

REVIEW

Anti-oxidants and air pollution in relation to indicators of asthma and COPD: a review of the current evidence

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Introduction

There is a growing recognition that air pollutants, such as ozone and particulate matter are related to acute respiratory effects, such as a decrease in pulmonary function and an increase in respiratory symptoms [1,2]. These acute effects are often mild and reversible in healthy individuals. However, repeated peak exposures to ambient air pollution might lead to the occurrence of chronic obstructive pulmonary diseases (COPD) and deteriorate the health in those subjects in whom chronic respiratory disease is present [3,4]. For both the acute respiratory effects of air pollution and the occurrence of asthma and COPD, oxidant processes and free radical reactions are probably involved in the mechanisms. Therefore, anti-oxidants may be protective in relation to acute respiratory effects of air pollution [5–7] and in relation to chronic conditions, such as asthma and COPD [8,18].

The question remains whether there is enough evidence in the current literature to conclude whether: (1) anti-oxidants could modulate acute effects of air pollution under ambient conditions and; (2) whether anti-oxidant vitamins are associated with asthma or COPD. We limit this review to anti-oxidants that are derived from diet, such as vitamin C, vitamin E and carotenoids.

Anti-oxidants

Anti-oxidants are defined by their mechanistic action. Anti-oxidant mechanisms involve any cell process that prevents the formation of free radicals, converts oxidants to less toxic species, directs reactive species away from vital cellular structures, or repairs oxidant injury. Anti-oxidant enzymes form a first line of defence in the lungs. Uric acid and the anti-oxidant (pro)-vitamins, such as vitamins E, C and carotenoids from diet form a second line of defence [19].

Vitamin C or ascorbic acid is water-soluble and is mainly derived from fruits, vegetables and potatoes. It is present in both extracellular and intracellular fluids in the lungs [19]. Vitamin E comes mostly from vegetable oils and margarines

and consists of four lipid-soluble tocopherols (α , β , δ , γ -tocopherol). α -Tocopherol is the most active antioxidant of the four tocopherols and is present in the lipid membranes and in the extracellular fluids [20]. Of all carotenoids, β -carotene, a lipid soluble anti-oxidant available in membranes of tissues, is best known. It is present in fruits and vegetables [19].

Anti-oxidants in relation to the acute respiratory effects of air pollution

Two mechanisms are proposed for a respiratory effect of oxidative air pollutants. The first mechanism involves a reduction of maximal inspiratory capacity through stimulation of the neural receptors in the upper airways by cyclooxygenase products of arachidonic acid [21]. Recently, Hazucha *et al.* [22] showed that an anti-inflammatory drug with anti-oxidant capacity (ibuprofen) suppressed the release of metabolites of arachidonic acid and decrements in lung function but not the release of inflammatory cells. Vitamins C and E have been shown to affect arachidonic acid metabolism, but their precise role in this metabolism is not fully understood [5,15,23].

The other mechanism involves recruitment of inflammatory cells. Ozone and to a smaller extent NO_2 react rapidly with poly-unsaturated fatty acids (PUFAs) in the lung initiating lipid peroxidation [24]. In addition, these substances can stimulate the release of arachidonic acid from the membrane bilayer in the lungs. Arachidonic acid, a precursor of prostaglandins and leukotrienes, is a PUFA which is prone to oxidation because of its four double bonds. Elevated levels of leukotrienes may cause tissue damage and attract inflammatory cells as was observed after ozone exposure [25,26]. Anti-oxidants, in particular, vitamin C, may modulate the reactivity of oxidant air pollution by reacting directly with the pollutants before lung tissue injury occurs [24]. Vitamin E is known for stopping the process of lipid peroxidation [24].

The mechanistic effect of particulate air pollution (PM) on the respiratory system has not extensively been studied. However, the levels of inflammatory cells and oxygen metabolites are probably increased after exposure to PM

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[27]. Anti-oxidants might also react with these oxygen metabolites preventing a further influx of inflammatory cells and thus decreasing the damage to lung tissues.

Anti-oxidants and oxidative air pollution

Table 1 summarizes studies on modulation of acute respiratory effects of air pollution by anti-oxidant supplementation. Some of these studies used controlled exposure to single pollutants. Other studies were conducted under ambient conditions of exposure to pollutant mixtures. Most studies had different health end-points, such as inflammatory markers, respiratory symptoms, airway reactivity and lung function.

The first experimental studies investigated a possible protective role of anti-oxidants on acute effects of ozone and NO₂. The first two experiments did not find that 10–12 weeks of vitamin E supplementation protected against acute effects on lung function and respiratory symptoms of a 2-hr 1000 µg/m³ ozone exposure while subjects were exercising [28]. However, a combination of supplemental vitamin C and vitamin E was shown to protect partly against acute effects of lower levels of ozone (600 µg/m³) on lung function in exercising subjects [5]. Acute effects of high levels (> 3000 µg/m³) of NO₂ on lipid peroxidation were measured in one study [29] and on hyperresponsiveness to metacholine in another [7]. After supplementation with vitamin C and E, subjects had lower levels of lipid peroxidation products in lung lavage and higher levels of α₁-antitrypsin in alveolar lining fluids compared to the placebo group [29]. Vitamin C supplementation alone showed an improvement of airway responsiveness compared to placebo [7]. No exercise was performed during exposure in both studies.

Most of these earlier studies used experimental protocols with single pollutants and a small number of subjects. In these studies, the levels of ozone and NO₂ were very high (mostly above 1000 µg/m³) and subjects were supplemented for relatively short periods with high doses of vitamin C or E. These doses were at least eight to 16 times the US Recommended Dietary Allowances (RDA) of vitamin C (60 mg/day) and 100 times the RDA of vitamin E (8 mg/day for women and 10 mg/day for men) [30].

Recent studies have addressed conditions in which the levels of ozone and supplement doses were lower. One experimental study among asthmatics challenges subjects after 45 min of exposure to ozone (240 µg/m³) with exercise to two concentrations of SO₂ (0.10 and 0.25 p.p.m.) for 10 min [31]. Preliminary results suggest that a cocktail of vitamin C (500 mg) and vitamin E (400 mg) protected against PEF decrements from SO₂ challenges after ozone exposure in the severe asthmatics (*n* = 6) only. The duration of supplementation in this study was unclear. The other recent experimental study exposed healthy subjects to relatively high levels of ozone (800 µg/m³) for 2 h while the subjects were exercising

[32]. Subjects were placed on a diet low in vitamin C for 3 weeks and then supplemented for 2 weeks with a relatively low dose of vitamin C (250 mg). Preliminary results, only 18 subjects of the total 30 subjects were included in the analysis, suggest that supplementation with vitamin C, E and a vegetable extract protected against pulmonary function decrements but not against an increase in inflammatory markers [32].

In the above mentioned experimental studies, FEV₁ decreased by 80 mL and FVC by 70 mL after 2 h of exposure to either 600 µg/m³ [5] or 800 µg/m³ ozone [32] in the placebo group while the anti-oxidant group showed a significantly lower decrease in FEV₁ and FVC of about 40 mL. Recently, it has been investigated whether acute effects of ambient ozone on lung function can be modulated by anti-oxidant supplementation [33–35]. In a pilot study, 26 cyclists performed 192 lung function measurements before and after exercise. Half of the group was randomly assigned to the supplementation group and were given 650 mg vitamin C, 75 mg vitamin E and 15 mg β-carotene daily for 10 weeks. The control group did not receive a placebo. The average 8-h mean ozone concentration prior to post-exercise lung function measurement was 101 µg/m³ (range 30–205 µg/m³) [33]. We repeated the study with a similar but placebo-controlled design. In this study 38 cyclists (380 lung function measurements) participated and anti-oxidant supplementation consisted of 100 mg vitamin E and 500 mg of vitamin C daily for 15 weeks. The average 8-h mean ozone concentration prior to post-exercise lung function measurements was 86 µg/m³ (range 32–199 µg/m³). In the pilot study, an increase of 100 µg/m³ ozone significantly decreased FEV₁ by 186 mL and FVC by 183 mL in the control group. The supplementation group did, however, not show a significant effect of ozone on FEV₁ (–20 mL) and FVC (25 mL) [33]. In the placebo-controlled study, an increase of 100 µg/m³ ozone decreased FEV₁ by 95 mL and FVC by 125 mL in the control group. In the supplementation group, FEV₁ (10 mL) and FVC (42 mL) did not decrease significantly. The 'treatment effect' was statistically significant in both studies. The third intervention study under ambient conditions had a placebo-controlled cross-over design and was conducted among street workers (*n* = 49) in Mexico City [34]. The workers received a similar cocktail as our cyclists in the pilot study and performed repeated lung function measurements. They were not exercising heavily but ambient ozone concentrations were high (mean 163 µg/m³). In the first phase of this study, an increase of 100 µg/m³ ozone decreased FEV₁ (179 mL) and FVC (148 mL) in the placebo group significantly more than in the supplementation group (FEV₁ 44 mL and FVC 44 mL). The second phase of this study did not show clear effects of ozone because the washout period (2 weeks) between the supplementation of anti-oxidants and placebos was probably too short [34]. The

Table 1. Evidence of acute effects of air pollution being modulated by anti-oxidant supplements

Study	Design	Subjects	Exposure	Supplements	Outcome	Beneficial association
Hackney <i>et al.</i> [28]	double-blind*	34 healthy adults	2-h 1000 $\mu\text{g}/\text{m}^3$ O_3 + exercise	0.8 g/day vit E for 10 week	Symptoms & lung function	—
	double-blind	22 healthy adults	2-h 1000 $\mu\text{g}/\text{m}^3$ O_3 + exercise	1.6 g/day vit E for 12 week	Symptoms & lung function	—
Chatham <i>et al.</i> [5]	double-blind cross-over	14 healthy adults	2-h 600 $\mu\text{g}/\text{m}^3$ O_3 + exercise	1 g vit C once 0.8 g/day vit E for 2 week (?)	Lung function	+
Mohsenin <i>et al.</i> [7]	double-blind cross-over	11 healthy adults	1-h 3760 $\mu\text{g}/\text{m}^3$ NO_2	0.5 g vit C 4 times/day for 3 days	Airway reactivity to metacholine	+
Mohsenin <i>et al.</i> [29]	double-blind	19 healthy adults	3-h 7520 $\mu\text{g}/\text{m}^3$ NO_2	1.5 g vit C/day 1.2 g vit E/day for 4 weeks	Lipid peroxidation & α_1 -antitrypsin in alveolar fluids	+
Trenga <i>et al.</i> [31]	double-blind cross-over	17 asthma adults	45 min 240 $\mu\text{g}/\text{m}^3$ O_3 + exercise	500 mg vitC, 400 mg vit E duration?	PEF	+
Samet <i>et al.</i> [32]	double-blind placebo	30 healthy adults	2-h 800 $\mu\text{g}/\text{m}^3$ O_3 + exercise	2-w daily 250 mg vit C, 100 mg vit E, vegetable cocktail	FEV ₁ , FVC	+
					Inflammatory markers (BAL)	—
Grievink <i>et al.</i> [33]	control group	26 cyclists exercise	mean level O_3 101 $\mu\text{g}/\text{m}^3$ +	650 mg vit C, 75 mg vit E, 15 mg β -carotene daily, 15 weeks	Repeated lung function FEV ₁ FVC	+
Grievink <i>et al.</i> [35]	double blind	38 cyclists exercise	mean level O_3 77 $\mu\text{g}/\text{m}^3$ +	500 mg vit C, 100 mg vit E daily 10 weeks	Repeated lung function FEV ₁ FVC	+
					PEF, MMEF	—
Romieu <i>et al.</i> [34]	double-blind cross-over	49 street workers	mean level O_3 163 $\mu\text{g}/\text{m}^3$	650 mg vit C, 75 mg vit E, daily, 11 weeks	Repeated lung function 15 mg β -carotene FVC, MMEF	FEV ₁ —
Bucca <i>et al.</i> [6]	double-blind cross-over	20 healthy PC	2-h traffic directing in winter	2 g vit C once	MEF50 & airway reactivity to histamine	+
	double-blind cross-over	20 healthy PC	4 day traffic directing in winter	2 g vit C/day for 4 days	PEF	+
Grievink <i>et al.</i> [36]	panel-study	227 subjects with chronic resp. symp.	Mean PM ₁₀ level 32–44 $\mu\text{g}/\text{m}^3$	Serum β -carotene Diet vit C, β -car	PEF	+
						tendency

* The term double-blind denotes placebo-controlled; vit C = vitamin C, vit E = vitamin E, β -car = β -carotene, O_3 = ozone, PM₁₀ = particulate matter with a 50% cut-off diameter of 10 μm , FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, MMEF = maximal mid-expiratory flow, MEF₅₀ = maximal expiratory flow at 50% FVC, PEF = peak expiratory flow, BAL = broncho-alveolar lavage, PC = police officers.

difference in decreases in lung function (treatment effect) between the study groups after exposure to ozone were smaller in the experimental studies than in the ambient studies. The experimental studies had, however, much higher levels of ozone for shorter duration which makes comparison difficult. Anti-oxidants and particulate air pollution There has only been one small study investigating a possible modulation of the acute effects of ambient winter air pollution (components and concentrations not given) on lung function by supplemental vitamin C (2 g) [6]. During winter, concentrations of ozone are usually low, whereas concentrations of particulate matter tend to be higher. In the first experiment, vitamin C supplementation prevented a decrease in lung function (MEF₅₀) and an increase in airway responsiveness to histamine. In the second experiment, vitamin C was supplemented and peak expiratory flow (PEF) measurements before and at the end of the working day were performed in policemen during four consecutive days of traffic directing. The PEF decreased during the working day in the control group but not in the vitamin group. We recently analysed the data of a panel study on a possible modulation of the acute respiratory effects of winter air pollution by dietary and plasma anti-oxidants [36]. Subjects with chronic respiratory symptoms performed daily PEF measurements in the morning and evening and reported their respiratory symptoms daily. Subjects with low levels of serum β -carotene had larger PEF decreases when particles $< 10 \mu\text{m}$ (PM₁₀) in diameter or black smoke levels were high compared to subjects with high levels of serum β -carotene. The same results tended to be observed for dietary vitamin C or β -carotene. Recently, the authors of a study on the long-term effect of inhalable particles on mortality observed that the risk of nonmalignant respiratory mortality in relation to PM₁₀ was larger among nonsmoking subjects with low antioxidant vitamin consumption (RR = 1.26) than those with high antioxidant consumption (RR = 1.08). No information was given whether this consumption included supplemental intake and which type of anti-oxidants were considered [37].

Conclusion

The evidence is convincing that a cocktail of anti-oxidant supplements can modulate the acute effects of ozone or NO₂ on lung function. This was found in both experimental studies at high ozone levels and under ambient conditions with relatively low ozone levels. Effects on inflammatory markers have not been sufficiently studied in relation to anti-oxidants to allow a firm conclusion. Modulation of acute respiratory effects of PM by antioxidants has also not been sufficiently studied to draw conclusions although what evidence there is points in the same direction as was found for the ozone studies.

Anti-oxidants in relation to asthma and COPD

Inflammatory processes playing a role in asthma and COPD can be triggered by endogenous factors, such as leukotrienes, fatty acids and immune complexes and by exogenous oxidants such as air pollutants, cigarette smoke and allergens. As a result a large amount of reactive oxygen species is produced [38]. The produced reactive oxygen species can cause epithelial damage. Anti-oxidants may neutralize the induced oxidative damage or the produced reactive oxygen species and protect against lipid peroxidation. Thus, an increased antioxidant status might decrease chronic inflammation [39]. In addition, anti-oxidants have been suggested to preserve the inhibitory activity of α_1 -antitrypsin and thus prevent the destruction of the alveolar membrane [40]. We will evaluate the epidemiological evidence for a beneficial effect of dietary anti-oxidants (vitamin C, vitamin E, carotenoids) on respiratory endpoints and focus on the distinction between indicators of asthma (bronchial reactivity and symptoms such as wheeze and shortness of breath) and indicators of COPD (airway obstruction and symptoms such as cough and phlegm). Some of the evidence from studies reporting on the intake of fruit and vegetables is not included in the tables when results are not presented as intake of vitamin C, E and β -carotene. A recent review of dietary influences on respiratory disease provides a more detailed description of the relevant epidemiological studies [41].

Indicators of asthma

The effect of anti-oxidants on bronchial reactivity was investigated in one case-control study and in several intervention studies where vitamin C supplements in high doses were given to either asthmatic or healthy subjects (Table 2). The case-control study showed that subjects with bronchial hyperreactivity (20% fall in FEV₁ after a metacholine challenge) had a lower dietary intake of vitamin C and β -carotene compared to subjects without bronchial reactivity [17]. The results of the intervention studies strongly suggest a short-term beneficial effect of vitamin C supplementation on bronchial hyperreactivity in healthy subjects and in asthmatics, in spite of the vast differences between these studies in measures of bronchial hyperreactivity, type of challenge and other test conditions [15,16,18,23,42]. The beneficial effect in asthmatics suggests that vitamin C may decrease frequency and severity of attacks. A small intervention study in asthmatics seems to support this by showing that the severity and frequency of attacks after daily supplementation of 1 g of vitamin C during 14 weeks was significantly reduced compared to the control group [43]. The relation between anti-oxidant vitamins and the prevalence of symptoms or incidence of asthma is investigated in several observational studies (Table 3). Blood levels of

Table 2 Evidence for a relation between anti-oxidants and bronchial reactivity

Reference	Study design & population	Anti-oxidant intake	Bronchial reactivity type of challenge & outcome measure	Reduction in reactivity observed*
Zuskin <i>et al.</i> [42]	Intervention 17 healthy individuals	500 mg vit. C supplement	Histamine, flow rates at 50% VC	+
Mohsenin <i>et al.</i> [15]	Intervention 14 asthmatics	1 g vit. C supplement	Metacholine, airway reactivity, PD ₄₀	+
Ogilvy <i>et al.</i> [23]	Intervention 6 healthy individuals	1 g vit. C supplement	Metacholine, airway conductance	+
Malo <i>et al.</i> [59]	Intervention 16 asthmatics	2 g vit. C supplement	Histamine, PC ₂₀ FEV ₁	-
Bucca <i>et al.</i> [16]	Intervention 9 subjects with URI ²	2 g vit. C supplement	Histamine, PC ₂₀	+
Bucca <i>et al.</i> [18]	Intervention 7 smokers 7 nonsmokers	2 g vit. C supplement	Histamine, PC ₂₅ MEF ₅₀	+ only in smokers
	Intervention 7 smokers	1 g vit. C for 1 week	Histamine, PC ₂₅ MEF ₅₀	+
Soutar <i>et al.</i> [17]	Observational 29 BHR cases	Dietary vit. C	Metacholine	+>
	58 controls	Dietary vit. E	PD ₂₀ FEV ₁	->
		Dietary β -carotene		+bs

bs = borderline statistically significant ($P < 0.10$); 1 + : reduction in BHR observed; -: no reduction in BHR observed 2 URI = upper respiratory infection.

vitamin C were beneficially associated with wheeze in adults [13,45] but not in children [47]. However dietary vitamin C was not associated with asthma or asthma-symptoms in any of the studies. Vitamin E (dietary and blood levels) was beneficially associated with asthma, only in studies on incident cases (adult onset wheeze and 10-yr incidence of asthma) [12,45], but not in studies with prevalent cases. No relation was observed between dietary β -carotene and asthma symptoms in two case-control studies, but, the relation with plasma- β -carotene was borderline significant [45,46]. Also, the relation between dietary total carotene and the incidence of asthma was borderline significant [12]. In general, beneficial associations were observed only in studies with blood levels of antioxidant vitamins as exposure variable or in studies with incident cases of asthma (adult onset asthma or 10-year incidence of asthma). The cross-sectional studies where dietary antioxidant vitamins were studied in relation to the prevalence of asthma symptoms, showed no associations. It is possible, that blood levels of anti-oxidant vitamins better reflect actual anti-oxidant exposure in the lungs than dietary intake. But, if we wish to evaluate the beneficial effect of dietary intake of anti-oxidants, it is necessary to shift from cross-sectional study designs to longitudinal designs in particular in children.

Indicators of COPD

Most of the studies on the relation between anti-oxidants and the prevalence or incidence of COPD symptoms evaluated the effect of dietary intake only (Table 4). These studies showed no beneficial association between the intake of vitamin C, β -carotene or vitamin E and symptoms of COPD [11,44,46,48]. The NHANES II study among 9000 subjects observed a beneficial association with both, dietary and serum vitamin C and bronchitis symptoms [13]. The potential beneficial effect of vitamin E and β -carotene in smokers was evaluated in the Alpha-Tocopherol Beta Carotene Trial (ATBC trial) among over 29 000 male smokers. A beneficial association between dietary vitamin E and β -carotene and presence of COPD symptoms was observed at baseline measurement before intervention [14]. However, supplementation of these male smokers for six years with α -tocopherol (50 mg/day) and β -carotene (20 mg/day), did not show a change in the incidence of COPD symptoms [14]. The inconsistency between the effect of baseline dietary intake and prospective anti-oxidant supplementation may have several reasons: supplementation may have been for too short a period or too late in the disease process, wrong substances or doses may have been administered for maximal effects of supplementation, or dietary anti-oxidants may be more effective than supplementation. In conclusion, the evidence for a protective effect of anti-oxidant vitamins on COPD symptoms is thin. Evidence of a relation between

Table 3. Epidemiological evidence for a relation between anti-oxidant vitamins and asthma

Reference	Study design & population	Anti-oxidants measured in	Respiratory outcome*	Association		
				Beneficial	Adverse	No
<i>Vitamin C</i>						
Schwartz <i>et al.</i> [13]	Cross-sectional 9074 adults	Diet	Wheeze	+		+
		Serum				
Grievink <i>et al.</i> [44]	Cross-sectional 6555 adults	Diet	Wheeze, SOB†			+
Bodner <i>et al.</i> [45]	Cross-sectional 94 adult cases	Diet	Current wheeze			+
	203 adult controls	Plasma		+		
Cook <i>et al.</i> [47]	Cross-sectional 278 children	Plasma	Wheeze			+
Troisi <i>et al.</i> [12]	Prospective 77 866 adult women	Diet	10-yrs incidence asthma		+	
<i>Vitamin E/ α-tocopherol</i>						
Grievink <i>et al.</i> [44]	Cross-sectional 6555 adults	Diet	Wheeze, SOB†			+
Bodner <i>et al.</i> [45]	Cross-sectional 94 adult cases	Diet		+		
	203 adult controls	Plasma§	Current wheeze	+		
Grievink <i>et al.</i> [46]	Cross-sectional 491 adult cases	Plasma	Asthma symptoms‡			+
	496 adult controls					
Troisi <i>et al.</i> [12]	Prospective 77 866 adult women	Diet	10-yrs incidence asthma	+		
<i>β-carotene</i>						
Grievink <i>et al.</i> [44]	Cross-sectional 6555 adults	Diet	Wheeze		+	
			SOB†			+
Grievink <i>et al.</i> [46]	Cross-sectional 491 adult cases	Plasma	Asthma symptoms‡	+ bs		
Bodner <i>et al.</i> [45]	Cross-sectional 94 adult-onset cases of asthma	Diet	Current wheeze			+
	203 adult controls	Plasma		+ bs		
Troisi <i>et al.</i> [12]	Prospective 77 866 adult women	Diet total carotene	10-yrs incidence asthma	+ bs		

bs = borderline statistically significant ($P < 0.10$). *Measured as prevalence unless otherwise indicated; †SOB = nocturnal attacks of shortness of breath; ‡asthma symptoms = wheeze with/without shortness of breath or SOB or ever asthma; §adjusted for triglycerides.

Table 4. Epidemiological evidence for a relation between anti-oxidant vitamins and COPD

Reference	Study design & population	Anti-oxidants measured in	Respiratory outcome*	Association		
				Beneficial	Adverse	No
Schwartz <i>et al.</i> [13]	Cross-sectional 9074 adults	<i>Vitamin C</i> Serum	Bronchitis	+		
Grievink <i>et al.</i> [44]	Cross-sectional 6555 adults	Diet	Cough	+		+
		Diet	Phlegm			+
Miedema <i>et al.</i> [10]	Prospective <i>n</i> = 793 adult men	Diet	Productive cough			+
		CNSLD2	25-yrs incidence			+
Tabak <i>et al.</i> [48]	Prospective Ecological: 16 cohorts of men	Diet	25-yrs COPD mortality			+
		<i>Vitamin E/ α-tocopherol</i>				
Grievink <i>et al.</i> [44]	Cross-sectional 6555 adults	Diet	Cough, phlegm			+
		Diet	Productive cough		+	
Grievink <i>et al.</i> [46]	Cross-sectional 491 adult cases 496 adult controls	Plasma	Chronic bronchitis			+
		Plasma	Dyspnea		+	
Rautalahti <i>et al.</i> [14]	Cross-sectional 29 133 adult male smokers	Diet	COPD symptoms	+		
		Serum		+		
Tabak <i>et al.</i> [48]	Prospective ecological: 16 cohorts of men	Diet	25-yrs COPD mortality			+
		<i>β-carotene</i>				
Rautalahti <i>et al.</i> [14]	Cross-sectional 29 133 adult male smokers	Diet	COPD symptoms	+		
		Serum		+		
Grievink <i>et al.</i> [44]	Cross-sectional 6555 adults	Diet	Cough, phlegm, Productive cough			+
Grievink <i>et al.</i> [46]	Cross-sectional 491 cases 496 controls	Plasma	COPD symptoms	+ bs		
Miedema <i>et al.</i> [10]	Prospective <i>n</i> = 793 adult men	Diet	25-yrs incidence CNSLD†			+
Tabak <i>et al.</i> [48]	Prospective ecological: 16 cohorts of men	Diet	25-yrs COPD mortality			+
		<i>Intervention with</i>				
Rautalahti <i>et al.</i> [14]	Prospective Intervention 29 133 adult male smokers	50 mg α -toc, 20 mg β -car per day	6-yrs incidence COPD-symptoms			+

bs = borderline statistical significant ($P < 0.10$). *Measured as prevalence unless otherwise indicated †CNSLD: Chronic Non-specific Lung Disease. Here the majority consisted of COPD.

Table 5. Epidemiological evidence for a relation between anti-oxidant vitamins and lung function

Reference	Study design & population	Anti-oxidants measured in	Outcome measure of lung function	Association	
				Beneficial	No
<i>Vitamin C</i>					
Khaw <i>et al.</i> [50]	Cross-sectional 96 adults	Serum	FEV ₁	+	
Ness <i>et al.</i> [9]	Cross-sectional 1860 adults	Plasma	FEV ₁ , FVC	+ (men)	+ (women)
Cook <i>et al.</i> [47]	Cross-sectional 278 children	Plasma	FEV ₁		+
Hu <i>et al.</i> [52]	Cross-sectional	Diet & plasma	FEV ₁	+	
	3085 adults (diet)	Diet	FVC	+	
	138 adults (plasma)	Plasma	FVC		+
		Diet	FEV ₁ , FVC	+	
Britton <i>et al.</i> [8]	Cross-sectional 2633 adults	Diet	FEV ₁ , FVC		+
Dow <i>et al.</i> [10]	Cross-sectional 178 elderly	Diet	FEV ₁ , FVC		+
Grievink <i>et al.</i> [44]	Cross-sectional 6555 adults	Diet	FEV ₁ , FVC	+	
Schwartz <i>et al.</i> [51]	Cross-sectional 2526 adults	Diet	FEV ₁	+	
Morabia <i>et al.</i> [60]	Cross-sectional 1165 adults	Diet	FEV ₁ /FVC ≤ 65%		+
<i>Vitamin E/ α-tocopherol</i>					
Britton <i>et al.</i> [8]	Cross-sectional 2633 adults	Diet	FEV ₁ , FVC		+
Dow <i>et al.</i> [10]	Cross-sectional 178 elderly	Diet	FEV ₁ , FVC	+	
Grievink <i>et al.</i> [44]	Cross-sectional 6555 adults	Diet	FEV ₁ , FVC		+
Morabia <i>et al.</i> [54]	Prospective 83 adults	Serum	FEV ₁ ≤ 75% FVC		+
Grievink <i>et al.</i> [53]	Cross-sectional 367 adults	Plasma	FEV ₁ , FVC		+
<i>β-carotene</i>					
Shahar <i>et al.</i> [55]	Cross-sectional 10 416 adults	Diet total carotene	FEV ₁ , FVC	+	
Chuwers <i>et al.</i> [56]	Cross-sectional 816 male asbestos exposed adults	Diet Serum	FEV ₁		+
			FVC	+	
Grievink <i>et al.</i> [44]	Cross-sectional 6555 adults	Diet	FEV ₁ , FVC	+	
Grievink <i>et al.</i> [53]	Cross-sectional 367 adults	Plasma	FEV ₁ ,		+
			FVC	+	
Morabia <i>et al.</i> [54]	Prospective 83 adults	Serum	FEV ₁ ≤ 75% FVC		+
Balmes <i>et al.</i> [57]	Prospective Intervention 3056 adults	Daily 30 mg β-car, 25 000 IU retinylpalmitate	11-year decline of FEV ₁		+

anti-oxidants and lung function is clearer than for respiratory symptoms (Table 5). Dietary and serum vitamin C have been consistently and beneficially associated with FEV₁ [50,51] and FVC in most studies [8,9,44,52]. Studies which did not observe significant associations between lung function and vitamin C contained a relatively small number of subjects ($n < 300$) [10,47,52] or used presence of bronchoconstriction as an outcome measure which is possibly less sensitive than a continuous measure of lung function. Most studies did not find associations between vitamin E (from diet and blood) and lung function [44,53] or airway obstruction [54]. One study observed a beneficial association which disappeared after vitamin C adjustment [8]. One of the first cross-sectional studies did not find an association between the intake of total carotene and lung function (FEV₁ and FVC) [55]. However, individual carotenoids might have different effects on lung physiology and only β -carotene is expected to have anti-oxidant activity. Serum β -carotene [56] and dietary β -carotene [44] were associated with a higher FEV₁ and FVC in two cross-sectional studies while serum β -carotene was not associated with the development of airway obstruction in a small study ($n = 83$) [54]. In addition, we recently observed that subjects with a higher plasma β -carotene level had a higher FVC and FEV₁ but this association was not statistically significant for FEV₁ [53]. The only large-scale intervention study (CARET-study) in which subjects were supplemented with a high dose of β -carotene and retinylpalmitate for 11 years did not observe a difference in the annual lung function decline between the supplementation and placebo group [57]. In conclusion, most cross-sectional studies showed a beneficial effect of dietary or serum vitamin C or β -carotene in relation to lung function. A possible explanation for the lack of agreement between the results on lung function and COPD symptoms is that the relevant lag-time for a beneficial effect of anti-oxidants on lung function differs from that for chronic respiratory symptoms. Since only cross-sectional studies showed beneficial associations between anti-oxidants and lung function, this suggest a relatively short lag-time. However, the time to develop chronic COPD symptoms may be longer than a decline in lung function and therefore most cross-sectional studies did not show associations between anti-oxidants and COPD-symptoms or were inconclusive in their results. Another explanation is simply that lung function is a more sensitive measure to detect small protective effects than respiratory symptoms.

Discussion

The evidence for modulation of air pollution effects on the respiratory system by anti-oxidants is still limited. Most studies conducted so far have looked at short-term effects on lung function. We still know very little about modulation of

short-term effects on other endpoints such as bronchial responsiveness and airway inflammation. We know even less about modulation of long-term effects of air pollution on survival or development of respiratory morbidity. Given the intriguing results of some of the studies that were conducted under ambient air pollution conditions, and within the normal range of anti-oxidant intake, further studies in this area are clearly called for. Most of the observational studies investigated whether anti-oxidants were directly associated with the prevalence or incidence of indicators of asthma or COPD. But if a protective effect of anti-oxidants is observed, it could be argued whether this is a direct effect. Anti-oxidants may modulate the occurrence of the chronic lung disease in the same way as they modulate the acute respiratory effects of air pollution. Asthma and COPD are suggested to be partly caused by external triggers, such as allergens in predisposed individuals, air pollution or cigarette smoke. All these external triggers increase the inflammation in the lungs. This inflammation might be decreased in subjects with an adequate anti-oxidant status. Thus anti-oxidants might only be beneficial in subjects exposed to these external triggers causing asthma or COPD, that is, subjects who have a low dietary intake or status of anti-oxidants and who are exposed by these triggers are more likely to develop asthma or COPD compared to subjects who have a high anti-oxidant intake or status. For example, most studies so far have been studying the effect of anti-oxidants on COPD in nonsmokers or in smokers only. Those studies who included subjects with both smoking status were mostly too small to detect a difference in effect between the two groups although there are some suggestions that the associations between anti-oxidants and indicators of asthma or COPD are slightly stronger in current smokers compared to never smokers [8,45,51,58].

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