoking, dampness and mould, and parental asthma</td>
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<tr>
<td>Omega-3 fatty acids</td>
<td>Troisi et al., 1995 (62)</td>
<td>Cohort study—10-year follow-up of the Nurses’ Health Study</td>
<td>77,866 nurses aged 34–68 years, United States</td>
<td>Omega-3 fatty acids, linoleic acid (FFQ)</td>
<td>No association found with omega-3 fatty acids or linoleic acid</td>
<td>Adjusted for age, smoking, body mass index, area, physician visits, calories, vitamin C, and carotene</td>
</tr>
<tr>
<td>Hodge et al., 1996 (75)</td>
<td>Cross-sectional, population-based</td>
<td>584 schoolchildren, including children with airway hyperreactivity and wheezing in the past 12 months, and healthy children; selected from a sample of 808 children aged 8–11 years, Australia</td>
<td>Current asthma (recent wheezing and airway hyperactivity)</td>
<td>Fish intake (yes/no) (FFQ)</td>
<td>Intake of fresh oily fish (&gt;2% fat) was related to a reduction in current asthma (OR = 0.26, 95% CI: 0.09, 0.72)</td>
<td>Adjusted for sex, ethnicity, country of birth, atopy, respiratory infection in the first 2 years of life, parental history of asthma, and smoking</td>
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* PD20, provocative dose (dose estimated to cause a 20% decrease in FEV₁ during a bronchial challenge test).
† OR, odds ratio; CI, confidence interval; NHANES II, Second National Health and Nutrition Examination Survey; FEV₁, forced expiratory volume in 1 second; FFQ, food frequency questionnaire.
children’s risk of respiratory infection, which in turn is a risk factor for the later development of asthma (4, 54). Children’s exposure to environmental tobacco smoke has also been related to higher immunoglobulin E levels and higher eosinophil counts and elevated skin-prick sensitivity (56), as well as increased airway hyperreactivity and an increase in respiratory symptoms (54). Similarly, several epidemiologic studies have shown that, among different populations of asthmatic children or adults, exposure to photoxidant gases (ozone or nitrogen dioxide) increases the frequency of respiratory symptoms and bronchial responsiveness (57). In addition, both experimental and epidemiologic studies have suggested that antioxidant supplementation could modulate the acute changes in lung function observed among people exposed to photoxidants (58–60). It is therefore reasonable to suggest that antioxidants could play an important role in asthma.

Six epidemiologic studies, four in adults and two in children, have investigated the association between antioxidant intake and airway hyperreactivity or asthma-like symptoms (table 2). In these studies, diet was assessed through administration of dietary questionnaires (24-hour recall) (42) or food frequency questionnaires including different numbers of foods (49, 61–64), or by measuring serum levels of antioxidant vitamins (42, 63). Analyses of the cross-sectional data of the Second National Health and Nutrition Examination Survey (NHANES II) have shown an association between vitamin C and respiratory health. Low serum vitamin C levels were associated with increased wheezing in the previous 12 months (42). After adjustment for age, sex, race, smoking, socioeconomic status, and total caloric intake, an increase of 12 mg/liter in serum vitamin C was related to a 41 percent decreased risk (odds ratio = 0.58, 95 percent CI: 0.43, 0.78) for asthma among participants of lower social class, who are likely to have a lower intake of antioxidants, and among smokers (61). However, in this study, information on dietary intake was obtained after the identification of cases and controls. In contrast with previous results, a prospective study conducted in a large cohort of nurses aged 34–68 years over a 10-year period (62) did not find an association between dietary intakes of vitamin C and carotene and onset of adult asthma, but women in the highest quintile of vitamin E intake (from diet, not from supplements) had a relative risk of 0.53 (95 percent CI: 0.33, 0.86) for asthma compared with women in the lowest quintile. The authors concluded that some of the effect noted was probably due to asthma patients’ avoiding nuts and peanut butter (foods with a high vitamin E content) as possible allergens.

Two recent cross-sectional studies conducted in children have suggested a beneficial impact of fresh fruit consumption on respiratory health. In a cross-sectional study of 2,650 schoolchildren aged 8–11 years from England and Wales, Cook et al. (63) reported that children who never ate any fruit had a mean FEV<sub>1</sub> 79 ml (4.3 percent) lower than that of children who ate fruit more than once per day (95 percent CI: 22, 136). This association was stronger among children with wheezeing, although wheezeing itself was not associated with fresh fruit consumption. Plasma vitamin C levels were unrelated to FEV<sub>1</sub> or to wheezeing, and they correlated poorly with fresh fruit consumption (63). Forastiere et al. (64) evaluated dietary intake of citrus and kiwi fruits in a large sample of children aged 6–7 years residing in northern and central Italy and recorded the occurrence of wheezeing and other respiratory symptoms. After adjustment for potentially confounding factors, intake of citrus/kiwi fruits was protective against wheezeing in the previous 12 months (odds ratio = 0.66, 95 percent CI: 0.55, 0.78) among children who ate such fruits 5–7 times per week as compared with less than once per week. Similar results were observed when respiratory symptoms were recorded 1 year after the assessment of citrus/kiwi fruit consumption. No clear dose response was observed, and the protective effect was evident even among children who ate such fruits only once or twice per week. A stronger effect was observed among children with a history of asthma.

Asthma patients have been reported to have lower-than-normal concentrations of vitamin C in their plasma and blood leukocytes (3), which suggests that asthma could be associated with a chronically lower concentration of vitamin C. However, providing asthmatic patients with vitamin C supplements has yielded conflicting results (15). Supplement studies have generally been conducted in a small number of asthma patients with doses of vitamin C ranging from 500 mg to 2 g, administered a few hours before bronchoconstrictor challenge or other assessments of pulmonary function. Results suggest that supplementation with large amounts of vitamin C may reverse airway hyperreactivity and other symptoms of asthma (15). In one study, this protective effect was abolished by indomethacin, which suggests that leukotriene production is modulated by vitamin C (65). Anderson et al. conducted two supplementation studies (66, 67) to evaluate the impact of vitamin C supplementation on pulmonary function and immune response in asthmatic children over a 6-month period. Vitamin C supplementation was demonstrated to improve neutrophil motility and decrease anti-streptolysin O levels; no clear effect on lung function was observed. Studies conducted among asthmatic adults and healthy controls have suggested that patients with asthma have a lower concentration of selenium in plasma (68) and whole blood (68, 69) and/or reduced glutathione peroxidase activity (69, 70). Results are inconsistent, and there is no clear mechanism for low selenium levels in the pathogenesis of asthma.

Cross-sectional and case-control studies suggest a protective effect of vitamin C on airway hyperreactivity and...
wheezing; however, results should be interpreted with caution, and it is premature to conclude that vitamin C is the critical nutrient. Fresh fruits, a main source of vitamin C, are also a source of other nutrients such as flavonoids, and vitamin C intake is highly correlated with intakes of carotene, vitamin A, and vitamin E, which may also have a beneficial effect on pulmonary health (29). In addition, consumption of fresh fruit is a marker of a healthy lifestyle, which may have a positive effect on respiratory health. A lack of adjustment for other dietary factors and body mass index may have confounded the associations. Additionally, because of the nature of these study designs (cross-sectional or case-control), a temporal relation between diet and pulmonary health could not be established. The negative result observed in the only prospective study (62) could be due to several factors: 1) that study focused on adult onset of asthma, which may differ substantially from childhood incidence because of differences in the immune system, exposure patterns, and other factors between children and adults; and 2) intake of vitamin C by nurses in that study was greater than average, with few having a low intake, and this may have masked an effect of vitamin C intake. Supplementation studies suggest a potential impact on acute airway hyperreactivity response (15). However, none of these studies provided evidence that consistent use of vitamin C has a positive effect on objective measures of pulmonary function or that vitamin C is beneficial in the treatment of chronic asthma. Vitamin E intake could be related to the risk of adult-onset asthma. However, further studies are needed to evaluate this association.

ω-3 and ω-6 fatty acids. The hypothesis that dietary fish intake may reduce people’s susceptibility to chronic airway diseases originated from the observation that Inuit (Eskimo) populations had a very low prevalence of asthma (71), whereas in most other populations, asthma rates had been increasing in parallel with an increase in dietary intake of polyunsaturated fat, particularly linoleic acid (ω-6 fatty acid) (72). While there are clearly many factors that distinguish traditional Inuit populations from a society with a Western lifestyle, the effect of dietary fish intake, particularly intake of oily fish with a high ω-3 fatty acid content, has attracted much interest. Data from NHANES II suggested that a high fish intake was associated with a lower occurrence of self-reported wheezing; however, this relation did not persist after adjustment for other factors, including serum vitamin C levels (42). In a cross-sectional study, no associations were found between fish consumption and wheezing, chest tightness, or asthma attacks among young Norwegian adults with a high overall fish intake (73). Similarly, no association was observed between adult onset of asthma and dietary intake of ω-3 fatty acids or dark fish meat in a large prospective study of US nurses (62).

In contrast, studies carried out among children have found a protective effect of fish intake on asthma incidence. In a cross-sectional study of Australian children, Peat et al. (74) observed that consumption of one serving of fish per week was associated with a reduced risk of asthma. Following this observation, in another cross-sectional study of 574 Australian children aged 8–11 years, Hodge et al. (75) reported that children who ate fresh oily fish (>2 percent fat) had a significantly reduced risk for current asthma (odds ratio = 0.29, 95 percent CI: 0.13, 0.67). A test for trend was not presented. Similar results were observed after adjustment for potentially confounding factors, including atopy, parental history of asthma, parental smoking, ethnicity, country of birth, early respiratory illness, and sex. There was no difference in consumption of nonoily fish between asthmatic children and nonasthmatic children, which suggests that parents of asthmatic children do not selectively prevent them from eating fish.

The central role played by airway inflammation in the pathogenesis of asthma and the recognition that leukotrienes are potent mediators of bronchoconstriction have led to investigations of the effect of ω-3 fatty acid supplementation among patients with asthma (71). Studies supplementing the diets of asthmatic patients with ω-3 fatty acids or fish oil have yielded varied results (76–79). Some researchers have suggested that the ratio of ω-3 fatty acid to ω-6 fatty acid may be important. Three recent studies evaluated the impact of increased ω-3 fatty acid and reduced ω-6 fatty acid in the diets of asthmatics. Broughton et al. (80) reported that asthmatic adults with a high ratio of ω-3 fatty acid intake to ω-6 fatty acid intake (0.5:1) had a lower rate of methacholine-induced respiratory distress than those consuming these fats in a low ratio (0.1:1), as well as lower 4-series leukotriene urinary excretion and higher 5-series leukotriene excretion. No significant effect on baseline spirometry was found. Villani et al. (81) reported that supplementation with 3 g/day of ω-3 fatty acids during a 30-day period decreased airway hyperreactivity, but no long-lasting effect was observed. Hodge et al. (82) observed no clinical difference in the severity of asthma between asthmatic children receiving ω-3 fatty acid dietary supplementation (1.2 g/day) for 6 months (a high ω-3:ω-6 ratio) and those receiving a diet rich in ω-6 fatty acids. In the group receiving ω-3 fatty acids, plasma levels of these fatty acids increased and the production of stimulated tumor necrosis factor-α, which has been implicated in asthma pathogenesis, decreased (82). These studies did not show clinical improvement in asthma patients using fish oil supplementation, despite some changes in inflammatory cell functions (3).

Black and Sharpe (72) have suggested that the decrease in the consumption ratio of ω-3:ω-6 fatty acids in the developed world could be related to an increase in allergic diseases. Fish oil may exert its beneficial effect by reducing consumers’ risk for allergic sensitization rather than by directly affecting their asthma (72). This could explain the inconsistency between the results of epidemiologic and supplementation studies and fish oil’s apparent lack of effect on the onset of asthma among adults, many of whom are not atopic. It is also important to mention that most of the nonexperimental studies (42, 73–75) used fish intake as a marker of ω-3 fatty acid consumption and did not account for other dietary sources of ω-3 fatty acid, such as canola and flaxseed oils. This, in addition to the fact that fish may be a source of potentially important nutrients other than ω-3 fatty acids, should be considered in interpreting the results.
Chronic obstructive pulmonary disease

Chronic obstructive airway disease can be defined as a process characterized by the presence of chronic bronchitis or emphysema that may lead to the development of airway obstruction. It is a major cause of death and disability among adults in the United States and throughout the world (83). Cigarette smoking is a major risk factor for chronic airway disease; however, differences in tobacco consumption do not fully account for the variations in population rates of this disease. Factors such as dietary intake could play a role in modulating the impact of environmental exposures on the lung. To assess the association between COPD and diet, most studies have focused on lung functions.

Sodium. Data from NHANES I suggested a positive association between the ratio of dietary sodium to dietary potassium and the prevalence of self-reported bronchitis among adults. This association persisted after adjustment for intake of other nutrients, including serum vitamin C (42).

Magnesium. In a study conducted among 2,633 adults aged 18–70 years, Britton et al. (25) reported that a 100-mg/day higher magnesium intake was associated with a higher FEV₁ (27.7 ml; 95 percent CI: 11.9, 43.5). This result corresponded to an increase of approximately 124 ml over a 95 percent range of magnesium intake (156.5–603 ml) or a 3.9 percent increase in the population mean FEV₁. Adjustment for potentially confounding factors, including age, sex, height, atopy, calcium, vitamin C, and total caloric intake, did not modify this result substantially. This result was not confirmed by Butland et al. (84).

Antioxidants. Lung function among adults has been related to intake of antioxidants, particularly vitamin C. Numerous studies have estimated consumption of fresh fruit or juice (85) and consumption of antioxidants using dietary questionnaires (42, 49, 85–94), dietary interviews (95), or blood levels of antioxidants (88, 93, 96, 97) (table 3).

Ten cross-sectional studies conducted in adults reported that vitamin C intake had a protective effect against decline in lung function (85–93, 96). In a study of 1,502 lifelong smokers and 1,357 current smokers aged 18–69 years, FEV₁ was 78 ml lower among subjects who drank no fruit juice or who ate fresh fruit less than once per week during the winter (86). However, total vitamin C intake was not assessed in that study. Britton et al. (87) observed in 2,633 adults that both FEV₁ and forced vital capacity were significantly related to subjects’ mean daily intakes of vitamin C and vitamin E. An increased vitamin C intake of 40 mg/day was related to a 25-ml higher FEV₁ and a 23.3-ml higher forced vital capacity. For vitamin E, an increase in intake of 6.1 mg/day was associated with a 20.1-ml higher FEV₁ and a 23.1-ml higher forced vital capacity. These results persisted after adjustment for age, sex, height, mean allergen skin wheal diameter, and pack-years of smoking. However, after adjustment for vitamin C intake, the authors found no independent effect of vitamin E. The effect of vitamin C intake on lung functions was slightly higher among current smokers and ex-smokers (87). In a cross-sectional population-based study that included 1,860 adults aged 45–75 years, higher plasma vitamin C levels were associated with higher pulmonary function: A 50-µmol/liter increase in plasma vitamin C was associated with an increase of 0.22 liter in FEV₁ (89). In NHANES I, FEV₁ was related to dietary vitamin C intake as estimated by 24-hour dietary recall; subjects in the lowest tertile of vitamin C intake (17 mg/day) had an average FEV₁, 40 ml lower than that of subjects in the highest tertile (170 mg/day). This difference corresponds to the effect of 10 pack-years of smoking or 1 year of aging (85).

More recently, in a study carried out among 3,085 subjects from 69 counties in China, researchers reported a positive association between vitamin C intake and lung function. An increase in vitamin C intake of 100 mg/day was associated with increases of 21.6 ml (95 percent CI: –0.4, 43.5) in FEV₁, and 24.9 ml (95 percent CI: 0.2, 49.6) in forced vital capacity (89). In a study of 178 elderly persons aged 76–90 years in England, FEV₁ and forced vital capacity were significantly related to vitamin E intake but not to vitamin C intake. After adjustment for age, sex, height, smoking habits, total energy intake, and vitamin C intake, researchers found that an increase of 1 mg/day in vitamin E intake was related to increases of 42 ml in FEV₁ and 54 ml in forced vital capacity (90). Data from the MORGEN Study, conducted in Dutch adults, have shown higher FEV₁ and forced vital capacity among subjects with higher intakes of vitamin C and β-carotene (91). When investigators compared subjects in the 10th and 90th percentiles of vitamin C consumption (a 144.4-mg/day difference), FEV₁ was 53 ml higher (95 percent CI: 23, 83) and forced vital capacity was 79 ml higher (95 percent CI: 42, 116) in the higher consumption group. With regard to β-carotene consumption, the same comparison (a 2.50-mg/day difference) showed increases of 60 ml (95 percent CI: 31, 89) for FEV₁, and 75 ml (95 percent CI: 40, 110) for forced vital capacity. No effect of vitamin E consumption was observed. Tabak et al. (92) studied the impact of fruit and vegetable consumption on FEV₁ among adults in three European countries. FEV₁ was higher in men with a combined fruit and vegetable intake above the median as compared with those whose intake of both types of food was below the median, but the finding did not reach statistical significance after adjustment for total caloric intake (92). The association of the individual dietary factors with pulmonary function was not consistent across countries. Two recent studies confirmed the positive association between FEV₁ and antioxidant nutrients, particularly vitamin E, vitamin C, and some carotenoids (93, 96).

Three longitudinal studies have evaluated the impact of antioxidant intake on chronic lung diseases (95–97). In a 25-year prospective study carried out among 793 middle-aged men in Zutphen, the Netherlands, Miedema et al. (95) compared subjects who consumed more than 70 g of solid fruit per day with those who consumed 14 g or less. After adjusting for age, body mass index, smoking, and total energy intake and other dietary factors, they observed that consumption of solid fruits was inversely related to the incidence of chronic nonspecific lung disease (a classification that grouped self-reported chronic respiratory symptoms with a diagnosis of emphysema, chronic bronchitis, or asthma). The incidence of chronic nonspecific lung disease
### Table 3. Observational epidemiologic studies of antioxidant acids and omega-3 fatty acids in relation to lung function in free-living adults

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<tr>
<th>Nutrient(s) and study</th>
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<td>Antioxidant vitamins</td>
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<tr>
<td>Shahar et al., 1994 (99)</td>
<td>Cross-sectional, population-based</td>
<td>10,416 middle-aged adults (part of the ARIC* cohort study, United States)</td>
<td>Airway obstruction (FEV/FVC* cutoff point, 65%)</td>
<td>Vitamin A intake (FFQ*)</td>
<td>Vitamin A intake was unrelated to airway obstruction. Except among current smokers with &gt;41 pack-years, risk of airway obstruction was higher in the lowest quartile of intake vs. the highest quartile (OR* = 1.7, 95% CI*: 1.1, 2.7)</td>
<td>Adjusted for age, sex, smoking, body mass index, and caloric intake</td>
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<td>Strachan et al., 1991 (86)</td>
<td>Cross-sectional, population-based</td>
<td>1,502 lifelong nonsmokers and 1,357 current smokers aged 16–69 years, United Kingdom</td>
<td>FEV₁</td>
<td>Fresh fruit and fruit juice (FFQ)</td>
<td>FEV₁ was lower among subjects who never drank fresh fruit juice and ate fresh fruit less than once per week during winter (78 ml; 95% CI: 24, 132); observed in lifelong nonsmokers and current smokers; significant trend</td>
<td>Adjusted for sex, age, height, cigarette smoking, region of residence, and household socioeconomic status</td>
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<tr>
<td>Schwartz and Weiss, 1994 (85)</td>
<td>Cross-sectional, population-based</td>
<td>NHANES I* (3,478 subjects aged 30–74 years, United States)</td>
<td>FEV₁</td>
<td>Vitamin C intake (24-hour recall)</td>
<td>40-ml difference in FEV₁ between highest and lowest tertiles of vitamin C (178 mg/day vs. 17 mg/day)</td>
<td>Adjusted for age, height, sex, race, body mass index, smoking (pack-years), and employment; No evidence of a stronger effect in smokers</td>
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<tr>
<td>Britton et al., 1995 (87)</td>
<td>Cross-sectional, population-based</td>
<td>2,633 subjects aged 16–70 years, England</td>
<td>FEV₁ and FVC</td>
<td>Vitamin C and vitamin E (FFQ)</td>
<td>40 mg/day increase in vitamin C intake was associated with higher FEV₁ (25.0 ml; 95% CI: 5.2, 48.8) and FVC (23.3 ml; 95% CI: 1.0, 45) 2.2-mg/day increase in vitamin E intake was associated with higher FEV₁ (20.1 ml; 95% CI: 1.3, 40.1) and FVC (23.1 ml; 95% CI: 1.0, 45) No independent effect of vitamin E was seen after controlling for vitamin C intake</td>
<td>Adjustment for age, sex, height, mean allergen skin wheal diameter, smoking history (pack-years), and vitamin E and vitamin C intakes</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Sample Details</td>
<td>Outcomes</td>
<td>Adjustments</td>
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<td>Ness et al., 1996 (88)</td>
<td>Cross-sectional, population-based</td>
<td>1,860 subjects aged 45–74 years, Great Britain</td>
<td>FEV, and FVC Vitamin C (FFQ) and plasma vitamin C Increase in vitamin C of 50 μmol/liter was associated with increase of 220 ml in FEV, and 230 ml in FVC among men; significant dose-response relation; no effect seen in women</td>
<td>Adjusted for age, height, and pack-years of cigarette smoking</td>
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<td>Dow et al., 1996 (90)</td>
<td>Cross-sectional</td>
<td>178 men and women aged 70–96 years with respiratory symptoms</td>
<td>FEV, and FVC Vitamin C and vitamin E (FFQ) Vitamin E intake was significantly associated with FEV, and FVC (increases of 42 ml in FEV, and 54 ml in FVC for an increase of 1 mg in daily intake)</td>
<td>Adjusted for age, gender, height, smoking habits, total energy intake, and vitamin C intake</td>
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<tr>
<td>Hu et al., 1998 (89)</td>
<td>Cross-sectional, population-based</td>
<td>3,085 subjects aged 35–64 years, China</td>
<td>FEV, and FVC Vitamin C (3-day weighed record of household food intake) 100-mg/day increase in vitamin C intake was associated with an increase of 21.6 ml (95% CI: 0.4, 43.5) in FEV, and an increase of 24.9 ml (95% CI: 0.2, 49.6) in FVC; no significant interaction with smoking status</td>
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<tr>
<td>Grievink et al., 1998 (91)</td>
<td>Cross-sectional, population-based</td>
<td>8,695 adults aged 20–29 years, the Netherlands</td>
<td>FEV, and FVC Vitamin C, vitamin E, and β-carotene (FFQ) FEV, and FVC were higher in subjects with higher intakes of vitamin C (144.9-mg difference) and β-carotene (2.50-mg difference) Vitamin C: FEV was 53 ml higher (95% CI: 23, 83) and FVC was 79 ml higher (95% CI: 42, 116) No effect of vitamin E</td>
<td>Age, sex, smoking status, and pack-years of smoking</td>
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<tr>
<td>Tabak et al., 1999 (92)</td>
<td>Cross-sectional, population-based; three European countries</td>
<td>Men aged 40–59 years from Finland (n = 1,248), Italy (n = 1,386), and the Netherlands</td>
<td>Forced expiratory volume (FEV₁ or FEV₃) Vitamin E, vitamin C, β-carotene, and fresh fruits and vegetables (diet history) FEV was associated with vitamin E intake in Finland, fruit consumption in Italy, and β-carotene in the Netherlands</td>
<td>Adjusted for age, height, body mass index, alcohol consumption, and total energy intake</td>
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<td>Butland et al., 2000 (84)</td>
<td>Follow-up (5 years), population-based, England</td>
<td>2,512 men aged 45–59 years</td>
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<td>Adjusted for age, height, body mass index, social class, work exercise, leisure exercise, and total caloric intake</td>
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was lower for men who consumed more than 70 g of solid fruit daily than for those who consumed less than 14 g/day (odds ratio = 0.68, 95 percent CI: 0.49, 0.95). In a prospective investigation using data from the 7-year follow-up examination of persons initially assessed in a cross-sectional study (as part of a UK survey of ventilatory function and winter fruit consumption), Carey et al. (94) examined 2,171 British adults aged 18–73 years (24 percent of the original sample) with no reported history of chronic respiratory disease. These authors assessed change in participants' FEV1 from baseline (1984–1985) to follow-up (1991–1992) and related it to fresh fruit and vegetable consumption as estimated by food frequency questionnaire. They found that changes in fresh fruit consumption, rather than average levels of fresh fruit consumption, were predictive of changes in FEV1 over the 7-year period. A decrease in consumption during the same time period was associated with a decline in FEV1, most importantly among subjects who reduced their fresh fruit intake the greatest as compared with persons with no change (107 ml; 95 percent CI: 36, 178). Trends were significant overall ($p < 0.002$) and were more pronounced among females, current smokers, and persons aged 32–45 years. The cross-sectional effect of fresh fruit consumption at the 7-year follow-up examination was consistent with previously published results (86). After adjusting for social class, region, and pack-years of smoking, researchers found that subjects in the first quintile (who consumed no fresh fruit) had a level of lung function 188 ml lower than that of subjects in the fifth quintile (who consumed 4.5–5 servings per day). Butland et al. (84) reported that apple consumption was positively related to lung function even after adjustment for age, height, smoking, body mass index, social class, exercise, and total energy intake. However, there was no indication that change in apple consumption over 5 years was related to a lesser decline in lung function. No significant effect was observed for vitamin C intake or vitamin E intake after adjustment for potentially confounding factors. The authors hypothesized that other antioxidant constituents of apples, such as flavonoids (e.g., quercitin), might play a role (84).

Morabia et al. (97) reported that subjects with lower serum retinol levels were more likely to have an FEV1 equal to or lower than 75 percent of forced vital capacity as determined 5 years later. However, serum retinol is a poor reflection of vitamin A status, given that the liver stores at least 90 percent of total vitamin A reserves (98). In later studies, no evidence of an association between vitamin A intake and airway obstruction was found (95, 99).

Cross-sectional and longitudinal studies strongly suggest that long-term vitamin C intake is significantly related to lung function. Although the amplitude of the effect varies from study to study, the consistency of the results suggests a real association between fresh fruit consumption and lung function. However, fresh fruit intake may be a marker of a healthier lifestyle, and other nutrients that were not accounted for may also have a beneficial effect on lung function. In addition, because cigarette smoking is a strong predictor of lung function, the observed effect of diet on lung function could be due to residual confounding.
ω-3 and ω-6 fatty acids. Three studies conducted in the United States have suggested that increased consumption of fish, as estimated by dietary questionnaire, could decrease the development of airway narrowing (99–101) (table 3). Schwartz and Weiss (100) reported a protective effect of fish intake on FEV₁ in a subsample (n = 2,526) of NHANES I participants aged ≥30 years. After controlling for height, age, cigarette smoking, and sex, they found that subjects who consumed fish less than once per week had an FEV₁ 1.35 percent lower than that of subjects who consumed fish once per week and an FEV₁ 2.51 percent lower than that of subjects who consumed fish more than once per week. The test for trend across categories was significant, and the effect was stronger among nonsmokers. However, the authors did not distinguish between different types of fish or adjust for intake of other nutrients. In a cross-sectional analysis of data from the Atherosclerosis Risk in Communities (ARIC) Study, which was conducted among 9,000 male smokers aged 45–64 years, results suggested that dietary fish intake had a protective effect on COPD risk. After adjustment for smoking, age, race, sex, education, height, and weight, the relative risk of COPD was 0.3–0.6 for persons in the highest quartile of fish oil intake as compared with those in the lowest quartile (99). However, results pertaining to lung functions were inconsistent. In an assessment of data from the Honolulu Heart Program, Sharp et al. (101) analyzed the relation between FEV₁ and self-reported frequency of fish consumption, categorized as less than twice per week and two or more times per week. Among 6,346 male smokers aged 45–68 years, after adjustment for cigarettes per day, age, height, and daily caloric intake, these authors found FEV₁ to be higher among subjects with a high dietary fish intake than among those with a low fish intake. From the difference observed, Sharp et al. predicted an FEV₁ 144 ml higher (95 percent CI: 62, 227) in the high-fish group at ≥40 years of smoking (101). The effect was larger among smokers of 30 or fewer cigarettes per day, which suggests a saturation effect. In contrast, fish intake showed no clear association with pulmonary function in other studies (84, 92). However, in those studies, no stratified analysis by smoking status was conducted.

To our knowledge, only one study has addressed the ω-3 hypothesis in a prospective data set (95). Results suggested that intake of linoleic acid (ω-6 fatty acid) was positively related to the incidence of chronic nonspecific lung disease (defined as chronic productive cough, diagnosed chronic bronchitis, emphysema, and asthma); however, over the 25-year study period, no association between ω-3 fatty acid intake and the incidence of chronic nonspecific lung disease was found.

Cross-sectional data suggest that ω-3 fatty acids may have a protective effect against COPD and decreases in lung function; however, study results are inconsistent in identifying the subgroups in which fish oil appears to have the greatest effect (71). None of these studies controlled for intake of other nutrients, such as antioxidant vitamins, which may be correlated with ω-3 fatty acid intake. Researchers who conducted the only known prospective study observed no protective effect for ω-3 fatty acids after adjusting for other nutrients (95); however, they did find that intake of solid fruit had a strong protective effect against chronic nonspecific lung disease.

SUMMARY

The results presented in this review suggest that the impact of nutrition on obstructive lung disease is most evident for antioxidant vitamins, particularly vitamin C and, to a lesser extent, vitamin E. By decreasing oxidant insults to the lung, antioxidants could modulate the development of chronic lung diseases and lung function decrement. Antioxidant vitamins could also play an important role in gene-environment interactions in complex lung diseases such as childhood asthma. Data also suggest that ω-3 fatty acids may have a potentially protective effect against airway hyperreactivity and lung function decrements; however, relevant data are still sparse. Although epidemiologic data suggest that consumption of fresh fruit may reduce risk of noncarcinogenic airway limitation, there are no clear data on which nutrients might be most relevant. While some studies evaluate daily intake of vitamin C, other studies use fruit consumption as a surrogate for antioxidant intake. Given the dietary intercorrelations among antioxidant vitamins, particularly vitamin C, β-carotene, and flavonoids, as well as other micronutrients, it may be difficult to isolate a specific effect. Some population subgroups with higher levels of oxidative stress, such as cigarette smokers, may be more likely to benefit from dietary supplementation, since some studies have suggested that antioxidant intake may have a greater impact in this group.

Studies of lung function decrement and COPD in adults suggest that daily intake of vitamin C at levels slightly exceeding the current Recommended Dietary Allowance (60 mg/day among nonsmokers and 100 mg/day among smokers) may have a protective effect (20). In the Schwartz and Weiss (85) and Britton et al. (87) studies, an increase of 40 mg/day in vitamin C intake led to an approximate 20-ml increase in FEV₁. Daily mean vitamin C intakes in these studies were 66 mg and 99.2 mg, respectively, and the highest intake level (178 mg/day) was approximately three times the Recommended Dietary Allowance. Although the amplitude of the effect was modest, if these effects accumulate over 20–30 years, they could have a meaningful impact on the rate at which pulmonary function declines, particularly in symptomatic subjects (85). Longitudinal data support the hypothesis that fresh fruit consumption has a beneficial impact on the lung (95). Among children, consumption of fresh fruit, particularly fruit high in vitamin C, has been related to a lower prevalence of asthma symptoms and higher lung function (64). This effect was observed even at low levels of fruit consumption (one or two servings per week vs. less than one serving per week), which suggests that a small increase in dietary intake could have a beneficial effect. Consumption of fish has also been related to lower airway hyperreactivity among children (75) and higher lung function in adults (100); however, longitudinal
data do not provide evidence that increased ω-3 fatty acid intake protects against lung disease (101).

Experimental studies of persons with asthma suggest that magnesium infusion may have a place in the acute treatment of asthma, but it does not seem to have long-term benefits. The studies of sodium, selenium, and fish oils do not show convincing evidence of clinical benefits. Studies of vitamin C supplementation suggest a short-term protective effect on airway responsiveness and pulmonary function. It remains to be proven whether consistent use of vitamin C would have a protective effect on the evolution of chronic asthma. Results from supplementation studies conducted among subjects exposed to high levels of oxidants (57-60) suggest that daily intake of antioxidant vitamins exceeding the Recommended Dietary Allowance may have a beneficial effect on lung airways and that intake higher than the Recommended Dietary Allowance should be recommended for populations chronically exposed to photooxidant air pollutants (such as ozone), cigarette smoking, or vigorous exercise. It is difficult to determine the amounts of antioxidant vitamins that people should consume. In particular, although vitamin C was shown to have maximum bioavailability when given in a single dose of 200 mg (102), experiments on which this finding was based were conducted under normal conditions. Guidelines from the US National Cancer Institute (103) recommend consumption of five servings of fruit and vegetables daily, corresponding to a vitamin C intake exceeding 200 mg. Dietary surveys carried out in the US population indicate that less than 12 percent of US children and adults meet this recommended level of intake (104).

Diet appears to be an important cofactor in the development of obstructive lung disease, although data are still sparse. There is a need for further research in experimental and epidemiologic settings to better understand the physiologic effects of antioxidant vitamins, ω-3 fatty acids, and other nutrients on lung tissues. The impact of diet on the incidence and evolution of asthma and COPD should be investigated using a cohort design that accounts for known risk factors. This will allow researchers to evaluate the exposure-disease relation over an adequate time frame and obtain insight into the causality of the relation. Some of these studies should enroll infants and young children to determine the impact of early diet on respiratory health. Research should also focus on the equally challenging policy issues—namely, finding effective methods of convincing people to increase their daily consumption of fresh fruits and vegetables, to stop smoking cigarettes, and to minimize their environmental and occupational exposure to pollutants and other agents that cause respiratory disease.

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REFERENCES


