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Associations between antioxidants and all-cause mortality among US adults with obstructive lung function

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Abstract

Chronic obstructive pulmonary disease is characterised by oxidative stress, but little is known about the associations between antioxidant status and all-cause mortality in adults with this disease. The objective of the present study was to examine the prospective associations between concentrations of α- and β-carotene, β-cryptoxanthin, lutein/zeaxanthin, lycopene, Se, vitamin C and α-tocopherol and all-cause mortality among US adults with obstructive lung function. Data collected from 1492 adults aged 20–79 years with obstructive lung function in the National Health and Nutrition Examination Survey III (1988–94) were used. Through 2006, 629 deaths were identified during a median follow-up period of 14 years. After adjustment for demographic variables, the concentrations of the following antioxidants modelled as continuous variables were found to be inversely associated with all-cause mortality among adults with obstructive lung function: α-carotene (P=0.037); β-carotene (P=0.022); cryptoxanthin (P=0.022); lutein/zeaxanthin (P=0.004); total carotenoids (P=0.001); vitamin C (P<0.001). In maximally adjusted models, only the concentrations of lycopene (P=0.013) and vitamin C (P=0.046) were found to be significantly and inversely associated with all-cause mortality. No effect modification by sex was detected, but the association between lutein/zeaxanthin concentrations and all-cause mortality varied by smoking status ($P_{interaction}$ = 0.048). The concentrations of lycopene and vitamin C were inversely associated with all-cause mortality in this cohort of adults with obstructive lung function.

Keywords

Antioxidants; Chronic obstructive pulmonary disease; Mortality

Chronic obstructive pulmonary disease (COPD) remains a potent public health problem in the USA and globally[1,2]. After decades of increased mortality from COPD in the USA, the rate of mortality has stabilised since 2000[3]. Although the prevalence of smoking is the chief driver of the rate of mortality from COPD, identifying other factors that may influence

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mortality and are amenable to interventions in individuals with COPD is of substantial interest.

Studies, mostly cross-sectional ones, have related nutritional factors including the intake of fruits and vegetables, which are rich sources of antioxidants, to pulmonary function and COPD[4–14]. Dietary intakes of vitamin C[15–19], vitamin E[20,21], β-carotene[18,19,22] and carotenoids[21] have been linked to lung function. Furthermore, circulating concentrations of antioxidants including carotenoids, vitamin C, vitamin E and vitamin A have been linked to pulmonary function in cross-sectional studies[23–31] and to change in pulmonary function in prospective studies[32–34].

Assuming that adequate nutritional status may help to preserve lung function and that preserved lung function reduces mortality, adequate nutritional status might reduce mortality among people with impaired lung function. An ecological study has suggested that increased intakes of fruits and fish are inversely correlated with COPD mortality[35]. Prospective studies have found that the intakes of fruits and vitamin E are inversely associated with mortality from COPD[36]. Yet, little is known about the associations between antioxidant concentrations and mortality in adults with obstructive lung function. Oxidation is considered to be a key factor in the pathogenesis of COPD[37–39], but very little is known about the role of oxidation in and any possible beneficial effects of antioxidants on the prognosis of this disease. Therefore, the objective of the present study was to examine the associations between circulating concentrations of carotenoids (α-carotene, β-carotene, cryptoxanthin, lutein/zeaxanthin, and lycopene), vitamin C, vitamin E, and Se and all-cause mortality in a cohort of US adults with obstructive lung function.

Methods

The present study is based on data obtained from the Third National Health and Nutrition Examination Survey (NHANES III) Linked Mortality Study (baseline examination from 1988 to 1994; mortality follow-up through 2006)[40,41]. A complex sampling design (stratified multistage probability design) was used to select participants, who constituted a representative sample of the civilian non-institutionalised population in the USA. The participants were interviewed at their homes and extended an invitation to undergo an examination in the mobile examination centre, where they completed additional questionnaires, underwent a series of examinations, and provided blood and urine samples. The interview and examination response rates were 86 and 78 %, respectively. NHANES III received approval from the Institutional Review Board.

A probabilistic match of participants' information with the National Death Index death certificate records was conducted to identify deceased participants. If a match was not made, the participant was assumed to be alive at the end of the follow-up period. International Classification of Diseases-10 codes I00–I99 and C00–C97 were used to define deaths from circulatory disease and cancer, respectively.

Adults were eligible for a pulmonary function test without post-bronchodilator testing. The procedures used to conduct spirometry have been detailed elsewhere[42]. The following

equations were used to calculate predicted forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) in adults:

FEV1:

$$\text{White men: } 0.5536-0.01303\times\text{age}-0.000172\times\text{age}^2+0.00014098\times\text{height}^2,$$

$$\text{African American men: } 0.3411-0.02309\times\text{age}+0.00013194\times\text{height}^2,$$

$$\text{Mexican American men: } 0.6306-0.02928\times\text{age}+0.00015104\times\text{height}^2+0.00015104\times\text{height}^2,$$

$$\text{White women: } 0.4333-0.00361\times\text{age}-0.000194\times\text{age}^2+0.00011496\times\text{height}^2,$$

$$\text{African American women: } 0.3433-0.01283\times\text{age}-0.000097\times\text{age}^2+0.00010846\times\text{height}^2,$$

$$\text{Mexican American women: } 0.4529-0.01178\times\text{age}-0.000113\times\text{age}^2+0.00012154\times\text{height}^2.$$

FVC:

$$\text{White men: } -0.1933+0.00064\times\text{age}-0.000269\times\text{age}^2+0.00018642\times\text{height}^2,$$

$$\text{African American men: } -0.1517-0.01821\times\text{age}+0.00016643\times\text{height}^2,$$

$$\text{Mexican American men: } 0.2376-0.00891\times\text{age}-0.000182\times\text{age}^2+0.00017823\times\text{height}^2,$$

$$\text{White women: } -0.3560+0.01870\times\text{age}-0.000382\times\text{age}^2+0.00014815\times\text{height}^2,$$

$$\text{African American women: } -0.3039+0.00536\times\text{age}-0.000265\times\text{age}^2+0.00013606\times\text{height}^2,$$

$$\text{Mexican American women: } 0.1210+0.00307\times\text{age}-0.000237\times\text{age}^2+0.00014246\times\text{height}^2.$$

Mild obstructive impairment was defined as a FEV1/FVC <.70 and a FEV1 ≥80 %, moderate obstructive impairment was defined as a FEV1/FVC <0.70 and a FEV1 50 to <80 % predicted, and severe obstructive impairment was defined as a FEV1/FVC <0.70 and a FEV1 <50 % predicted. Participants with mild, moderate or severe COPD were combined for analyses that examined associations between antioxidant concentrations and mortality risk.

The serum concentrations of five carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene), vitamin C and α-tocopherol were measured using an isocratic reversed-phase HPLC. The serum concentrations of Se were measured using graphite furnace atomic absorption spectroscopy.

The following covariates were included in the analyses: age; sex; self-reported race or ethnicity (white, African American and other); educational level (<12, 12, or >12 years); smoking status; alcohol consumption; leisure-time physical activity; use of vitamin or mineral supplements; systolic blood pressure; HDL-cholesterol; non-HDL-cholesterol; BMI; C-reactive protein; urinary albumin:creatinine ratio; health status; histories of myocardial infarction and stroke; diabetes. Socio-demographic and lifestyle variables were included in the analyses because these variables are generally strongly associated with mortality. Furthermore, these variables are also associated with antioxidant concentrations. Lipid concentrations were included in the analyses because many of the antioxidants are lipid soluble. C-reactive protein as a marker of inflammation was included in the analyses because sources of inflammation can reduce antioxidant concentrations. Systolic blood pressure, BMI, urinary albumin:creatinine ratio, health status, diabetes, and histories of myocardial infarction and stroke were included in the analyses because these risk factors and conditions predict mortality and are associated with antioxidant concentrations.

Participants who reported that they had smoked at least 100 cigarettes during their lifetime and that they still smoke were designated as current smokers. Participants who reported that they had smoked at least 100 cigarettes during their lifetime and that they no longer smoke were designated as former smokers. Participants reporting not having smoked at least 100 cigarettes were designated as never smokers. Using information from a FFQ, the frequency of alcohol consumption per month was estimated. Participants who engaged three or more times per week in an activity with a metabolic equivalent level ≥6 (for those aged ≥60 years) and with a metabolic equivalent ≥7 (for those aged <60 years) were considered to be vigorously active, participants who engaged five or more times per week in activities of which no more than two could be considered vigorous were considered to be moderately active, participants who engaged in activities that were not vigorous or moderate were considered to be lightly active, and participants who engaged in no leisure-time physical activity were considered to sedentary. Use of any vitamins or minerals by the participants was determined from the responses provided to the question `Have you taken any vitamins or minerals in the past month?'

The second and third systolic blood pressure measurements were averaged. BMI (kg/m^2) was calculated from the measured weight and height. The concentrations of HDL-cholesterol were measured on a Hitachi 704 analyser (Boehringer Mannheim Diagnostics)

after precipitation of other lipoproteins with a heparin–manganese chloride mixture. The concentrations of non-HDL-cholesterol were calculated by subtracting the concentration of HDL-cholesterol from that of total cholesterol. The serum concentrations of C-reactive protein were measured using latex-enhanced nephelometry on the Behring Nephelometer Analyzer System (Behring Diagnostics, Inc.). The urinary concentrations of albumin were measured using a fluorescent immunoassay on a Sequoia-Turner fluorometer (Sequoia-Turner Corporation). The urinary concentrations of creatinine were measured from the rate of colour formation on a Beckman Synchron AS/ASTRA clinical analyser (Beckman Instruments, Inc.).

Participants with a history of myocardial infarction or stroke were identified from the responses provided to the questions `Has a doctor ever told you that you had a heart attack?' and `Has a doctor ever told you that you had a stroke?', respectively. Participants who provided a positive response to the question `Have you ever been told by a doctor that you have diabetes or sugar diabetes?' or had glycated Hb concentration ≥6.5% were considered to have diabetes.

Men and non-pregnant women aged 20–79 years who underwent a spirometric examination in the mobile examination centre and had reproducible FEV1 and FVC results were included in the analyses. Using the direct method, age adjustment was done to the projected year 2000 US population for adults aged 20–79 years. Least-squares adjusted mean concentrations of antioxidants were calculated. Proportional-hazards analysis was used to estimate hazard ratios for antioxidants and mortality. In these multivariable models, antioxidants were modelled as continuous variables and again as quintiles calculated from the distributions of antioxidants among participants with obstructive lung function. To better approximate a normal distribution of several antioxidants, the following transformations were used in regression analyses: log transformation for β-carotene, lutein/zeaxanthin, lycopene, total carotenoids, and vitamin E and square root transformation for vitamin C. SAS (SAS Institute Inc.) and SUDAAN (Research Triangle Institute) were used to conduct statistical analyses.

Results

Of the 15 033 men and non-pregnant women aged 20–79 years who visited the mobile examination centre, 14 082 had reproducible FEV1 and FVC results. After exclusion of participants with an unreliable examination result, 13 134 remained. Of these participants, 1746 had obstructive lung function and 12 168–12 516 participants had a measurement of the antioxidants. After exclusion of participants with missing study variables, the analytical sample size was reduced to 1492 participants with obstructive lung function.

The 1492 participants with obstructive lung function included 907 men, 585 women, 903 whites, 315 African Americans, 232 Mexican Americans, and forty-two participants of another race or ethnicity. The mean and median ages were 55.7 and 58.0 years, respectively.

Among adults with obstructive lung function, 629 had died. The mean and median follow-up periods were 12.9 and 14.0 years, respectively. Differences in the means and percentages of

study variables between participants who died and those who remained alive among adults with obstructive lung function are given in Table 1. Decedents had lower age-adjusted mean concentrations of α-carotene, β-carotene, cryptoxanthin, lutein/zeaxanthin, and total carotenoids than survivors.

In age-adjusted regression models, the concentrations of all antioxidants, except Se, modelled as continuous variables were inversely associated with all-cause mortality (Table 2). With progressive increasing levels of adjustment, the statistical significance of the hazard ratios for most antioxidants dwindled until only the concentrations of lycopene (P=0.013) and vitamin C (P=0.046) remained significantly and inversely associated with all-cause mortality in the maximally adjusted model (Table 2).

The concentrations of none of the antioxidants were significantly associated with mortality from circulatory diseases (Table 3). However, the concentrations of vitamin C were inversely associated with mortality from cancer. In addition, the concentrations of lutein/zeaxanthin and lycopene were inversely associated with mortality from causes other than circulatory disease and cancer.

To examine the possibility of nonlinearity in the associations between antioxidant concentrations and all-cause mortality, a term for the squared concentrations of antioxidants was added to the proportional-hazards models, which proved to be statistically significant for lutein/zeaxanthin, total carotenoids, Se, vitamin C and vitamin E. Adjusted hazard ratios by quintiles of antioxidant concentrations are given in Table 4.

The associations between antioxidant concentrations and mortality did not vary by sex ($P_{\text{interactions}}$ >0.050). When possible interactions by race or ethnicity were examined, only the interaction term for lycopene was found to be statistically significant (Table 5). Except for β-carotene, the adjusted mean concentrations of antioxidants varied by race or ethnicity.

Detection for the presence of two-way interactions between antioxidant concentrations modelled as continuous variables and all-cause mortality was done. Significant interactions were found between the concentrations of vitamin E and those of β-carotene, cryptoxanthin, and lutein/zeaxanthin. Furthermore, significant interactions were found between the concentrations of lutein/zeaxanthin and those of cryptoxanthin and lycopene. When the concentration of each of the antioxidants was dichotomised using the median concentration and a four-level variable for each pair of antioxidants was created, none of the four-level variables was found to be a statistically significant predictor of mortality and, thus, shed little light on the interactions.

In general, antioxidant concentrations were lowest in participants who were current smokers and highest in participants who had never smoked (Table 6). Only the association between log-transformed lutein/zeaxanthin concentrations and all-cause mortality varied by smoking status ($P_{\text{interaction}}$ for continuous variable = 0.048). The maximally adjusted hazard ratios for continuous log-transformed concentrations were 0.62 (95% CI 0.46, 0.83) for current smokers, 1.03 (95% CI 0.71, 1.48) for former smokers, and 1.54 (95% CI 0.78, 3.04) for never smokers (Table 6). The concentrations of lutein/zeaxanthin, lycopene and total carotenoids were inversely associated with all-cause mortality in current smokers.

Discussion

Oxidation is a critical factor in the pathogenesis and pathophysiology of COPD[37–39]. Although less clear, ongoing oxidative stress may exert a deleterious effect on the prognosis of those afflicted with this condition. If so, adequate antioxidant defences might be especially important for the welfare of people with COPD. The results of the present study showing that the concentrations of vitamin C and lycopene are inversely associated with all-cause mortality in the study cohort with obstructive lung function provide measured support for this contention.

If the results of the present study do not represent chance findings, a couple of alternate explanations deserve consideration. First, vitamin C and lycopene may have in fact exerted beneficial effects in adults with obstructive lung function. Second, vitamin C and lycopene may represent risk markers for other factors that are responsible for the observed associations between the two antioxidants and mortality. Because fruits and vegetables are rich sources of both substances, one or more of the other compounds in fruits and vegetables may have been responsible for the observed associations. Along the same lines, antioxidants may represent markers for certain lifestyle characteristics that favourably affect mortality.

Prospective studies have reported that carotenoid concentrations are inversely associated with mortality[43–67], but not all studies have done so[52,68–70]. These studies are supported by prospective studies of dietary or supplemental intakes of carotenoids[64,71–74], although other studies have failed to observe significant associations between antioxidant intake and mortality[70,75–78]. Furthermore, in randomised trials of β-carotene, mortality was found to increase in the experimental group[77,79]. However, we were unable to find studies that have examined whether antioxidant concentrations predict mortality in adults with obstructive lung function. Therefore, the results of the present study present novel information.

Evidence regarding the association between circulating concentrations of lycopene and mortality is mixed, with several studies providing supportive evidence[57,58,60,65] and others failing to do so[49,67,80]. If lycopene reduces mortality, it is possible that COPD adults with higher lycopene concentrations would experience beneficial effects similar to those experienced by the population at large. The literature pertaining to the health effects of lycopene has zeroed in mostly on cancer[81]. Of the carotenoids, the concentrations of lycopene had the strongest association with lung cancer[82], a condition to which adults with COPD are particularly susceptible given their smoking history. It is possible that lycopene may exert a favourable effect on all-cause mortality by reducing the risk of lung cancer. Adults with COPD are at an increased risk of mortality from CVD[83]. Research has suggested that the intake and circulating concentrations of lycopene may be inversely associated with CVD[84–86]. Besides being a strong singlet oxygen quencher[87], lycopene has been shown to affect endothelial function[88,89], HDL function[90], and matrix metalloproteinase-9 induction[91].

Whether the beneficial effects of adequate lycopene status specific to adults with COPD exist is less clear. Antioxidants including carotenoids, vitamin A and α-tocopherol have been demonstrated in lung tissue samples and bronchoalveolar lavage fluids[92,93], and

supplementation with β-carotene has been shown to lead to increases in β-carotene concentrations in cells of bronchoalveolar lavage fluids[94]. As pointed out earlier, evidence points to inverse associations between intake and circulating concentrations of antioxidants and pulmonary function. In a trial of vegetable juice supplementation, young adults who received the vegetable juice rich in lycopene were found to experience significantly smaller reductions of FEV1 and FVC after a challenge with ozone compared with control participants[95]. Such potential protection could be important in adults with COPD whose respiratory reserve capacity is compromised. Lycopene has also been found to limit the inflammatory response exhibited by airway epithelial cells after a challenge with rhinovirus infection[96]. Because acute exacerbations of COPD due to respiratory infections result in excess mortality in adults with COPD, agents that could lessen the risk of respiratory infections or limit the damage caused by respiratory infections could possibly lead to reductions in mortality. However, a great deal of study is necessary to test the effects of antioxidant supplements on morbidity and mortality among adults with obstructive lung function.

Vitamin C, which is a water-soluble essential vitamin, is involved in numerous physiological processes critical to maintaining internal homeostasis of the human body. Besides acting as a cofactor in various enzymatic reactions, it serves as an important antioxidant scavenging both reactive oxygen species and reactive N species[97].

Observational prospective studies suggest that the intake and circulating concentrations of vitamin C are inversely associated with all-cause mortality or cause-specific mortality from leading chronic conditions[45–47,68,71,73,98–104]. In other observational studies, however, vitamin C intake was found to have no apparent effect on mortality[52,62,75,78,105–107], and a systematic review concluded that supplementation with vitamin C has no beneficial effects on mortality[77]. We are not aware of studies that have examined the effect of circulating concentrations of vitamin C on mortality among adults with obstructive lung function.

The prevalence of cigarette smoking is high among adults with obstructive lung function. In the present study, about 44 % of the participants reported being current smokers. Consequently, the excess mortality among adults with COPD is in part attributable to the high prevalence of smoking. Because smoking is a prime source of oxidative stress, bolstering antioxidant defences through supplementation with antioxidants could potentially mitigate some of the ravages from smoking-induced damage to the lungs and the downstream adverse effects of oxidative stress. It has been suggested by two large trials of supplementation with β-carotene and α-tocopherol in smokers and β-carotene and retinyl palmitate in participants who had been exposed to asbestos or were heavy smokers that yielded negative consequences for the experimental groups that caution needs to be exercised while extrapolating the findings of observational studies to recommendations for using antioxidant supplementation as an approach to primary or secondary prevention[108,109]. The results of the present study did not show that the concentrations of β-carotene and vitamin E in current smokers were significantly associated with all-cause mortality.

The results of the present study should be viewed in the context of several limitations. A larger sample size would have provided additional statistical power to detect significant associations, to examine the associations between antioxidant concentrations and mortality in separate groups of participants with mild, moderate, and severe obstructive lung function, and to examine associations between antioxidant concentrations and cause-specific mortality. The concentrations of antioxidants were measured at a single point in time and may not have represented the usual concentrations of the study participants. Concentration data of only α-tocopherol were available in NHANES III. Interest in the health effects of γ-tocopherol has grown, and future investigations into the association between γ-tocopherol concentrations and mortality in adults with obstructive lung function would be of interest. Although a substantial number of covariates were included in the analyses, residual confounding remains a possibility as in most observational studies.

In conclusion, the concentrations of lycopene and vitamin C were inversely associated with all-cause mortality among adults with obstructive lung function. The failure of trials of β-carotene and α-tocopherol supplementation in smokers to show benefits and of antioxidant supplementation in trials of secondary prevention suggest that caution needs to be exercised before recommending antioxidant supplementation in patients with COPD. Because limited studies have examined the associations between circulating concentrations of antioxidants and all-cause mortality and cause-specific mortality in adults with COPD, additional studies in this area are needed. In addition, studies examining the intake of antioxidants from diet and supplements in adults with COPD may also yield valuable data. Lastly, trials of antioxidant supplementation in patients with COPD may be needed to fully gauge the beneficial or harmful effects of antioxidant supplementation on complications from COPD. Regardless, physicians may evaluate the nutritional status of their patients with COPD and their diets and make recommendations consistent with current dietary recommendations.

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The authors' contributions are as follows: E. S. F. conceived the study; E. S. F. and C. L. participated in the design and conduct of the study; E. S. F. conducted the analyses and drafted the manuscript; T. J. C. and J. B. C. contributed to the analysis, interpretation, and critical revision of the manuscript. All authors approved the final manuscript.

Abbreviations

COPD	chronic obstructive pulmonary disease
FEV1	forced expiratory volume in 1 s
FVC	forced vital capacity
NHANES III	Third National Health and Nutrition Examination Survey

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Table 1

Age-adjusted baseline means and percentages of study variables among adults aged 20–79 years with obstructive lung function, by mortality status, National Health and Nutrition Examination Survey III (1988–94)

(Mean values or percentages with their standard errors)

			Mortality status				
	Total (*n* 1492)		Dead (*n* 629)		Alive (*n* 863)		
	Mean	SE	Mean	SE	Mean	SE	*P*
Age (years)	55.7	0.7	65.8	0.7	50.5	0.8	<0.001
Education (years)	12.3	0.2	11.0	0.3	12.5	0.2	<0.001
No. of drinks (per month)	10.4	0.8	9.9	2.1	10.4	0.9	0.818
Systolic blood pressure (mmHg)	121.4	0.6	124.5	1.3	120.3	0.7	0.005
HDL-cholesterol (mmol/l)	1.3	0.0	1.1	0.1	1.3	0.0	0.015
Non-HDL-cholesterol (mmol/l)	4.1	0.1	4.2	0.1	4.1	0.0	0.291
BMI (kg/m^2)	26.5	0.3	27.6	0.9	26.5	0.3	0.227
Albumin:creatinine ratio (mg/g)	17.8	1.4	22.3	3.4	14.0	1.0	0.021
α-Carotene (μmol/l)	0.08	0.00	0.06	0.01	0.09	0.00	<0.001
β-Carotene (μmol/l)	0.34	0.01	0.26	0.01	0.35	0.01	<0.001
Cryptoxanthin (μmol/l)	0.15	0.00	0.11	0.01	0.16	0.01	<0.001
Lutein/zeaxanthin (μmol/l)	0.37	0.01	0.33	0.02	0.37	0.01	0.015
Lycopene (μmol/l)	0.45	0.01	0.41	0.03	0.46	0.01	0.120
Total carotenoids (μmol/l)	1.38	0.03	1.17	0.06	1.42	0.03	<0.001
Se (nmol/l)	1.61	0.02	1.60	0.03	1.62	0.02	0.581
Vitamin C (mmol/l)	39.4	1.8	33.8	4.0	40.9	1.9	0.103
Vitamin E (μmol/l)	27.0	0.6	27.1	1.4	27.0	0.6	0.977
FEV1 (litres)	2.8	0.0	2.7	0.1	2.9	0.0	0.291
FVC (litres)	4.4	0.0	4.4	0.1	4.4	0.1	0.848
FEV1 (% predicted)	79.8	0.7	75.9	2.6	81.5	0.7	0.040
FVC (% predicted)	98.9	0.7	96.8	2.4	100.2	0.7	0.206
Men (%)	59.8	1.8	80.5	2.3	56.8	1.9	<0.001
Race or ethnicity							
White (%)	83.5	1.8	80.8	5.3	83.9	1.8	0.569
African American (%)	7.5	0.9	16.1	5.0	6.8	0.9	0.070
Mexican American (%)	2.2	0.4	1.4	0.7	2.2	0.4	0.247
Other (%)	6.8	1.5	1.7	1.0	7.1	1.6	0.007
High-school graduate or higher (%)	74.0	2.6	45.0	4.2	77.1	2.9	<0.001
Smoking status							
Current smoker (%)	44.8	2.5	59.7	7.3	41.0	2.7	0.028
Former smoker (%)	27.0	1.9	13.4	1.3	28.5	2.2	<0.001
Never smoker (%)	28.2	2.5	26.9	7.5	30.5	2.8	0.676
Moderate-vigorous leisure-time physical activity (%)	45.0	2.4	39.8	7.8	46.4	2.9	0.429
Vitamin or mineral supplement use during past 30 d (%)	40.3	2.2	35.2	7.5	41.8	2.3	0.397

			Mortality status				
	Total (*n* 1492)		Dead (*n* 629)		Alive (*n* 863)		
	Mean	SE	Mean	SE	Mean	SE	*P*
C-reactive protein >3mg/l (%)	29.5	2.1	36.2	5.7	28.3	2.6	0.249
≥Good health status (%)	84.6	2.4	74.1	6.8	87.2	2.0	0.029
Diabetes (%)	5.3	0.7	5.6	0.8	4.2	0.8	0.212
History of myocardial infarction (%)	3.8	0.7	4.9	1.5	2.7	0.7	0.196
History of stroke (%)	1.7	0.4	3.0	1.5	1.2	0.4	0.230

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 2

Associations between antioxidant concentrations and all-cause mortality among US adults aged 20 – 79 years with obstructive lung function, National Health and Nutrition Examination Survey III Linked Mortality File 1988 – 94 to 2006

(Hazard ratios and 95 % confidence intervals)

Antioxidants*	Hazard ratio	95 % CI	*P*
Model 1†			
α-Carotene (μmol/l)	0.04	0.00, 0.33	0.004
β-Carotene (μmol/l)	0.76	0.66, 0.88	<0.001
Cryptoxanthin (μmol/l)	0.10	0.02, 0.46	0.004
Lutein/zeaxanthin (μmol/l)	0.68	0.55, 0.85	0.001
Lycopene (μmol/l)	0.71	0.61,0.81	<0.001
Total carotenoids (μmol/l)	0.59	0.48, 0.73	<0.001
Se (nmol/l)	0.77	0.41, 1.46	0.416
Vitamin C (mmol/l)	0.88	0.84, 0.92	<0.001
Vitamin E (μmol/l)	0.71	0.52, 0.98	0.039
Model 2‡			
α-Carotene (μmol/l)	0.12	0.02, 0.88	0.037
β-Carotene (μmol/l)	0.83	0.70, 0.97	0.022
Cryptoxanthin (μmol/l)	0.18	0.04, 0.77	0.022
Lutein/zeaxanthin (μmol/l)	0.71	0.57, 0.89	0.004
Lycopene (μmol/l)	0.75	0.64, 0.87	<0.001
Total carotenoids (μmol/l)	0.65	0.51, 0.82	0.001
Se (nmol/l)	0.83	0.44, 1.58	0.568
Vitamin C (mmol/l)	0.91	0.87, 0.95	<0.001
Vitamin E (μmol/l)	0.88	0.66, 1.19	0.412
Model 3§			
α-Carotene (μmol/l)	0.52	0.08, 3.56	0.499
β-Carotene (μmol/l)	0.88	0.74, 1.04	0.133
Cryptoxanthin (μmol/l)	0.36	0.10, 1.35	0.127
Lutein/zeaxanthin (μmol/l)	0.80	0.64, 1.00	0.052
Lycopene (μmol/l)	0.78	0.67, 0.91	0.002
Total carotenoids (μmol/l)	0.74	0.58, 0.94	0.017
Se (nmol/l)	1.00	0.55, 1.81	1.000
Vitamin C (mmol/l)	0.94	0.90, 0.99	0.021
Vitamin E (μmol/l)	0.98	0.73, 1.32	0.884
Model 4‖			
α-Carotene (μmol/l)	0.55	0.07, 4.34	0.566
β-Carotene (μmol/l)	0.89	0.75, 1.07	0.210
Cryptoxanthin (μmol/l)	0.42	0.12, 1.53	0.184
Lutein/zeaxanthin (μmol/l)	0.81	0.62, 1.05	0.111

Antioxidants*	Hazard ratio	95 % CI	*P*
Lycopene (μmol/l)	0.80	0.69, 0.94	0.007
Total carotenoids (μmol/l)	0.75	0.57, 1.00	0.051
Se (nmol/l)	0.97	0.55, 1.74	0.930
Vitamin C (mmol/l)	0.95	0.91, 1.00	0.042
Vitamin E (μmol/l)	1.00	0.67, 1.49	0.989
Model 5¶			
α-Carotene (μmol/l)	0.62	0.08, 5.06	0.653
β-Carotene (μmol/l)	0.92	0.78, 1.09	0.309
Cryptoxanthin (μmol/l)	0.42	0.13, 1.39	0.151
Lutein/zeaxanthin (μmol/l)	0.86	0.66, 1.11	0.235
Lycopene (μmol/l)	0.80	0.67, 0.95	0.013
Total carotenoids (μmol/l)	0.78	0.59, 1.03	0.075
Se (nmol/l)	0.96	0.52, 1.79	0.900
Vitamin C (mmol/l)	0.95	0.91, 1.00	0.046
Vitamin E (μmol/l)	1.02	0.69, 1.50	0.922

*Estimates for each antioxidant were not adjusted for the concentrations of other antioxidants.

†Adjusted for age.

‡Adjusted for variables in model 1 plus sex, race or ethnicity, and education.

§Adjusted for variables in model 2 plus smoking status, alcohol consumption, leisure-time physical activity, and use of vitamin or mineral supplements.

//Adjusted for variables in model 3 plus systolic blood pressure, HDL-cholesterol, non-HDL-cholesterol, BMI, C-reactive protein and albumin:creatinine ratio.

¶Adjusted for variables in model 4 plus health status, diabetes, history of myocar-dial infarction, and history of stroke.

Table 3

Associations between antioxidant concentrations and cause-specific mortality among US adults aged 20–79 years with obstructive lung function, National Health and Nutrition Examination Survey III Linked Mortality File 1988–94 to 2006*

(Adjusted hazard ratios and 95% confidence intervals)

Antioxidants	Hazard ratio	95% CI	*P*
Circulatory disease deaths (225 deaths)			
α-Carotene (μmol/l)	4.10	0.37, 45.19	0.243
β-Carotene (μmol/l)	1.16	0.90, 1.51	0.245
Cryptoxanthin (μmol/l)	1.12	0.38, 3.31	0.829
Lutein/zeaxanthin (μmol/l)	1.04	0.72, 1.49	0.828
Lycopene (μmol/l)	0.92	0.68, 1.23	0.560
Total carotenoids (μmol/l)	1.11	0.74, 1.65	0.604
Se (nmol/l)	1.04	0.32, 3.32	0.952
Vitamin C (mmol/l)	1.04	0.94, 1.16	0.448
Vitamin E (μmol/l)	1.14	0.62, 2.08	0.664
Cancer deaths (204 deaths)			
α-Carotene (μmol/l)	0.76	0.01, 41.30	0.889
β-Carotene (μmol/l)	0.90	0.70, 1.17	0.433
Cryptoxanthin (μmol/l)	0.20	0.01, 4.52	0.303
Lutein/zeaxanthin (μmol/l)	0.88	0.57, 1.36	0.560
Lycopene (μmol/l)	0.83	0.63, 1.09	0.176
Total carotenoids (μmol/l)	0.77	0.51, 1.17	0.221
Se (nmol/l)	0.93	0.41, 2.12	0.868
Vitamin C (mmol/l)	0.85	0.78, 0.91	<0.001
Vitamin E (μmol/l)	0.64	0.22, 1.88	0.412
Other deaths (200 deaths)			
α-Carotene (μmol/l)	0.06	0.00, 1.98	0.113
β-Carotene (μmol/l)	0.76	0.58, 1.01	0.055
Cryptoxanthin (μmol/l)	0.19	0.02, 1.51	0.113
Lutein/zeaxanthin (μmol/l)	0.70	0.41, 1.17	0.171
Lycopene (μmol/l)	0.70	0.51, 0.95	0.024
Total carotenoids (μmol/l)	0.58	0.36, 0.93	0.024
Se (nmol/l)	0.85	0.28, 2.58	0.775
Vitamin C (mmol/l)	0.99	0.90, 1.10	0.919
Vitamin E (μmol/l)	1.39	0.60, 3.23	0.435

* Log transformations for the concentrations of β-carotene, lutein/zeaxanthin, lycopene, total carotenoids and vitamin E. Square root transformation for the concentration of vitamin C. Adjusted for age, sex, race or ethnicity, education, smoking status, alcohol consumption, leisure-time physical activity, use of vitamin or mineral supplements, systolic blood pressure, HDL-cholesterol, non-HDL-cholesterol, BMI, C-reactive protein, albumin:creatinine ratio, health status, diabetes, history of myocardial infarction and history of stroke. Estimates for each antioxidant were not adjusted for the concentrations of other antioxidants.

Table 4

Associations between quintiles of antioxidants and all-cause mortality among US adults aged 20–79 years with obstructive lung function, National Health and Nutrition Examination Survey III Linked Mortality File 1988–94 to 2006
(Adjusted hazard ratios and 95% confidence intervals)

	Quintiles*									
	1		2		3		4			
Antioxidants†‡	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	5	*P*-adjusted Wald *F*
α-Carotene	1.23	0.74, 2.06	1.01	0.59, 1.73	0.83	0.52, 1.32	0.99	0.69, 1.42	1.00	0.065
β-Carotene	1.40	0.94, 2.07	1.05	0.77, 1.42	0.84	0.58, 1.21	1.10	0.84, 1.45	1.00	0.178
Cryptoxanthin	1.56	0.99, 2.45	1.45	1.06, 1.99	1.39	0.96, 2.03	1.24	0.87, 1.76	1.00	0.239
Lutein/zeaxanthin	1.09	0.75, 1.59	0.99	0.71, 1.37	0.59	0.40, 0.87	0.71	0.49, 1.03	1.00	0.001
Lycopene	1.33	0.87, 2.03	1.37	0.90, 2.10	1.05	0.69, 1.62	1.00	0.71, 1.41	1.00	0.358
Total carotenoids	1.18	0.83, 1.69	0.93	0.66, 1.31	1.01	0.76, 1.35	0.78	0.58, 1.05	1.00	0.077
Se	1.17	0.80, 1.71	0.84	0.57, 1.25	0.87	0.65, 1.16	0.79	0.53, 1.17	1.00	0.057
Vitamin C	1.47	1.01, 2.15	1.20	0.82, 1.75	1.08	0.73, 1.60	0.93	0.65, 1.33	1.00	0.189
Vitamin E	0.85	0.56, 1.30	0.94	0.68, 1.30	1.01	0.69, 1.47	1.05	0.76, 1.45	1.00	0.872

*Quintiles for α-carotene: ≤0.02, >0.02–0.04, >0.04–0.07, >0.07–0.11, and >0.11 μmol/l; quintiles for β-carotene: ≤0.13, >0.13–0.22, >0.22–0.34, >0.34–0.54, and >0.54 μmol/l; quintiles for cryptoxanthin: ≤0.05, >0.05–0.09, >0.09–0.13, >0.13–0.20, and >0.20 μmol/l; quintiles for lutein/zeaxanthin: ≤0.21, >0.21–0.30, >0.30–0.39, >0.39–0.51, and >0.51 μmol/l; quintiles for lycopene: ≤0.20, >0.20–0.32, >0.32–0.43, >0.43–0.56, and > 0.56 μmol/l; quintiles for total carotenoids: ≤ 0.87, >0.87–1.15, > 1.15–1.49, > 1.49–1.97, and > 1.97 μmol/l; quintiles for Se: ≤1.42, > 1.42–1.52, > 1.52–1.61, > 1.61–1.75, and > 1.75 nmol/l; quintiles for vitamin C: ≤14.76, > 14.76–35.20, > 35.20–49.97, > 49.97–63.59, and > 63.59 mmol/l; quintiles for vitamin E: ≤20.39, > 20.39–24.68, > 24.68–28.96, > 28.96–35.67, and > 35.67 μmol/l.

†Adjusted for age, sex, race or ethnicity, education, smoking status, alcohol consumption, leisure-time physical activity, use of vitamin or mineral supplements, systolic blood pressure, HDL-cholesterol, non-HDL-cholesterol, BMI, C-reactive protein, albumin:creatinine ratio, health status, diabetes, history of myocardial infarction and history of stroke.

‡Estimates for each antioxidant were not adjusted for the concentrations of other antioxidants.

Table 5

Baseline adjusted mean concentrations of antioxidants associated with all-cause mortality among US adults aged 20–79 years with obstructive lung function, by race or ethnicity, National Health and Nutrition Examination Survey III Linked Mortality File 1988–94 to 2006*
(Mean values with their standard errors; adjusted hazard ratios and 95% confidence intervals)

	White (*n* 903, 388 deaths)		African American (*n* 315, 138 deaths)		Mexican American (*n* 232, 92 deaths)		
	Mean	SE	Mean	SE	Mean	SE	*P*-adjusted Wald *F*
α-Carotene (μmol/l)	0.09	0.00	0.07	0.01	0.11	0.01	0.002
β-Carotene (μmol/l)	0.29	0.01	0.29	0.02	0.32	0.02	0.470
Cryptoxanthin (μmol/l)	0.16	0.00	0.17	0.01	0.29	0.02	<0.001
Lutein/zeaxanthin (μmol/l)	0.34	0.01	0.43	0.02	0.45	0.03	<0.001
Lycopene (μmol/l)	0.35	0.01	0.31	0.01	0.33	0.02	0.045
Total carotenoids (μmol/l)	1.28	0.02	1.36	0.05	1.59	0.09	0.001
Se (nmol/l)	1.61	0.02	1.52	0.01	1.62	0.02	<0.001
Vitamin C (mmol/l)	38.70	1.34	28.89	1.76	41.96	2.52	<0.001
Vitamin E (μmol/l)	27.70	0.37	25.54	0.55	28.56	1.00	<0.001

	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*	$P_{interaction}$
α-Carotene (μmol/l)	0.55	0.06, 5.40	0.598	0.09	0.00, 17.70	0.359	0.02	0.00, 7.52	0.186	0.818
β-Carotene (μmol/l)	0.91	0.73, 1.14	0.406	0.85	0.65, 1.10	0.212	0.75	0.51, 1.12	0.154	0.582
Cryptoxanthin (μmol/l)	0.40	0.10, 1.54	0.176	0.15	0.01, 4.04	0.251	0.59	0.11, 3.19	0.531	0.927
Lutein/zeaxanthin (μmol/l)	0.88	0.66, 1.16	0.362	0.55	0.36, 0.85	0008	0.71	0.35, 1.45	0.344	0.324
Lycopene (μmol/l)	0.75	0.63, 0.90	0.003	1.34	0.96, 1.87	0082	0.69	0.41, 1.16	0.162	0.010
Total carotenoids (μmol/l)	0.75	0.55, 1.03	0.076	0.71	0.42, 1.21	0.204	0.58	0.34, 0.98	0.042	0.377
Se (nmol/l)	0.98	0.50, 1.92	0.942	0.73	0.26, 2.09	0.553	0.36	0.12, 1.08	0.067	0.548
Vitamin C (mmol/l)	0.95	0.90, 1.00	0.065	1.01	0.92, 1.12	0.775	0.91	0.81, 1.03	0.122	0.095
Vitamin E (μmol/l)	1.03	0.66, 1.60	0.909	0.59	0.20, 1.73	0.328	0.44	0.12, 1.64	0.217	0.355

* Log transformations for the concentrations of β-carotene, lutein/zeaxanthin, lycopene, total carotenoids and vitamin E. Square root transformation for the concentration of vitamin C. Adjusted for age, sex, education, smoking status, alcohol consumption, leisure-time physical activity, use of vitamin or mineral supplements, systolic blood pressure, HDL-cholesterol, non-HDL-cholesterol, BMI, C-reactive protein, albumin:creatinine ratio, health status, diabetes, history of myocardial infarction and history of stroke.

Table 6

Baseline adjusted mean concentrations of antioxidants associated with all-cause mortality among US adults aged 20–79 years with obstructive lung function, by smoking status, National Health and Nutrition Examination Survey III Linked Mortality File 1988–94 to 2006*
(Mean values with their standard errors; adjusted hazard ratios and 95% confidence intervals)

	Current (*n* 560, 254 deaths)		Former (*n* 543, 252 deaths)		Never (*n* 389, 123 deaths)		
	Mean	SE	Mean	SE	Mean	SE	*P*-adjusted Wald *F*
α-Carotene (μmol/l)	0.07	<0.01	0.10	<0.01	0.11	0.01	<0.001
β-Carotene (μmol/l)	0.23	0.01	0.31	0.02	0.36	0.02	<0.001
Cryptoxanthin (μmol/l)	0.12	0.00	0.17	0.01	0.19	0.01	<0.001
Lutein/zeaxanthin (μmol/l)	0.30	0.01	0.37	0.01	0.39	0.01	<0.001
Lycopene (μmol/l)	0.32	0.01	0.35	0.01	0.37	0.01	0.017
Total carotenoids (μmol/l)	1.10	0.03	1.37	0.04	1.51	0.04	<0.001
Se (nmol/l)	1.56	0.02	1.63	0.02	1.63	0.02	0.001
Vitamin C (mmol/l)	30.05	1.66	40.63	1.79	46.39	2.38	<0.001
Vitamin E (μmol/l)	26.56	0.37	27.66	0.41	28.62	0.62	<0.001

	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*	$P_{interaction}$
α-Carotene (μmol/l)	0.30	0.00, 36.44	0.614	2.34	0.16, 33.90	0.527	0.11	0.00, 8.31	0.314	0.293
β-Carotene (μmol/l)	0.81	0.64, 1.02	0.072	0.97	0.77, 1.23	0.827	0.98	0.64, 1.50	0.918	0.141
Cryptoxanthin (μmol/l)	0.03	0.00, 1.15	0.059	0.51	0.16, 1.59	0.238	1.30	0.05, 31.04	0.868	0.285
Lutein/zeaxanthin (μmol/l)	0.62	0.46, 0.83	0.002	1.03	0.71, 1.48	0.894	1.54	0.78, 3.04	0.207	0.048
Lycopene (μmol/l)	0.73	0.59, 0.91	0.005	0.78	0.61, 1.00	0.053	0.78	0.52, 1.18	0.236	0.536
Total carotenoids (μmol/l)	0.56	0.38, 0.83	0.004	0.86	0.59, 1.26	0.434	1.17	0.63, 2.16	0.614	0.141
Se (nmol/l)	0.96	0.30, 3.00	0.936	0.57	0.25, 1.27	0.163	4.45	1.37, 14.43	0.014	0.266
Vitamin C (mmol/l)	0.94	0.87, 1.02	0.129	0.95	0.87, 1.03	0.219	0.98	0.82, 1.18	0.864	0.681
Vitamin E (μmol/l)	0.64	0.27, 1.48	0.288	0.96	0.59, 1.56	0.871	2.32	0.71, 7.58	0.158	0.207

* Log transformations for the concentrations of β-carotene, lutein/zeaxanthin, lycopene, total carotenoids and vitamin E. Square root transformation for the concentration of vitamin C. Means were back-transformed. Adjusted for age, sex, race or ethnicity, education, alcohol consumption, leisure-time physical activity, use of vitamin or mineral supplements, systolic blood pressure, HDL-cholesterol, non-HDL-cholesterol, BMI, C-reactive protein, albumin:creatinine ratio, health status, diabetes, history of myocardial infarction and history of stroke. Estimates for each antioxidant were not adjusted for the concentrations of other antioxidants.