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Epidemiologic Evidence Linking Antioxidant Vitamins to Pulmonary Function and Airway Obstruction

[Articles]

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; ATBC,

Alpha-Tocopherol Beta-Carotene Cancer; CARET, Carotene and Retinol Efficacy

Trial; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume

in 1 second; FVC, forced vital capacity; NHANES, National Health and Nutrition Examination Survey.

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INTRODUCTION

Reduced pulmonary function and indicators of airway obstruction have been shown to be strong predictors of mortality in numerous epidemiologic studies ([1-3](#)). Interestingly, even mild reductions in pulmonary function in nonsmokers have been linked to increased mortality ([4](#)). Although smoking is the major risk factor for chronic obstructive pulmonary disease (COPD), several issues remain to be resolved ([5](#)). For example, why do only 10-20 percent of smokers develop COPD ([6](#))?

The balance between the negative effects resulting from exposure to oxidants, for example, from cigarette smoke and air pollutants, and the defense by antioxidants has been suggested to play a role in both the pathogenesis of airway obstruction and the link between reduced pulmonary function and mortality ([7-12](#)). In particular, the role of antioxidant *vitamins* in protection against lung disease has attracted considerable clinical and epidemiologic interest because diseases associated with airway obstruction, such as COPD and asthma, present immense public health problems ([13-15](#)). This subject, however, has not been reviewed systematically. The present article is a qualitative systematic review of the epidemiologic and other evidence that deals with the association of antioxidant vitamins with pulmonary function and airway obstruction ([16-18](#)).

Definitions

Chronic airway obstruction is associated with impaired pulmonary function, and the forced expiratory volume in one second (FEV₁) is often used as an indicator of disease severity. There are numerous definitions and classifications of diseases associated with airway obstruction. In this review we will use the following definitions and terminology.

Chronic obstructive pulmonary disease (COPD) is an all-inclusive and nonspecific term that refers to a defined set of breathing-related symptoms (e.g., chronic cough, expectoration, exertional dyspnea) and is characterized by the presence of airflow obstruction with a slow, progressive decline in FEV₁ ([19, 20](#)). *Chronic bronchitis* is defined as the presence of productive cough for 3 months in 2 successive years in the absence of a cause of cough ([19](#)). *Emphysema* is defined as abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis ([19](#)). *Asthma* is defined as a chronic inflammatory airway disorder in which various cells and cellular elements play a role. This inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible. The inflammation also causes an associated increase in the existing

bronchial hyperresponsiveness to a variety of stimuli (21). There is increasing evidence that inflammatory processes also play a significant role in conditions currently summarized as COPD (22).

The use of outcomes such as COPD, asthma, or chronic nonspecific lung disease in epidemiologic investigations is problematic because of the inconsistency in the criteria that have been applied to define these diseases (23, 24). Therefore, the utilization of objective and more precisely defined endpoints has been recommended in studies of respiratory health and disease (23, 25). In particular, FEV₁ or simple respiratory symptoms (e.g., wheeze or productive cough) should be considered as factors associated with airflow obstruction (25) and are also used as outcome measures in this review. It should not be neglected, however, that these endpoints may be associated with airway disease of different pathogenesis with overlap in symptoms.

Normal growth of pulmonary function and risk factors of impairment

Although the ratio of the forced expiratory volume in 1 second to the total vital capacity (FEV₁/FVC) is used to define airway obstruction, FEV₁ is the pulmonary function test used to define its severity and has often been used to describe pulmonary function in epidemiologic studies. Therefore, it is pertinent to examine the normal phases of rise, plateau, and fall of the FEV₁ over a person's life span. Age, gender, height, and race are the major determinants of pulmonary function (26). Of these determinants, height has the strongest relation to FEV₁ in childhood. FEV₁ steadily increases during growth in childhood and early adult life (27), and pulmonary function in childhood is a predictor of adult pulmonary function (28). Asthma, gender, and active and passive tobacco smoke exposure are important determinants of early pulmonary function (29-36). Exposure to cigarette smoke even as early as in the prenatal period may influence pulmonary function growth (37, 38). Active smoking during adolescence reduces the maximally achieved pulmonary function, which is developed approximately at 20 years of age in women and 25 years in men (27). In the absence of risk factors of impairment of pulmonary function and in the absence of respiratory disease, pulmonary function then plateaus until the age of 35 years. During this phase, the presence of chronic respiratory symptoms and smoking are factors associated with premature decline in pulmonary function (35, 39). After the age of 35, pulmonary function starts to decline in nonsmokers. During this period, cigarette smoking is the most important predictor for airway obstruction and accelerated pulmonary function decline, although it explains only about 15-20 percent of variability in FEV₁ in that age group (40). How airway obstruction develops will be described in the next section.

Natural history of airflow obstruction

The original "British hypothesis" stated that smoking increases mucus hypersecretion due to bronchitis, which in turn causes airway obstruction (25, 41, 42). This hypothesis was later questioned by Fletcher and colleagues based on their landmark longitudinal study in working men in London (43, 44). They suggested that neither mucus hypersecretion nor bronchial infection causes or accelerates chronic airflow obstruction. Furthermore, chronic airflow

obstruction and mucus hypersecretion affect different parts of the lung. Although mucus hypersecretion has its origin in the large bronchi, chronic airflow obstruction is a condition associated with small airway disease and emphysema (42). These authors showed that the decline of FEV_1 with age is enhanced by smoking (figure 1) (35). However, a large proportion of smokers appear to be resistant to the development of airflow obstruction, and their rate of FEV_1 decline is similar to that of nonsmokers. It is not clear what determines this difference in susceptibility to cigarette smoke. The work by Fletcher and colleagues also suggested that the evolution of chronic airflow obstruction is a slow process that develops over the course of decades and that low levels of FEV_1 in middle age are likely to be correlates of accelerated loss of FEV_1 (45).

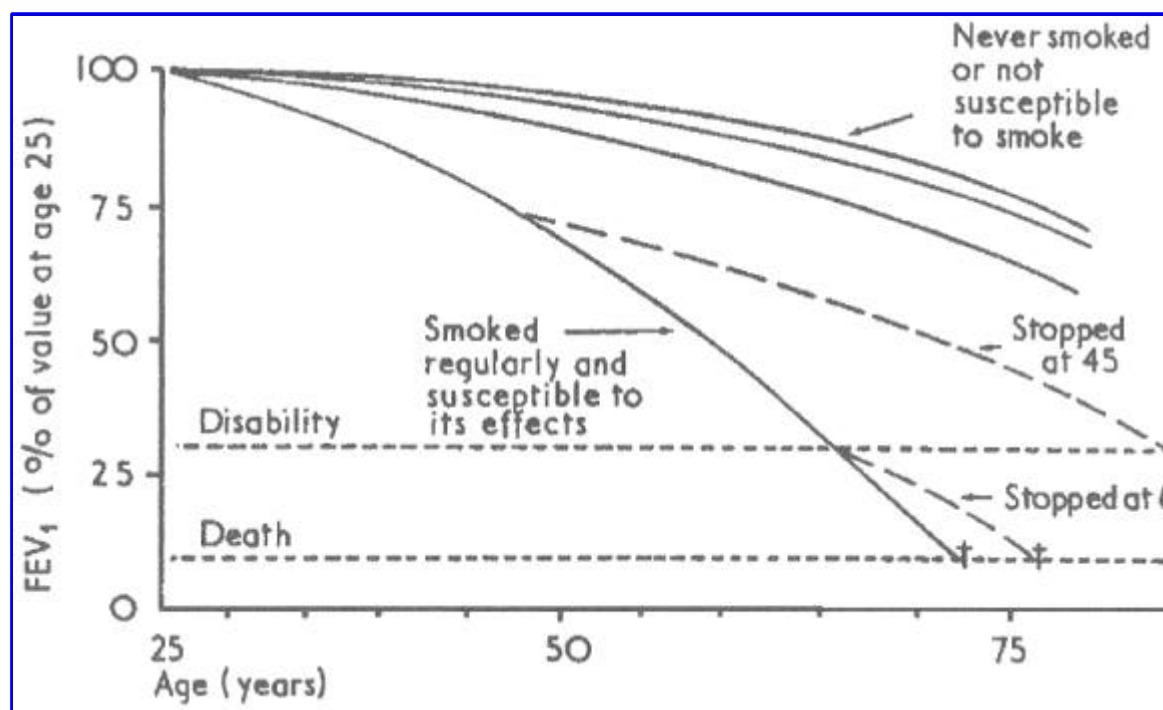


FIGURE 1. Risk for various men if they smoke: Differences between these lines illustrate the effects that smoking and stopping smoking can have on the forced expiratory volume in 1 second (FEV_1) of a man who is liable to develop chronic obstructive lung disease if he smokes. †, death, the underlying cause of which is irreversible chronic obstructive lung disease, whether the immediate cause of death is respiratory failure, pneumonia, cor pulmonale, or aggravation of other heart disease by respiratory insufficiency. Although this shows the rate of loss of FEV_1 for one particular susceptible smoker, other susceptible smokers will have different rates of loss, thus reaching "disability" at different ages. Reproduced with permission from Fletcher and Peto (43).

An alternative "Dutch hypothesis" implied an endogenous susceptibility for an asthmatic constitution that is a prerequisite for the development of any form of airway obstruction (46). The basis of the Dutch hypothesis is that both asthma and COPD are characterized by airway and lung tissue inflammation, resulting in airway obstruction (47).

Burrows (48) described two different forms of airway obstruction: one form associated with an allergic or asthmatic constitution and the other resulting from a combination of emphysematous changes in the lungs and permanent reduction in the caliber of small airways. Burrows et al. (49) also suggested that the overall course in patients with the asthmatic type of airways obstruction is more favorable. Later it was shown that asthma and airway hyperresponsiveness are predictors for the development of COPD (35, 50).

More recently O'Byrne and Postma (37) summarized the development of airway obstruction and FEV_1 decline (shown in figure 2). At least three mechanisms can result in reduced FEV_1 in adults and increase the risk of development of fixed airways obstruction: premature decline from the plateau phase (line 1), reduced pulmonary function growth (line 2), or increased reduction of FEV_1 (line 3). A combination of all three suggested courses and, thus, a more complex interaction of impaired growth and decline of FEV_1 is also conceivable (line 4).

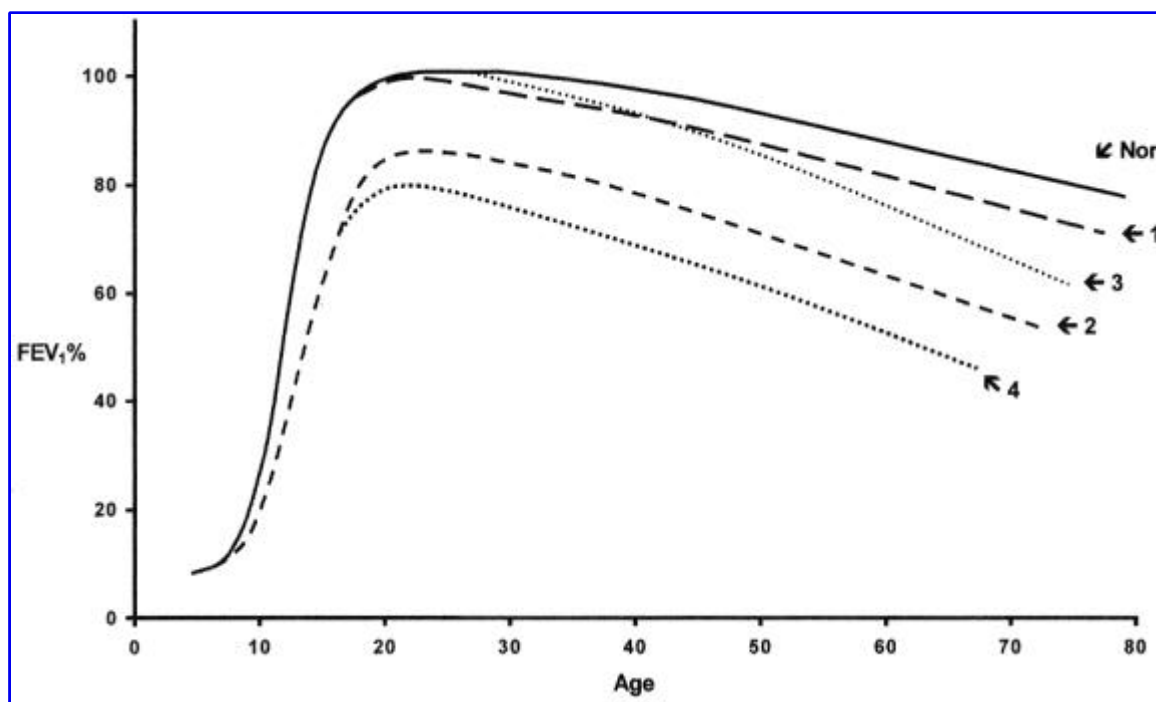


FIGURE 2. Growth and decline of pulmonary function depicted as the forced expiratory volume in 1 second (FEV_1) as a percentage of the maximum achieved value at age 20-25 years in a normal person. The line entitled "normal" shows the normal growth and decline of pulmonary function over a person's life span. Line 1 shows premature decline from the plateau phase, line 2 shows reduced growth and normal decline, and line 3 shows increased pulmonary function loss after normal growth. Line 4 depicts a potential combination of the suggested courses. Note that the life span is shortened by reduced FEV_1 . Adapted from O'Byrne and Postma (37) and Fletcher and Peto (43) with permission.

There are several proposed pathologic mechanisms for the development of

airway obstruction (37). Oxidative injury, as a result of exposure to oxidants from diverse sources including air pollution, cigarette smoke, and endogenous oxidants or resulting from a lack of antioxidants in the body, may at least in part be related to reduced FEV₁ and, therefore, contribute to airflow obstruction (11). Mechanisms that can result in oxidative injury of the lung are described in the following section and depicted in figure 3.

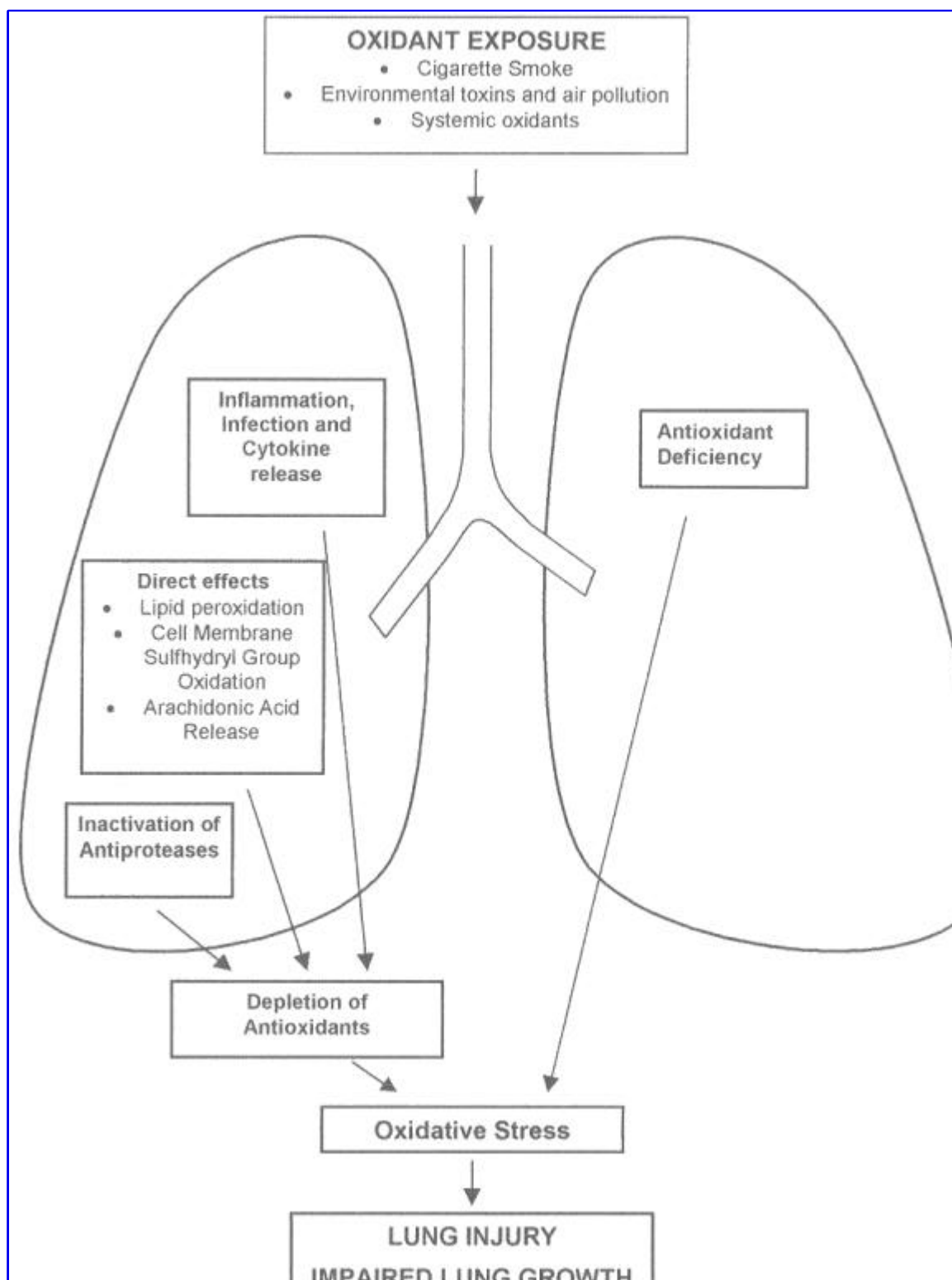


FIGURE 3. Mechanisms of oxidative stress-induced lung injury. Oxidant exposure from various sources (e.g., tobacco smoke, air pollution, systemic oxidants) can induce numerous reactions that lead to antioxidant depletion followed by oxidative stress. In the presence of antioxidant deficiency, oxidative stress can arise directly from oxidant exposure. Oxidative stress leads ultimately to lung injury and impairment of lung growth and function.

Mechanisms-oxidative stress in the pathogenesis of airway obstruction

Oxidant injury appears to underlie a number of inflammatory, obstructive, and fibrotic lung disorders (51, 52). Because the lung surface is exposed constantly to oxidants from ambient air, the respiratory tract lining fluids act as an interface between the environment and toxic exposure (e.g., cigarette smoke and air pollutants) on one side and respiratory tract epithelial cells on the other side (53). Additional oxidative burden arrives from endogenous or ingested compounds with oxidant activity. Oxidant defenses include both enzymatic and nonenzymatic antioxidants; antioxidant vitamins are among the nonenzymatic moiety within the lung tissue and respiratory tract lining fluids. If the concentration of prooxidants exceeds that of antioxidants, oxidative stress and injury may occur (54-57).

The potential role of oxidative stress in airway obstruction has been discussed recently. Inactivation of antiproteases, inflammation, infection, direct cell damage, and disturbances in the antioxidant defense are primary mechanisms that appear to be involved (figure 3) (9, 10, 58, 59).

Antiprotease hypothesis. One of the underlying mechanisms for lung injury is the inactivation of antiproteases by oxidants in the lung, a process which enables the enzyme elastase to exert toxic effects (60, 61). Elastase degrades elastin and damages airspaces, extracellular membrane proteins, and glycoproteins. Oxidant-mediated damage of lung connective tissue causes loss of parenchyma and leaves lungs excessively compliant that, in turn, can lead to early airway closure during expiration, air trapping, and ultimately emphysema. Elastase also stimulates interleukin-8 release and as a result can lead to inflammation (62).

Inflammation, infection, and activation of transcription factors.

Inflammation in COPD is associated with recruitment and deposition of neutrophils, and it has been shown that the airways of smokers with airway obstruction have significantly higher numbers of neutrophils than those without (63). In addition, neutrophils sequestered as a consequence of infection release oxidants (64), and the association of airway obstruction with high eosinophil counts in airways and blood could be mediated, at least in part, by oxidant release from these cells (65-67). There is evidence that alveolar macrophages generate free radicals and contribute to oxidative stress in the lung (68, 69). Oxidative stress can, in turn, cause further inflammation of respiratory epithelial cells and morphologic changes that may lead to airway obstruction and ultimately alter pulmonary function (70, 71). Several studies have shown that oxidants can activate transcription factors and induce transcription of genes that code for cytokines. Cytokine release can result in

inflammatory reactions that may lead to damage of respiratory epithelium ([72-75](#)).

Direct effects. Membrane damage and cell death can result from lipid peroxidation of membrane lipids as a result of oxidant exposure ([76](#)). In addition, membrane functions can be altered through oxidation of membrane sulfhydryl groups. For example, membrane receptors (e.g., adrenoreceptors) can be damaged functionally ([77, 78](#)). It is conceivable that direct toxic effects could cause airway narrowing, because epithelial permeability is increased and cilia function is impaired ([79](#)) or because oxidant-induced release of arachidonic acid could lead to bronchoconstriction ([77](#)).

Although all of the mechanisms described above may not play a role under physiologic circumstances when the supply of antioxidants is sufficient, they could be significant when the antioxidant supply is inadequate or deficient. Among the antioxidants that are thought to play a role in the prevention of oxidative lung injury are vitamin C (ascorbic acid), vitamin E ([alpha]-tocopherol), vitamin A (retinol), and carotenoids ([51, 80](#)). Although small, clinical studies have been conducted earlier, researchers began to focus on diet and respiratory health in population-based studies only recently ([81](#)).

METHODS

We searched the scientific literature for studies concerning antioxidant vitamins and pulmonary function in the general population until November 1999. Peer-reviewed articles from 1) a computer-assisted MEDLINE and CURRENT CONTENTS search to look for primary references, 2) secondary references listed in articles obtained from the primary search, and 3) the authors' own database were reviewed. We used the following keywords for the literature search: airway obstruction, asthma, chronic bronchitis, COPD, FEV₁, FVC, lung function, pulmonary function, respiratory symptoms, antioxidant vitamins, antioxidants, ascorbic acid, carotenoids, [beta]-carotene, lycopene, retinol, tocopherol, vitamin C, vitamin E, and vitamin A. The dietary and respiratory keywords, respectively, were combined to avoid duplication of references. We then limited the search to those citations that included at least one of the dietary keywords and one of the respiratory keywords. Each abstract was screened for relevance and content. The following criteria were used for considering studies for this review.

Types of studies and participants. Population-based epidemiologic studies were included. We excluded studies that were performed in small convenience samples, failed to report details on subject selection, or were restricted to patient or special exposure cohorts ([82-84](#)).

Types of exposure. To fulfill inclusion criteria, at least one of the following exposure measures had to be present: antioxidant vitamin A (retinol), C, or E or carotenoid intake; intake of food items rich in one of the antioxidant vitamins (i.e., fruit or vegetable); or serum levels of one of the antioxidant vitamins.

Types of outcomes. Studies were included if they used one of the following

outcomes: 1) spirometry data (FEV₁, FVC, or FEV₁/FVC); 2) diagnosis of asthma, COPD, or chronic bronchitis; or 3) respiratory symptoms associated with airway obstruction (e.g., wheeze or cough).

Carrying out a systematic review about antioxidant vitamins and respiratory health is made difficult by the heterogeneous nature of the exposure and outcome variables. The translation of the findings into quantitative summaries would have been much easier if the review were restricted to a single outcome and exposure. Given the relative paucity of studies in each of the various exposure and outcome groups, this approach would have been of limited utility. Therefore, the criteria by Hill (85) for causal inference applied to systematic reviews as described by Oxman and Guyatt (86, 87) were used to qualitatively assess the overall strength of the causal relation and to summarize the available evidence from the included studies. These criteria are listed in table 1 and described in detail in the evaluation of the evidence for vitamin C, but they are only described briefly in the evaluation of the other nutrients and foods, because the evidence is often derived from the same studies.

Criteria for causal inference
1. Temporal relation
2. Strength of the evidence (study design)
3. Magnitude of the effect
4. Dose-response relation
5. A priori hypothesis testing (was the study, at least in part, designed to investigate this hypothesis?)
6. Small number of hypotheses explored (how many hypotheses are investigated in each article and in related articles?)
7. Consistency across studies
8. Indirect evidence
9. Have other plausible competing hypotheses been ruled out?

TABLE 1. Criteria for causal inference

RESULTS AND DISCUSSION

The search strategy yielded 314 citations. Abstracts of all identified studies were reviewed; of these, 20 studies met the inclusion criteria, and one additional title was identified by hand searching. In these studies, exposure was defined as fresh fruit or vegetable intake or antioxidant vitamin intake calculated from 24-hour recall instruments, food frequency questionnaires, or household food weighed records or as vitamin blood levels.

These important differences in the study design and exposure assessment lead

to considerable heterogeneity among the identified studies. Furthermore, in a complete evaluation of the relation between diet and effects on health, there needs to be acknowledgment that micronutrient and food intake data have substantial differences. It is important to examine whether major foods contributing to a specific nutrient are also related to the studied health outcome (88). Thus, in the context of antioxidant vitamin intake, the major food sources (fruits and vegetables) of specific vitamins should be considered. If the major food sources show similar associations with the outcome, it provides support for an association with the nutrient or some correlated nutrient. If there were a discrepancy in the findings between those for foods and nutrients, the observed relation is more questionable. As noted above, there are important differences between pulmonary function and symptoms of disease that also need to be taken into account when outcomes are evaluated.

Bearing these differences and caveats in mind, we can proceed to assess the relation between antioxidant vitamins and respiratory health outcomes. It has to be noted that many of the identified studies investigated various nutrients or food items simultaneously and, therefore, several studies are mentioned more than once for the sake of clarity.

In the reviewed studies, vitamin C (ascorbic acid), vitamin E ([alpha]-tocopherol), and fresh fruit and vegetable intake (as a proxy for vitamin C intake) have been studied frequently together, and these studies will be presented first. The studies on retinol and carotenoids (often summarized as total vitamin A) will be described thereafter.

Vitamin C, vitamin E, and fresh fruit and vegetable intake

The characteristics and results of the included studies are listed in [table 2](#) (serum and dietary vitamin C), [table 3](#) (serum and dietary vitamin E), and [table 4](#) (fresh fruit or vegetable intake). Of the identified studies four were prospective cohort studies ([table 5](#)).

Authors, year (reference no.), and origin	Study population and study name	Instrument for exposure assessment	Exposure studied	Adjusted outcome measure (95% confidence interval) and p value	Comments
Vitamin C intake, serum levels, and respiratory symptoms					
Schwartz and Weiss, 1990 (89), United States	9,074 men and women, aged 30–74 years, NHANES II	24-Hour recall	Dietary vitamin C (2-SD increase) Serum C (2-SD increase)	Bronchitis: OR* = 0.70 (0.54, 0.92)† Wheezing: n.s.‡ (p not provided) Bronchitis: OR = 0.55 (0.48, 0.58) Wheezing: OR = 0.71 (0.58, 0.88)	Vitamin C remained a significant predictor after exclusion of smokers
Grievink et al., 1998 (90), the Netherlands	6,555 men and women, aged 20–59 years, MORGEN*	Food frequency questionnaire	Dietary vitamin C (90th vs. 10th percentile)	Cough: OR = 0.66 (0.50, 0.87)	Multiple symptoms tested; no association with phlegm, productive cough, or wheez
Bodner et al., 1999 (91), Scotland†	94 cases and 203 controls, men and women, aged 39–45 years	Food frequency questionnaire, vitamin C plasma levels	Tertiles of vitamin C intake (low vs. high) Vitamin C plasma (μmol/liter)	Ever wheeze: OR = 1.45 (0.71, 2.97) Current wheeze: OR = 2.06 (0.88, 4.82) Ever wheeze: OR = 0.99 (0.97, 1.00), p = 0.055 Current wheeze: OR = 0.58 (0.36, 0.99), p = 0.017	Effects absent in never smoker stronger in subjects perform manual labor, possible residual confounding by smoking
Vitamin C intake, serum levels, and pulmonary function					
Grievink et al., 1998 (90), the Netherlands	6,555 men and women, aged 20–59 years, MORGEN	Food frequency questionnaire	Dietary vitamin C (90th vs. 10th percentile)	FEV ₁ : 53 (23, 83) ml FVC*: 79 (42, 118) ml	No adjustment for socioeconomic status
Cook et al., 1987 (94), England and Wales	2,650 children, aged 8–11 years	Food frequency questionnaire administered to parents, serum	Fresh fruit intake (more than once per day vs. never) Serum vitamin C (n = 278)	FEV ₁ : 79 (22, 136) ml FVC: 132 (53, 210) ml FEV ₁ : r = -0.01, p = 0.82	Low correlation of vitamin C intake with serum vitamin C
Schwartz and Weiss, 1994 (95), United States	2,526 men and women, aged 30–74 years, NHANES I	24-hour recall and food frequency questionnaire	Dietary vitamin C (100 mg/day) Dietary vitamin C (highest vs. lowest tertile)	FEV ₁ : 35 ml, p = 0.01‡ FEV ₁ : 40 ml higher, p not provided	Effect independent of smoking status
Britton et al., 1996 (96), England	2,833 men and women, aged 18–70 years	Semiquantitative food frequency questionnaire	Dietary vitamin C (1-SD increase)	FEV ₁ : 25.0 (5.2, 44.8) ml FVC: 23.3 (0.8, 45.7) ml	Effect independent of smoking status
Dow et al., 1996 (97), England	178 elderly men and women, aged 70–96 years	Food frequency questionnaire	Dietary vitamin C (100-mg/day increase)§	FEV ₁ : 70 (–100, 300) ml, p = 0.534 FVC: 100 (0, 300) ml, p = 0.356	Small sample size; low mean vitamin C intake; survivors a previous study
Hu et al., 1998 (98), China	3,085 men and women, aged 35–64 years	Three-day weighed household food records, serum samples pooled by region	Dietary vitamin C (100-mg/day increase) Vitamin C levels (1-mg/dl increase)	FEV ₁ : 21.6 (–0.4, 43.5) ml FVC: 24.9 (0.2, 49.5) ml FEV ₁ : 143 ml, p = 0.003 FVC: 94 ml, p = 0.15	Effect similar in never and ever smokers, no change after adjustment for intake of other vitamins
Ness et al., 1996 (99), England	1,860 men and women, aged 45–74 years, EPIC*	Plasma vitamin C§	Plasma vitamin C levels (10 μmol/liter men Plasma vitamin C levels (10 μmol/liter women)	FEV ₁ : 43.1 ml, p < 0.001 FVC: 45.6 ml, p < 0.01 FEV ₁ : 8.6 ml, p = n.s. FVC: 11.5 ml, p = n.s.	Samples collected nonfasting; stronger, statistically significant positive association was present in women who smoked
Morabia et al., 1989 (100), United States	2,327 men and women, aged 25–74 years, NHANES I	24-Hour recall	Dietary vitamin C intake (lowest vs. highest quartile)	FEV ₁ /FVC ≤ 65%: OR = 1.2, p = n.s.	No analysis of continuous pulmonary function variable

* SD, standard deviation; OR, odds ratio; NHANES, National Health and Nutrition Examination Survey; n.s., not statistically significant; MORGEN, monitoring project on risk factors and health in the Netherlands; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; EPIC, European Prospective Investigation of Cancer.
† Individual logistic regression model.
‡ Case-control study.
§ Data calculated from cited reference and expressed for mean pulmonary function level.

TABLE 2. Cross-sectional and case-control studies concerning the relation of vitamin C with respiratory outcomes

Authors, year (reference no.), and origin	Study population and study name	Instrument for exposure assessment	Exposure studied	Adjusted outcome measure (95% confidence interval) and p value	Comments
Grievink et al., 1998 (90), 1999 (102), the Netherlands	6,555 men and women, aged 20–59 years, MORGEN*	Food frequency questionnaire Serum α-tocopherol (n = 367)	Dietary vitamin E (90th vs. 10th percentile) Serum vitamin E (90th vs. 10th percentile)	Productive cough: OR* = 1.26 (1.02, 1.56) FEV ₁ : 27.9 (–12.9, 68.7) ml FVC*: 18.2 (–32.2, 68.6) ml FEV ₁ : 23.2 ml, p > 0.10 FVC: 35.6 ml, p < 0.10	No adjustment for socioeconomic status
Bodner et al., 1999 (91), Scotland†	94 cases and 203 controls, men and women, aged 39–45 years	Food frequency questionnaire, vitamin E plasma levels	Tertiles of vitamin E intake (low vs. high) Vitamin E triglyceride ratio, plasma (log)	Ever wheeze: OR = 1.93 (0.79, 4.72) Current wheeze: OR = 4.02 (1.30, 12.42) Ever wheeze: OR = 0.45 (0.24, 0.83), p = 0.010 Current wheeze: OR = 0.34 (0.16, 0.72), p = 0.004	Effects were absent in never smokers and stronger in subjects performing manual labor, possible residual confounding by smoking
Britton et al., 1996 (96), England	2,833 men and women, aged 18–70 years	Semiquantitative food frequency questionnaire	Dietary vitamin E (1-SD increase)	FEV ₁ : 20.1 (1.3, 40.4) ml FVC: 23.1 (1.0, 45.0) ml	No independent effect of vitamin E after adjustment for vitamin C
Dow et al., 1996 (97), England	178 elderly men and women	Food frequency questionnaire	Dietary vitamin E (mg/day increase)	FEV ₁ : 42 (10, 74) ml, p = 0.012 FVC: 54 (18, 89) ml, p = 0.003	Small sample size
Morabia et al., 1990 (101), United States	83 men, aged 18 years or older	Stored blood samples	Serum vitamin E (lowest vs. highest tertile)	FEV ₁ /FVC ≤ 75%: OR = 1.0, p for trend = 0.99	No continuous data for pulmonary function reported, case-control design used for analysis

* OR, odds ratio; MORGEN, monitoring project on risk factors and health in the Netherlands; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation.
† Case-control study.

TABLE 3. Cross-sectional and case-control studies of vitamin E, pulmonary function, and indicators of obstruction of airways

Authors, year (reference no.), and origin	Study population and study name	Instrument for exposure assessment	Exposure studied	Adjusted outcome measure (95% confidence interval) and p value	Comments
Fresh fruit and vegetable intake and indicators of airway obstruction					
Butland et al., 1999 (92), England, Scotland, Wales	11,352 men and women, aged 33 years	Food frequency questionnaire	Summer fresh fruit consumption (more than once daily vs. never)	Prevalent wheeze: OR† = 1.04 (0.77, 1.40), p = 0.45 Frequent wheeze*: OR = 0.58 (0.46, 1.00), p = 0.02 Severe wheeze*: OR = 0.41 (0.20, 0.83), p = 0.034 Frequent wheeze by smoking status: Never smokers: OR = 0.88 (0.58, 1.33) Former smokers: OR = 0.42 (0.24, 0.72) Current smokers: OR = 0.64 (0.49, 0.84)	Effect could be attributed predominantly to former and current smokers
La Vecchia et al., 1998 (93), Italy	45,693 men and women, aged 15 years or older	Servings of vegetables per week from a household survey	Vegetable intake (highest vs. lowest tertile)	Chronic bronchitis: OR = 0.69 (0.61, 0.80) Bronchial asthma: OR = 0.70 (0.61, 0.78)	Dietary instrument not validated
Cook et al., 1997 (94), England and Wales	2,650 children, aged 8–11 years	Food frequency questionnaire administered to parents	Daily fruit consumption (increase from never to > daily)	Wheeze (% wheezed), χ^2 for trend = 0.23, p = 0.63	Low correlation of vitamin C intake with serum vitamin C
Fresh fruit and vegetable intake and pulmonary function					
Schwartz and Weiss, 1994 (95), United States	2,525 men and women, aged 30–74 years, NHANES I	24-Hour recall and food frequency questionnaire	Vitamin C-rich vegetable (10 portions/week)	FEV ₁ †: 5.1 ml, p = 0.15‡	Effect independent of smoking status
Monabia et al., 1989 (100), United States	2,327 men and women, aged 25–74 years, NHANES I	Food frequency questionnaire	Vitamin C-rich fruit (lowest vs. highest quartile)	FEV ₁ /FVC† ≤ 85%: OR = 2.2 (0.9, 5.3)	No analysis of continuous pulmonary function variable
Strachan et al., 1991 (103), England, Scotland, Wales	2,839 men and women, aged 18–69 years	Food frequency questionnaire	Winter fresh fruit and fruit juice consumption (ever vs. never)	FEV ₁ : 78 (24, 132) ml Current smokers: 65.8 (–1.71, 133.3) ml Never smokers: 85.2 (–9.9, 180.5) ml	Subjects free of respiratory symptoms. Former smokers were excluded
* Prevalent wheeze, history of wheeze in prior 12 months; frequent wheeze, ≥5 episodes in prior 12 months; severe wheeze, history of wheeze limiting ability to speak; p values for trend. † OR, odds ratio; FEV ₁ , forced expiratory volume in 1 second; NHANES, National Health and Nutrition Examination Survey; FVC, forced vital capacity. ‡ Individual logistic regression model. Data calculated from cited reference and expressed for mean pulmonary function level.					

TABLE 4. Cross-sectional and case-control studies concerning the relation of fresh fruit and vegetable intake with respiratory outcomes

Authors, year (reference no.), and origin	Study population and study name	Instrument for exposure assessment	Exposure studied	Adjusted outcome measure (95% confidence interval) and p value	Comments
Tabak et al., 1990 (104), Seven Countries†	12,673 men aged 40–59 years, Seven Countries	1- to 7-day food records	10% increase in dietary intake from the mean: Vitamin C Vitamin E Total fruits Citrus fruits	25-Year COPD* mortality Rate ratio = 0.50 (0.16, 1.78) Rate ratio = 0.95 (0.85, 1.05) Rate ratio = 0.57 (0.37, 0.88) Rate ratio = 0.94 (0.79, 1.13)	Misclassification of COPD is of concern. Small increases in exposure studied
Medema et al., 1993 (105), the Netherlands	793 men, aged 41–60 years, Zutphen	Cross-check dietary method, interview	Total fruit intake (highest vs. lowest quartile) Solid fruit intake (highest vs. lowest quartile)	CLD*: RR* = 0.73 (0.53, 0.99) CLD: RR = 0.63 (0.45, 0.86)	No longitudinal assessment of dietary habits
Troisi et al., 1995 (106), United States	77,866 female nurses, aged 33–55 years, Nurses' Health Study	Food frequency questionnaire to assess dietary intake of different food items over the past year	Dietary C (highest vs. lowest quintile) Dietary and supplemental vitamin C (highest vs. lowest quintile) Dietary vitamin E (highest vs. lowest quintile) Dietary and supplemental vitamin E (highest vs. lowest quintile)	Adult onset asthma RR = 1.11 (0.69, 1.77) RR = 1.69 (1.28, 2.23) RR = 0.53 (0.33, 0.86) RR = 0.83 (0.64, 1.08)	Supplemental vitamin use may have been initiated prior to diagnosis when symptoms occurred
Caney et al., 1998 (107), England, Scotland, Wales	2,171 men and women, aged 25–75 years	Food frequency questionnaire	Fresh fruit consumption: Change from highest to lowest consumption measured 7 years apart Baseline average fresh fruit consumption	FEV ₁ * decrease: 107 (36, 178) ml No association with change in FEV ₁ observed	Observed effects were stronger in current smokers
* COPD, chronic obstructive pulmonary disease; CLD, chronic lung disease (chronic cough or phlegm or clinical diagnosis of asthma, chronic bronchitis, wheeze, and emphysema); RR, relative risk; † Finland, Italy, Greece, former Yugoslavia, Japan, United States, and the Netherlands.					

TABLE 5. Prospective studies concerning the relation of fresh fruit and vegetable intake and vitamins C and E with pulmonary function

Cross-sectional and case-control studies. Indicators of airway obstruction. In two cross-sectional studies and one case-control study, there was a negative association between serum or dietary vitamin C and cough, wheeze, or a diagnosis of bronchitis (table 2) (89-91). Although the case-control study by Bodner et al. (91) showed an inverse association with dietary and serum vitamin E, a positive association with cough was seen in the cross-sectional study by Grievink et al. (90) (table 3). Two large European cross-sectional studies found inverse relations between fruit and vegetable intake and frequent wheeze, reported bronchitis, or asthma (92, 93) (table 4), but in the

only identified study in children a weak and not statistically significant trend for wheeze was observed (94).

Pulmonary function. Five of the eight cross-sectional studies (90, 94-100) found a positive association between vitamin C in the diet and serum with pulmonary function (table 2). Of the four cross-sectional studies (table 3) that included measurement of dietary or serum vitamin E, three observed a weak positive association with pulmonary function (90, 96, 97, 101, 102). Fresh fruit or vegetable consumption was positively related to pulmonary function in three studies (table 4) (95, 100, 103).

Prospective cohort studies. COPD mortality after 25 years of follow-up was inversely related to vitamin C, vitamin E, and total fruit intake in the "Seven Countries Study" at baseline (table 5). Included in the Seven Countries Study are data from the Zutphen study in which, in an earlier analysis, an inverse association of chronic lung disease incidence with baseline fruit intake was observed (104, 105). A different outcome was investigated in the Nurses' Health Study by Troisi et al. (106) who reported that vitamin C intake from both diet and supplements but not from diet alone was associated with an elevated risk of adult-onset asthma. In this latter study, vitamin E intake from diet alone was inversely related to asthma risk. Finally, in the only identified study that measured pulmonary function longitudinally, there was a greater decline in FEV₁ associated with a large reduction in fruit consumption from baseline intake (107).

Criteria for causal inference. Vitamin C. Most of the studies evaluating the relation between serum or dietary vitamin C intake and the respiratory health outcomes included in this review report a beneficial association. However, when we apply the first two criteria for causal inference (temporal relation and strength of the evidence) (table 1), the temporal relation between exposure and outcome cannot be established because most studies are cross-sectional. Only two prospective cohort studies evaluated dietary vitamin C: one with asthma incidence as the outcome and the other, COPD mortality. The reduction in mortality risk associated with increase in vitamin C consumption in the Seven Countries Study was not statistically significant. The increased incidence of asthma in the Nurses' Health Study was found only after inclusion of vitamin C supplement users. For the Nurses' Health Study, the authors speculated that increased vitamin supplement use precipitated by health problems and health awareness is one possible explanation (106). This explanation is conceivable as nurses are likely to be more health conscious, and a possible protective effect of vitamin C against respiratory symptoms may be known among this professional group. This hypothesis is further supported by the observation that long-term use (more than 10 years) of vitamin C supplements was not associated with an increased asthma risk.

Thus, these two prospective studies do not unequivocally support either a beneficial or a harmful effect on outcomes such as COPD or asthma. The differences in the results may reflect the distinctive pathologic mechanisms for COPD and asthma. The effects of vitamin C on pulmonary function or respiratory symptoms have not been studied prospectively, leaving us with no evidence to support or reject such an association based on the temporal relation between exposure and outcome.

There is only a weak association of low serum levels or dietary intake of vitamin C with wheezing (third criterion, the magnitude of the observed effect). The association of vitamin C intake with pulmonary function could be of significance. The adjusted increase in FEV₁ associated with a 100-mg increase in daily vitamin C intake ranged from approximately 21 ml in the study using data from China (98) to 70 ml in the small study by Dow et al. (97); the weighted mean increase in FEV₁ obtained from all studies is approximately 37 ml per 100-mg increase in daily vitamin C intake. This increase in FEV₁ is equivalent to the negative effect of approximately 5-10 pack-years of smoking or 1-2 years of aging on FEV₁ (95, 96). Although small, such an increase would not be negligible at the population level, because of the inverse association between FEV₁ and mortality. However, caution is required when dietary intake data obtained with different instruments are pooled. Although several studies used food frequency questionnaires to measure vitamin C intake, in the studies using data from the First and Second National Health and Nutrition Examination Survey (NHANES I and II) (89, 95, 100), dietary information was mainly obtained from a single 24-hour recall. This method is problematic because of the relatively high measurement error for vitamin C intake and because of intraindividual variation in intake (108). Therefore, the true association between pulmonary function and vitamin C intake in these studies could be stronger than the one observed.

A positive dose-response relation (fourth criterion) between dietary and serum vitamin C with pulmonary function levels was reported in a number of the cross-sectional studies (90, 91, 96, 98, 99) and lends support to the hypothesis of a protective effect of vitamin C on lung function and respiratory symptoms.

The fifth criterion whether in the cited studies a hypothesis was tested a priori is difficult to assess. For the most part, these studies were designed to investigate diet and respiratory disease based on the fact that respiratory outcomes were included in the study protocol. It is clear, however, that in many studies respiratory outcomes were not the only outcomes of interest and that the relation of diet with respiratory health was investigated after initial reports had been published (89, 95, 100, 101). Consequently, there are numerous hypotheses that have been explored in these investigations (sixth criterion, number of hypotheses explored). For example, NHANES data have been used to explore a variety of research questions, including the association of other antioxidant vitamins with pulmonary function. However, it is unlikely that large observational studies such as NHANES or the Nurses' Health Study would be conducted to test a single hypothesis because of the resources involved. Thus, the latter two criteria should be investigated in the context of whether the design was appropriate to investigate the specific research question and whether other studies confirm the findings.

It is noteworthy that studies using similar outcome measures are consistent (seventh criterion) in their findings (although the instruments for exposure assessment differed). The association of vitamin C intake with FEV₁ showed similar effect sizes across the range of intake and, therefore, supports a causal relation (90, 95-98). Ness et al. (99) speculated that uncontrolled confounding explained why they found a positive correlation of serum vitamin C levels

with both FEV₁ and FVC only in men. The choice of the outcome measure may explain the different results obtained by different authors in the analysis of NHANES I. Morabia et al. (100) found no association of dietary vitamin C intake with airway obstruction (FEV₁/FVC ≤ 65 percent), but FEV₁ and FVC considered separately were positively related to vitamin C intake in the analysis of Schwartz and Weiss (95). These authors (95) speculated that the choice of the case-control design in the study by Morabia et al. (100) probably limited the ability to detect an association. Although the study by Dow et al. (97) observed the strongest association of dietary vitamin C with FEV₁, the results were not statistically significant. This latter study had limited power to detect an association and included only a relatively small percentage (54 percent) of elderly survivors from a previous study in which patients with respiratory symptoms were probably oversampled (109). Therefore, these results should be generalized cautiously.

The last two criteria (indirect evidence and whether other plausible competing hypotheses have been ruled out) can be considered together. There is a body of literature that demonstrates the antioxidant properties of vitamin C (51) and provides plausible biologic, indirect evidence. Apart from the regeneration of vitamin E, vitamin C scavenges reactive oxygen species and counteracts lipid peroxidation (110). In addition, vitamin C appears to have an effect on immune defense: It deactivates oxidants that are released by activated neutrophils (111, 112). The interaction of ascorbic acid with methacholine in experimentally induced airway constriction is evidence for a modulation of prostaglandin synthesis and bronchial reactivity (113). It has also been suggested that vitamin C may play a role in the repair of lung tissue through its effects on collagen synthesis (98, 114).

Because of the strong intercorrelation of vitamin C with other nutrients in fruits and vegetables, it is almost impossible to separate the effects of the individual nutrients. Thus, other plausible competing hypotheses, for example, effects on lung function from other nutrients found in fruits and vegetables or a healthy lifestyle in general, cannot be ruled out. However, support for a causal vitamin C effect is provided by studies in different populations with different dietary sources of vitamin C. For example, the results of the study by Hu et al. (98) in China are particularly important with respect to the observation that dietary sources and total intake of vitamin C in rural China differ from those in the US population. In China, total vitamin C intake is approximately 50 percent higher than in the United States, and only 2 percent of the vitamin C is derived from fruits, and 73 percent is from vegetables (98, 115).

It is also interesting that in several studies an association of pulmonary function with vitamin C persisted after stratification by smoking status (96, 98, 102). The findings among nonsmokers would argue that the results are not related to uncontrolled confounding by smoking, although other factors such as passive smoking have not been examined. Nevertheless, the associations for current and former smokers are stronger in other studies (95, 99). Whether a stronger association is a result of residual confounding by smoking, poor dietary habits of smokers, or increased need for vitamin C in smokers is unknown. It has been shown that cigarette smoke experimentally reduces

vitamin C levels in plasma (116) and that smokers have lower vitamin C serum levels (117). Both of the latter observations favor increased requirements of vitamin C in smokers and could explain stronger effects of vitamin C on pulmonary function in smokers.

In summary, after consideration of the criteria that corroborate a cause-effect relation, there is some evidence for a beneficial role of vitamin C in pulmonary function and airway obstruction. The strength of the evidence is reduced predominantly by the cross-sectional design of most of the available studies. The consistency among the studies on vitamin C and pulmonary function, however, is noteworthy and supported by several studies that measured symptom-based outcomes.

Vitamin E. Vitamin E has been studied less extensively than vitamin C in relation to pulmonary function and indicators of airway obstruction. In the prospective cohort studies, no effect of vitamin E intake on COPD mortality was observed in the Seven Countries Study (104), while in the Nurses' Health Study (106) high dietary intake of vitamin E but not vitamin E from supplements was associated with reduced asthma incidence over a period of 10 years.

There is a consistent effect of vitamin E on pulmonary function in the identified cross-sectional studies, although the association was not statistically significant in one of these studies (90). The size of the effect varied considerably, ranging from approximately 12 to 200 ml for a difference of 1 standard deviation in daily vitamin E intake. The smallest effect was observed in the study with the highest measured vitamin E intake (102), and the largest difference was found in the study with the lowest mean intake (97). Morabia et al. (101) failed to observe any relation of vitamin E with pulmonary function, but the study focused on the FEV₁/FVC ratio, and the sample size was small, limiting the power to detect an association. The differences in the mean dietary intake of vitamin E among these studies could explain the differences in the effects on FEV₁.

One report showed a positive association of vitamin E intake with productive cough (90), but these authors tested multiple hypotheses investigating numerous symptoms, and the results could be due to chance. A case-control study found a reduction in the risk for wheezing (91). Thus, the relation between vitamin E status and respiratory symptoms is uncertain because of the few available studies.

Evidence for a role of vitamin E is weakened by the observation that in at least one of the three cross-sectional studies the effect of vitamin E intake on pulmonary function was reduced after taking the effects of vitamin C into account (96). This attenuation of an association by another nutrient is a frequently encountered problem in the analysis of dietary data, and it is related to the intercorrelation of nutrients in the diet (108). Differences in the degree of measurement error between measured nutrients can result in spuriously stronger associations of the nutrient with smaller measurement error. Because dietary vitamin E intake is more difficult to measure and is associated with a greater measurement error than vitamin C intake (108), the authors may have failed to observe a stronger relation of vitamin E with pulmonary function. On

the other hand, it has been suggested that the antioxidant function of vitamin E depends on vitamin C as a recycling agent (118). These results could indicate that vitamin C may be the more important determinant of antioxidant activity in the lung and that the function of vitamin C to recycle vitamin E to its reduced state in cell membranes does, in fact, influence the effect of vitamin E (96). If this were the case, one would have expected an inverse association of asthma with vitamin C intake in the Nurses' Health Study as well, but it is also conceivable that a vitamin E effect in asthma is related to a different mechanism (119) or that vitamin E can act independently of vitamin C. Support for an independent mechanism comes from in vitro studies that report that other compounds can function as coantioxidants with vitamin E, for example, bilirubin and glutathione (120-122).

Although the epidemiologic evidence is weak, it is supported by the observed biologic functions of vitamin E. Vitamin E acts as an antioxidant by conversion of reactive oxygen species into less active forms and as a chain-breaking antioxidant in lipid peroxidation (123, 124). Because it is membrane bound, it also protects against cell membrane injury (125). Thus, in summary, there is some support for a protective role of dietary vitamin E in asthma and for an association of pulmonary function with vitamin E intake, but the available evidence is weak and is primarily based on data from cross-sectional studies.

Fruit and vegetable intake. Effects from nutrients in serum and diet can differ from effects related to the intake of fruits and vegetables. For example, Morabia et al. (100) observed a stronger inverse association of airway obstruction with intake of fruit rich in vitamin C than with vitamin C intake. Although different dietary instruments were used to measure nutrient and food intake, this difference could indicate that other nutrients in fruits protect against airway obstruction.

Studies using fruit and vegetable intake have consistently demonstrated beneficial associations of fresh fruit and vegetable intake with respiratory symptoms and disease, as well as pulmonary function. In one study, however, consistently low levels of fresh fruit intake did not appear to increase pulmonary function decline in adults (107). This intriguing observation needs to be confirmed by other investigations, because no other sources of vitamin C were considered except for fresh fruit intake. In this study, the mean for summer and winter intake was used as an indicator of usual intake, and other seasonal adjustments were not made. The results by Strachan et al. (103), however, suggest that differences in summer and winter intake would be expected and, in addition, subjects who consume large quantities of fruit in the winter may differ considerably in other lifestyle factors from those with low winter fruit intake.

If the relation between fruit intake and pulmonary function were confirmed, higher than average pulmonary function in adulthood may be the result of the influence of diet on lung development and growth in childhood. Cook et al. (94) observed that fresh fruit intake but not vitamin C plasma levels were positively associated with FEV₁ in children. Although in this study only a weak inverse trend with wheeze was observed, fruit intake in childhood could reduce the risk of asthma and, thus, preserve pulmonary function in adult life

(35). Again, one could speculate that the effect is not due to vitamin C because no association of pulmonary function with plasma vitamin C was observed, but that it is due to other compounds with antioxidant activity, for example, selenium and flavonoids (114, 126, 127). However, the results could also indicate that methodological problems with plasma vitamin C determination or high intraindividual variation in vitamin C intake were present and, therefore, no association was observed.

A weak dose-response relation has been found in several of the studies that measure fruit and vegetable intake (93, 94, 103), supporting a causal relation, but as observed for vitamin C intake most of these studies also had different initial study aims and, thus, investigated a number of different hypotheses.

In summary, the evidence of a protective effect of fruit and vegetable intake on pulmonary function and outcomes associated with airways obstruction is somewhat stronger than for vitamins C or E based on three prospective cohort studies that show an association with respiratory outcomes. However, it is impossible at present to identify the nutrients or specific fruits or vegetables associated with this effect or to exclude that this effect is related to other healthy lifestyle habits in persons who consume fruits and vegetables.

Vitamin A and carotenoids

Only recently, carotenoids have been separated from the effects of vitamin A (retinol) and, in several of the studies measuring dietary intake, retinol and carotenoids are summarized as vitamin A. Eight studies were included, of which three are prospective cohort studies. One additional study used milk intake as a proxy for vitamin A consumption (81). Details of the included studies are listed in tables 6 and 7.

Authors, year (reference no.), and origin	Study population and study name	Instrument for exposure assessment	Exposure studied	Adjusted outcome measure (95% confidence interval) and p value	Comments
Tockman et al., 1986 (81), United States	2,539 men and women, 20 years or older	Questionnaire	Milk intake (daily vs. never) as a proxy for vitamin A	Difference in prevalence of chronic bronchitis*: 11.7% vs. 17.7%, $p < 0.01$	No difference in never-smokers; separate analysis, but large difference in smokers
Grievink et al., 1998 (90), 1999 (102), the Netherlands	6,555 men and women, aged 20–59 years, MORGEN†	Food frequency questionnaire	Dietary β -carotene (90th vs. 10th percentile)	Wheeze: OR† = 1.27 (1.04, 1.55) FEV ₁ : 50 (31, 89) ml FVC†: 75 (40, 110) ml FEV ₁ : 73 ml, $p = 0.22$ FVC: 147 ml, $p = 0.05$	Wheeze showed a positive association with intake of β -carotene, no association with other symptoms (e.g., cough phlegm)
Bodner et al., 1999 (91), Scotland‡	94 cases and 203 controls, men and women	Food frequency questionnaire, β -carotene and retinol plasma levels	Serum β -carotene ($n = 367$) Tertiles of β -carotene intake (low vs. high)	Ever wheeze: OR = 0.68 (0.45, 1.75) Current wheeze: OR = 0.89 (0.40, 1.94)	Cases had significantly lower β -carotene plasma levels than controls. No difference in plasma retinol levels between cases and controls
			Tertiles of vitamin A intake (low vs. high)	Ever wheeze: OR = 0.58 (0.29, 1.18) Current wheeze: OR = 0.59 (0.26, 1.33)	
			β -carotene in plasma ($\mu\text{mol/liter}$)	Ever wheeze: OR = 0.66 (0.30, 1.45), $p = 0.308$ Current wheeze: OR = 0.53 (0.12, 1.01), $p = 0.253$	
			Retinol in plasma ($\mu\text{mol/liter}$)	Ever wheeze: OR = 1.29 (0.95, 1.74), $p = 0.100$ Current wheeze: OR = 1.32 (0.94, 1.86), $p = 0.113$	
Monabia et al., 1989 (100), United States	2,327 men and women, aged 25–74 years, NHANES‡ I	24-Hour recall and food frequency questionnaire	Dietary vitamin A intake (lowest vs. highest quartile)	Airway obstruction defined as FEV ₁ /FVC $\leq 65\%$ OR = 2.5, p for trend < 0.01	Case-control approach within cross-sectional study. Effect modification by smoking showing stronger effects in smokers
Monabia et al., 1990 (101), United States	83 men, aged 18 or older	Stored blood samples	Serum retinol and carotenoids (lowest vs. highest tertile)	Airway obstruction defined as FEV ₁ /FVC $\leq 75\%$ Retinol: OR = 4.3, p for trend = 0.04 Total carotenoids: OR = 1.1, p for trend = 0.92 Carotenoids other than β -carotene or lycopene: OR = 2.3, p for trend = 0.21	Small sample of participants from previous population-based study
Shahar et al., 1994 (128), United States	10,416 men and women, aged 45–64 years, ARIC‡	Food frequency questionnaire recall over previous 1 year	Dietary vitamin A intake (lowest vs. highest quartile)	Airway obstruction defined as FEV ₁ /FVC $\leq 65\%$: OR = 1.1 (0.5, 1.9)	Case-control approach within cross-sectional study. Intra odds ratio only in heavy smokers

* Defined as self-reported cough and phlegm production.

† OR, odds ratio; MORGEN, monitoring project on risk factors and health in the Netherlands; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NHANES, National Health and Nutrition Examination Survey; ARIC, Atherosclerosis Risk in Communities Study.

‡ Case-control study.

TABLE 6. Cross-sectional and case-control studies investigating vitamin A and carotenoids in relation to pulmonary function and indicators of airway obstruction

Authors, year (reference no.), and origin	Study population and study name	Instrument for exposure assessment	Exposure studied	Adjusted outcome measure (95% confidence interval) and p value	Comments
Tabak et al., 1998 (104), Seven Countries†	12,673 men, aged 40–59 years, 1- to 7-day food records	Seven Countries Study	10% increase in dietary intake from the mean: β -carotene	25-Year COPD* mortality Rate ratio: 1.01 (0.94, 1.08)	Misclassification of COPD is of concern. Small increases in exposure studied
Medema et al., 1993 (105), the Netherlands	793 men, the Zutphen Study	Cross-check dietary method, interview	Dietary vitamin A and β -carotene intake at baseline	Baseline vitamin A and β -carotene intake did not differ among those who developed CLD* and those who did not	No multivariate analysis for vitamin A and β -carotene provided
Troisi et al., 1995 (106), United States	77,886 female nurses, Nurses' Health Study	Food frequency questionnaire	Dietary carotene (highest vs. lowest quintile)	Adult onset asthma: RR* = 0.82 (0.65, 1.05), $p = 0.08$ for trend across quintiles	No association with supplemental vitamins

* COPD, chronic obstructive pulmonary disease; CLD, chronic lung disease (chronic cough or phlegm or clinical diagnosis of asthma, chronic bronchitis, wheeze, and emphysema); RR, relative risk.

† Finland, Italy, Greece, former Yugoslavia, Japan, United States, and the Netherlands.

TABLE 7. Prospective cohort studies investigating vitamin A and carotenoids in relation to pulmonary function and indicators of airway obstruction

Cross-sectional and case-control studies. Indicators of airway obstruction. In an early investigation, Tockman et al. (81) found a negative association of milk intake as a crude proxy for vitamin A intake (never vs. daily) with chronic bronchitis (table 6). The results of one case-control and one cross-sectional study relating dietary and serum [beta]-carotene and vitamin A (retinol) to wheeze are contradictory (90, 91) and, in general, only weak associations have been observed.

Pulmonary function. Three of the four cross-sectional studies observed a positive association of serum or dietary vitamin A and carotenoids with pulmonary function, including NHANES I (table 6) (90, 100, 101, 128). However, although analyzed similarly, results of the Atherosclerosis Risk in Communities (ARIC) Study (128) differed considerably from results of NHANES I. In the ARIC Study a positive association was found only in the

group of heavy smokers, and even in this subgroup only a modest effect was observed (odds ratio = 1.7, 95 percent confidence interval: 1.1, 2.7 in the lowest compared with the highest tertile of vitamin A intake in heavy smokers).

Prospective cohort studies. Results of the Nurses' Health Study (106) suggested a reduced risk for new onset asthma for participants in the highest quintile of carotene intake (table 7), but no association with supplemental vitamin A was reported in this study. Miedema et al. (105) observed no differences in baseline vitamin A or [beta]-carotene intake between cases and "noncases" of chronic lung disease, and the Seven Countries Study showed no association of [beta]-carotene intake with COPD mortality (table 7) (104).

Criteria for causal inference. Vitamin A (retinol). The literature with regard to vitamin A and pulmonary function in population-based studies is limited, and different outcomes have been measured in the two prospective cohort studies (105, 106). Unfortunately, results of multivariate analysis for dietary intake of vitamin A were not reported in these studies. Misclassification of COPD from death records and of self-reported asthma is a plausible concern in these studies. Dietary vitamin A intake and other nutrients were not measured longitudinally, but it is conceivable that dietary habits could change during follow-up, in particular in individuals who quit smoking.

In cross-sectional studies, vitamin A was investigated mainly in relation to the FEV₁/FVC ratio as an indicator of airway obstruction. The findings for vitamin A from the two larger studies showed a protective effect for heavy smokers but were otherwise contradictory (100, 128). Shaha et al. (128) had more statistical power to explore the association in strata of smoking status. In addition, these investigators used a food frequency questionnaire with recall over the preceding year, while in NHANES I (100) a 24-hour recall instrument was used. The former is a more reliable instrument for measurement of a habitual diet and may better reflect long-term effects of diet on pulmonary function (108). The association observed for heavy smokers in both studies would suggest a lack of antioxidants in the diet or increased need for such substances in smokers, although Shaha et al. (128) speculated that in their study the observed association in heavy smokers may have been due to chance.

The inclusion of dietary carotenoids in the measurement of total vitamin A intake may further explain the differences in the studies using vitamin A intake. Intake of carotenoids is of particular interest because some of these compounds exhibit strong antioxidant activity (110). A smaller case-control study showed a trend toward a small increase in the risk of wheezing with increasing plasma retinol levels but not with vitamin A intake (91). Although this internal consistency can be a result of a lack of association between the calculated intake from the dietary instrument and plasma levels, it may indicate that retinol in serum is associated with other nutrients or lifestyle habits that have negative effects on the lung.

Several biologic mechanisms for a protective role of vitamin A against respiratory impairment have been proposed. Vitamin A has been associated with protection of the respiratory epithelium against inflammation (129), and

retinol has more recently been shown to have an antioxidant function ([130-132](#)). Further indirect evidence comes from the observed association between milk intake and low prevalence of chronic bronchitis in smokers by Tockman et al. ([81](#)). However, in this study no vitamin A intake was calculated, and other possible explanations cannot be ruled out, for example, confounding by other nutritional factors, uncontrolled confounding by smoking, or avoidance of milk by smokers or those participants suffering from chronic bronchitis.

In summary, prospective cohort studies have not provided detailed assessment of the hypothesis that vitamin A is related to airway obstruction, while methodological differences in exposure assessment could explain contradictory results from cross-sectional studies. It is possible that a protective effect is stronger in smokers because two studies observed an effect modification by smoking, but overall the evidence for a role of vitamin A (retinol) in the protection against airway obstruction is weak.

Carotenoids. The results of studies that investigated the role of [beta]-carotene in airway obstruction are also inconsistent. Of the three prospective studies one found a weak inverse association between dietary carotenoids and adult onset asthma ([106](#)). The two other prospective cohort studies found no association between baseline [beta]-carotene intake and chronic lung disease incidence ([105](#)) or COPD mortality ([104](#)). Contradictory results for [beta]-carotene intake and plasma levels in relation to wheezing were observed in two observational studies ([90, 91](#)). Similar to the limitations related to measurement of vitamin C and vitamin E intake, measurement error, the choice of the dietary instrument, and the differences in outcome assessment are likely to be, at least in part, responsible for the contradictory results. Evidence for a role of [beta]-carotene in respiratory health comes from the Dutch MORGEN Study that found an association between FEV₁ and [beta]-carotene in serum and diet, the latter measured by a food frequency questionnaire ([90, 102](#)).

How do these results compare with other available evidence? There are two large chemoprevention trials. The Carotene and Retinol Efficacy Trial (CARET) and the Alpha-Tocopherol Beta-Carotene Cancer (ATBC) Prevention Study were designed to investigate the effect of [beta]-carotene supplementation on lung cancer incidence ([133, 134](#)). These studies were restricted to populations at high risk for lung cancer, namely, smokers and smokers exposed to asbestos ([133](#)). The ATBC Prevention Study suggested that in smokers, aged 50-69 years, carotenoids from dietary, but not from supplemental, intake appear to provide at least mild protection against COPD exacerbations ([135](#)). However, the Seven Countries Study showed no effect of carotenoid intake on COPD mortality ([104](#)). Serum [beta]-carotene levels at baseline were associated with lower prevalence of respiratory symptoms in the pilot phase of CARET ([82](#)). It is also conceivable that it is not [beta]-carotene but other correlated carotenoids that play a role in protection against respiratory disease. To date, more than 600 carotenoids are known ([136](#)), and many of them have strong antioxidant activity as singlet oxygen radical scavengers ([110](#)). In fact, the suggested inverse relation of carotenoids other than [beta]-carotene and lycopene with airway obstruction in the study by Morabia et al. ([101](#)) could indicate that these nutrients play a role.

In summary, there is weak evidence that total carotenoid intake has a protective effect on asthma incidence in adults and that it may be related to pulmonary function. No definite evidence exists whether carotenoids have an effect on respiratory symptoms or COPD mortality. Other studies have shown that [beta]-carotene supplementation increases the risk for lung cancer in smokers ([137, 138](#)); it is possible, however, that carotenoids other than [beta]-carotene have effects on respiratory health, but other carotenoids have not been studied systematically.

Methodological considerations

Bias and confounding. The use of self-reported symptoms or disease as outcome is prone to bias because of differences in education, health awareness, and access to medical care ([139-141](#)). Although wheezing and cough can be symptoms of asthma, they may also indicate the presence of COPD and, therefore, can lead to misclassification ([23, 142, 143](#)). It is also possible that participants who report very low fruit intake differ with regard to other lifestyle factors not adequately adjusted for in the analysis (e.g., [103](#)). For example, Grievink et al. ([90](#)) did not adjust for education level in their analysis because it was felt that controlling for education in the analysis would "overadjust." Thus, there may be uncontrolled confounding by socioeconomic status. Higher education may be associated with both higher intake of antioxidants and lower degrees of environmental and occupational exposure to toxins that can influence pulmonary function. Because participation in several of the population-based studies was approximately 50 percent, generalizability of the observed results may be limited ([90, 96](#)), although the internal validity of the findings is probably high ([144](#)).

Exposure and outcome assessment. Exposure and outcome assessments frequently vary across studies and, because of methodological differences or the applied disease definitions, it is difficult to compare the results ([23, 25, 145](#)). For the measurement of diet, there is the uncertainty as to whether dietary questionnaires addressing fresh vegetable and fruit intake correspond to actual tissue availability of vitamin C and other nutrients. Studies using serum samples may be helpful in exploring the hypotheses ([119, 128](#)). In a study by Redlich et al. ([146](#)), lung tissue levels of vitamin E and carotenoids were more strongly correlated with serum levels than with dietary intake of these nutrients. Serum samples of antioxidant vitamins, however, are more likely to reflect short-term antioxidant intake and are not necessarily representative of a subject's long-term intake ([108](#)).

FEV₁ may be a more reliable outcome measure than respiratory symptoms or self-reported disease ([23](#)). If symptom-based outcomes are investigated, only standardized questionnaires should be used to assess respiratory health and symptoms. The latter are important in particular for the measurement of asthma prevalence, because asthma is associated with variable airflow obstruction ([147](#)). A number of questionnaires are available ([148-152](#)).

If pulmonary function is measured, the protocol should follow available guidelines ([153](#)). Some of the included studies probably underestimated the true FEV₁ ([99, 103](#)), because more than three maneuvers may be necessary to

achieve the maximal FEV₁ (153). If there were a systematic underestimation of FEV₁ proportional to the measured FEV₁, the true observed difference in FEV₁ between participants with low and high fruit or vitamin intake would be higher than reported.

Only four prospective studies have evaluated the impact of dietary antioxidants on respiratory health in general population samples. Although a prospective design reveals stronger evidence for a true relation, none of the studies provided data on both vitamin intake and pulmonary function. In particular, longitudinal measurements are lacking.

Publication bias. In general, it is noteworthy that with the exception of very few studies (90, 91, 106) there was a remarkable absence of studies with negative findings. While this observation could indicate that there is no harmful effect of antioxidant vitamins or of a diet rich in fruit and vegetables on airway obstruction or pulmonary function, publication bias is a concern because negative findings could remain unpublished (154). For the evaluation of a benefit from antioxidant vitamins, these negative studies would add important information. After reports of a positive association between [beta]-carotene supplementation and lung cancer incidence (137, 138), it is likely that there will be more interest in such findings.

CONCLUSION

Several of the epidemiologic studies examining associations between antioxidant vitamin status and indicators of airway obstruction and pulmonary function have found these to indicate protective effects. However, the results are somewhat inconsistent for vitamin E, vitamin A, and carotenoids. The largest body of literature exists for vitamin C and fresh fruit and vegetable intake in relation to various indicators of airway obstruction.

Healthy diet versus specific nutrients

The existing studies cannot distinguish an effect related to specific nutrients from that of a generally healthy diet with a combined effect of several nutritional factors. There are several other compounds with known antioxidant properties that are found in fruits and vegetables. Limited evidence exists that selenium intake may have protective effects in asthma (155). Flavonoids have strong antioxidant activity and protective effects in cardiovascular disease, but their role in respiratory disease remains to be explored (93, 156-158). Therefore, it is important to measure other potential antioxidants in future studies. It was pointed out by Burney (119) that, until data from trials are available, studies involving serum levels of nutrients will be particularly useful in exploring the hypotheses, in confirming results for antioxidant status derived from dietary intake, and in the identification of other potential antioxidants. However, even studies including the measurement of blood levels are subject to measurement error and to confounding by smoking and dietary factors, but they could provide additional support for large-scale trials with vitamin supplements.

Public health recommendations

What does it mean if antioxidant vitamin intake is related only to FEV₁ and not to respiratory symptoms or disease? A substantial public health benefit may still exist because reduced FEV₁ is related to mortality from respiratory and nonrespiratory disease in both ever-smokers and never-smokers (4). Only approximately 50-60 percent of the biologic variability of FEV₁ as an indicator of pulmonary function can be explained by factors such as sex, age, height, and other established covariates (26, 159). Therefore, examination of additional factors, including diet, is of growing interest.

Based on the available evidence, a recommendation to the general population to consume a diet high in vegetables and fruits containing vitamin C is appropriate, particularly because of the lack of significant side effects and other known positive effects of these foods (e.g., see recommendations by the American Heart Association, the National Cancer Institute, and the American Cancer Society). The evidence is insufficient to recommend use of any supplemental vitamins for prevention and treatment of respiratory impairment. In fact, supplementation with high doses of [beta]-carotene in smokers is dangerous, because of the associated risk of lung cancer, even if there is a slight chance of reducing symptoms of COPD or impairment of FEV₁. Routine use of supplemental vitamins C and E may also have adverse effects (160, 161).

Future studies

Several epidemiologic investigations have obtained pulmonary function data by spirometry or are currently underway (162). A recent National Heart, Lung, and Blood Institute workshop underlined the importance of investigating the association between diet and pulmonary function (162). Cross-sectional and longitudinal data will add to the knowledge of a relation between pulmonary function and antioxidant vitamins. Longitudinal studies using determinations of vitamins in blood samples or other tissues will be of particular importance, and more studies in children are needed because of a paucity of data in children. Whether there is a benefit of slower decline of pulmonary function from high vegetable, fruit, or vitamin C intake also needs to be determined from longitudinal studies. Finally, important evidence as to whether specific antioxidant vitamins have a positive effect on respiratory health will come from large-scale, randomized, controlled trials that include supplemental vitamin interventions in their protocols. From this review it is obvious that future studies of airways obstruction should include a combination of standardized outcome measures, such as validated symptom-based questionnaires and quantitative pulmonary function measurements.

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After completion of the literature review, new evidence has become available. A reference list of recent studies is available from the corresponding author.

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