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Lung Function in Relation to Intake of Carotenoids and Other Antioxidant Vitamins in a Population-based Study

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Accumulating evidence suggests that dietary antioxidant vitamins are positively associated with lung function. No evidence exists regarding whether dietary carotenoids other than β-carotene are related to pulmonary function. In 1995–1998 the authors studied the association of forced expiratory volume in 1 second and forced vital capacity as the percentage of the predicted value (FEV_1% and FVC%, respectively) after adjustment for height, age, gender, and race with the intakes of several carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene) in a random sample of 1,616 men and women who were residents of western New York State, aged 35–79 years, and free from respiratory disease. They observed significant associations of lutein/zeaxanthin and vitamins C and E with FEV_1% and FVC% using multiple linear regression after adjustment for total energy intake, smoking, and other covariates. When they analyzed all of these antioxidant vitamins simultaneously, they observed the strongest association of vitamin E with FEV_1% and of lutein/zeaxanthin with FVC%. The differences in forced expiratory volume in 1 second and forced vital capacity associated with a decrease of 1 standard deviation of dietary vitamin E or lutein/zeaxanthin were equivalent to the influence of approximately 1–2 years of aging. Their findings support the hypothesis that carotenoids, vitamin C, and vitamin E may play a role in respiratory health and that carotenoids other than β-carotene may be involved. *Am J Epidemiol* 2002;155:463–71.

airway obstruction; antioxidants; carotenoids; lung diseases, obstructive; oxidants; oxidative stress; respiratory function tests; vitamins

Decreased pulmonary function consistently predicts mortality in the general population (1–3). As a result of this finding, scientists have focused attention on factors that could influence pulmonary function, among them the role of the balance between oxidants and antioxidants (4–6).

Accumulating evidence suggests that dietary antioxidant vitamins, such as vitamin C, vitamin E, and β-carotene, are positively associated with lung function. Although vitamins C and E have been studied in some detail, the evidence is still inconsistent (7). Dietary intake of β-carotene was positively associated with pulmonary function in several cross-sectional studies (8–10), but the information on other carotenoids is limited. This lack of information is surprising, because many of the more than 600 carotenoids are found in the diet and have strong antioxidant activity (11, 12).

Recently, Grievink et al. (13) have reported that *serum* levels of the carotenoids lycopene, α-carotene, and β-carotene were positively associated with lung function in an elderly sample of the Dutch population. We also observed that serum levels of carotenoids were positively associated with forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) as indicators of lung function in a general population sample (14). However, we found the strongest association for the serum carotenoids β-cryptoxanthin and lutein/zeaxanthin (14). There is no "gold standard" for assessing antioxidant status, and dietary data could provide additional useful information. Until now, no epidemiologic study has investigated the association of lung function with these carotenoids in the diet.

Therefore, the goal of this study was to describe the relation of dietary antioxidant carotenoids (α-carotene, β-cryptoxanthin, lutein/zeaxanthin, β-carotene, and lycopene) and other dietary antioxidant vitamins with pulmonary function (FEV_1 and FVC) in the general population.

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Abbreviations: FEV_1, forced expiratory volume in 1 second; FEV_1%, forced expiratory volume in 1 second as the percentage of the predicted value; FVC, forced vital capacity; FVC%, forced vital capacity as the percentage of the predicted value; NHANES III, Third National Health and Nutrition Examination Survey.

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MATERIALS AND METHODS

This study reports data from a general population sample drawn from Erie and Niagara counties in New York State between September 1995 and December 1998. A detailed description of the study design, participant recruitment, and methodology has been reported (14).

Study population

In brief, New York State Department of Motor Vehicles and Health Care Finance Association lists were utilized to randomly select participants aged 35–79 years. Of the 4,946 eligible subjects we initially contacted, 2,537 (1,322 female and 1,215 male) agreed to participate (51.3 percent). Exclusion criteria for this analysis were race other than Caucasian or African American ($n = 33$); missing information on diet ($n = 111$); missing information on height, weight, smoking status, or education ($n = 170$); missing pulmonary function tests ($n = 250$); unacceptable or not reproducible pulmonary function tests ($n = 108$); or a history of chronic obstructive pulmonary disease, asthma, or pulmonary fibrosis ($n = 249$). The remaining 1,616 participants are included in this report. Excluded participants for whom information was available were comparable with included participants in the distribution of gender and race and were similar in their mean age, height, weight, dietary antioxidant intake, and total energy intake ($p > 0.05$). However, excluded subjects had lower levels of pulmonary function and education and were more likely to be smokers ($p < 0.05$).

Examination

The examination included an in-person interview about lifestyle habits, a self-administered questionnaire, anthropometric measurements, and spirometry. Spirometry was performed between 6:30 and 9:30 a.m. according to 1994 American Thoracic Society guidelines (14, 15). We then used multiple linear regression to derive FEV_1 and FVC prediction equations for men and women.

Nutrient intake

We assessed usual diet over the 12-month period starting 24 months before the interview and ending 12 months prior to the interview for each participant using the 100-item Health Habits and History Food Frequency Questionnaire ("Block") (16). Individual mean daily nutrient intake from foods and beverages was calculated using the DietSys (version 3.7) nutrient analysis software developed specifically for that questionnaire and updated to reflect current values for individual carotenoids; lutein and zeaxanthin were analyzed as lutein/zeaxanthin (17, 18). Nutrient intake calculations were based on food composition data available from the US Department of Agriculture using the following formula (16): portion size (g) × nutrient content (per g) × frequency.

Less than 5 percent of the participants reported intake of carotenoid supplements in the 30 days prior to the interview. Of these participants the majority reported use of β-carotene, and only one participant used lutein supplements, three used lycopene supplements, and six used cryptoxanthin supplements. Because of the small number of carotenoid supplement users, we did not calculate carotenoid intake from supplements. For vitamins C and E, we collected information on regular supplement use with the food frequency questionnaire, and we repeated the analyses for vitamins C and E adding the intakes of these two vitamins derived from supplements. All nutrient intakes are expressed as daily consumption.

Statistical methods and analysis

Based on values obtained from lifelong nonsmokers who did not report a history of chronic lung disease for men ($n = 277$) and women ($n = 418$), we obtained the following prediction equations for pulmonary function in men:

$$\text{Predicted } FEV_1 = -0.835 - 0.0322 \times \text{age (years)} + 3.592 \times \text{height (m)} - 0.455 \times \text{race}$$

$$\text{Predicted FVC} = -2.308 - 0.0380 \times \text{age (years)} + 5.227 \times \text{height (m)} - 0.728 \times \text{race}$$

and in women:

$$\text{Predicted } FEV_1 = -0.243 - 0.0283 \times \text{age (years)} + 2.773 \times \text{height (m)} - 0.326 \times \text{race}$$

$$\text{Predicted FVC} = -1.395 - 0.0323 \times \text{age (years)} + 4.103 \times \text{height (m)} - 0.556 \times \text{race}$$

where race was a dummy variable (Caucasian = 0, African American = 1). We then calculated FEV_1 and FVC as the percentage of the predicted value (FEV_1% and FVC%, respectively) for all participants adjusted for age, height, and race (14).

We examined the distributions of the continuous variables to determine if they were normally distributed and calculated the mean values and standard deviation. The analyzed dependent variables showed normal distributions, and we used natural logarithmic transformation for dietary variables because they were not normally distributed. To examine the correlations among variables we calculated simple Pearson's and partial correlation coefficients (r). To analyze the shape of the relation between antioxidants and lung function, we calculated the mean FEV_1% and FVC% levels by quartiles of carotenoids, retinol, and vitamins C and E. We then calculated the differences between the highest and lowest quartiles with adjustment for covariates using general linear models.

To further investigate the association between antioxidant intake and FEV_1 or FVC, respectively, we used multiple linear regression analysis. The dependent variables were FEV_1% and FVC%, and the independent variables were

dietary vitamins C and E, retinol, α-carotene, β-carotene, lutein/zeaxanthin, lycopene, and β-cryptoxanthin. Previously, we found that weight, eosinophil count, education, smoking status, and cumulative tobacco smoke exposure in pack-years of smoking predict FEV_1% with the largest variance explained and, therefore, included these variables in the baseline model (14). Eosinophil count is a predictor of FEV_1 independent of the presence of asthma and, thus, we included it in the model after excluding persons with asthma from the analysis (19). We used the same variables in the models predicting FVC%.

First, we investigated each of the antioxidant variables separately after inclusion of total energy intake in the regression models (after logarithmic transformation). We then included all statistically significant dietary antioxidant vitamins simultaneously as independent variables in the regression model. For comparison among the various antioxidant vitamins in the regression models, the vitamin variables were expressed as a change of 1 standard deviation in intake.

We also examined models where the actually measured FEV_1 and FVC and not FEV_1% and FVC% were the dependent variables. For these analyses the baseline models also included age, height, gender, and race. Furthermore, we repeated the analyses using an external prediction equation based on data from the Third National Health and Nutrition Examination Survey (NHANES III) (20). We did not observe important differences using these analytical approaches and present only the results for FEV_1% and FVC% obtained with our prediction equations.

To define statistical significance we used the conventional level of $p < 0.05$ but determined that interaction terms would be significant if the level of significance was $p < 0.1$. We investigated interaction by including interaction terms of antioxidant vitamin intake, smoking status, and other covariates. For the analyses we utilized the Statistical Package for Social Sciences (21) and S-PLUS software (22).

RESULTS

Demographic characteristics, spirometry, and nutrient intake

Table 1 shows the characteristics of the study participants. The average age was 59.6 years and, based on the mean body mass index, participants tended to be overweight. The sample included a slightly higher number of women than men and a small percentage of African Americans. Approximately 43 percent were never smokers, and 13.7 percent were current smokers. Intakes of nutrients were within the expected range, and almost one fourth of the participants reported daily supplemental vitamin intake.

We observed a moderate to strong correlation among the dietary carotenoids; the correlation coefficients after adjustment for gender, age, and total daily energy intake ranged from $r = 0.24$ to $r = 0.71$. Vitamin C intake was also moderately to strongly correlated with carotenoid intake (from $r = 0.32$ to $r = 0.53$), but the correlation of dietary vitamin E was weak with carotenoids ($r < 0.20$) and moderate with vitamin C ($r = 0.29$).

TABLE 1. Characteristics of participants, Erie and Niagara counties, New York, 1995–1998

Variable (unit)	Mean (SD*)
Age (years)	59.6 (10.8)
Height (m)	1.68 (0.09)
Weight (kg)	79.7 (16.9)
BMI* (kg/m^2)	28.1 (5.2)
FVC* (liter)	3.86 (1.03)
FEV_1* (liter)	2.93 (0.81)
FVC%*	99.1 (15.3)
FEV_1%*	97.3 (16.6)
Pack-years of smoking	14.5 (22.5)
Dietary nutrient intake	
α-Carotene (μg/day)	422.6 (436.8)
β-Carotene (μg/ml)	3,156.6 (2,197.9)
Cryptoxanthin (μg/day)	224.9 (154.6)
Lutein/zeaxanthin (μg/day)	2,024.4 (1,821.5)
Lycopene (μg/day)	2,806.2 (2,223.8)
Vitamin C (mg/day)	128.4 (72.5)
Vitamin E (mg/day)	9.8 (6.9)
Retinol (μg/day)	746.6 (677.5)
	%
Women	51.2
African American	6.4
Vitamin supplement use†	24.9
Smoking	
Never smoker	43.0
Former smoker	43.3
Current smoker	13.7

* SD, standard deviation; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FVC%, forced vital capacity as percentage of predicted value; FEV_1%, forced expiratory volume in 1 second as percentage of predicted value.

† Defined as history of one or more daily supplemental oral vitamins on average.

Analysis of FEV_1% and FVC% by quartiles of vitamin intake

Table 2 shows the mean FEV_1% and FVC% by quartiles of vitamins C and E, carotenoids, and retinol after adjustment for other covariates (total pack-years of smoking, smoking status, weight, education, eosinophil count, and total daily energy intake). For each of the antioxidant vitamins, pulmonary function was higher in the upper quartiles compared with the lowest quartiles. We observed the greatest differences between the bottom and the top quartiles for the antioxidants vitamin C, vitamin E, and lutein/zeaxanthin.

Multiple linear regression analysis

Table 3 summarizes the results of multiple linear regression analysis after inclusion of all covariates. Multiple linear regression of FEV_1% revealed independent associations with pack-years of smoking history, smoking status, education, eosinophil count, and weight; these variables were included in the baseline model. FVC% was associated with pack-years of smoking history, weight, and education, but it

TABLE 2. Mean FEV_1%* and FVC%*,† by quartiles of dietary vitamins C and E, carotenoid, and retinol intake, Erie and Niagara counties, New York, 1995–1998

	Variable						
	I	II	III	IV	Difference between quartiles IV and I	95% CI*	*p* value
				Vitamin C			
FEV_1%	95.5	97.5	98.2	97.9	2.4	0.0, 4.8	0.047
FVC%	98.0	98.9	99.4	100.3	2.3	0.0, 4.5	0.051
				Vitamin E			
FEV_1%	95.4	96.4	97.8	99.4	4.0	1.0, 6.9	0.008
FVC%	96.9	99.1	100.3	100.3	3.4	0.6, 6.2	0.017
				α-Carotene			
FEV_1%	96.9	96.8	97.2	98.2	1.3	−1.1, 3.6	0.227
FVC%	99.3	98.3	99.1	99.8	0.5	−1.7, 2.7	0.657
				β-Carotene			
FEV_1%	96.9	96.7	96.4	99.0	2.1	−0.3, 4.5	0.083
FVC%	99.0	98.2	98.7	100.7	1.7	−0.5, 4.0	0.132
				Cryptoxanthin			
FEV_1%	95.7	98.0	97.4	97.9	2.2	−0.2, 4.6	0.067
FVC%	98.3	99.5	99.1	99.6	1.3	−1.0, 3.5	0.277
				Lutein/zeaxanthin			
FEV_1%	96.3	96.2	97.4	99.1	2.8	0.5, 5.0	0.016
FVC%	97.3	98.7	98.9	101.7	4.4	2.3, 6.6	<0.001
				Lycopene			
FEV_1%	96.5	96.9	98.3	97.3	0.8	−1.5, 3.1	0.496
FVC%	98.6	98.8	99.7	99.5	0.8	−1.4, 3.0	0.452
				Retinol			
FEV_1%	95.5	97.7	97.6	98.2	2.7	−0.1, 5.6	0.057
FVC%	98.8	99.2	99.0	99.6	0.8	−1.9, 3.5	0.558

* FEV_1%, forced expiratory volume in 1 second as percentage of predicted value; FVC%, forced vital capacity as percentage of predicted value; CI, confidence interval.

† Adjusted for smoking status, total pack-years of smoking, weight, education, eosinophil count, and total daily energy intake.

showed no statistically significant association with eosinophil count and no additive effect of smoking status after we included pack-years of smoking in the baseline model. For the analysis of dietary variables, models were also adjusted for total daily energy intake. We observed a statistically significant association of vitamins C and E and lutein/zeaxanthin with FEV_1% and FVC% when we added these variables individually and separately to the baseline regression models. Among all the carotenoids, lutein/zeaxanthin was the only carotenoid that showed a statistically significant association.

Table 4 shows regression coefficients for the significant antioxidant variables when we included all statistically significant variables simultaneously in the model. Although for FEV_1% vitamin E was the only significantly correlated antioxidant variable, lutein/zeaxanthin was the only significant correlate of FVC%. We observed no statistically significant interaction of antioxidant intake with smoking (smoking status or pack-years of smoking history). However, because of possible effect modification of smoking on pulmonary function by nutrient intake, we performed analyses separately by smoking status.

Important antioxidant correlates of FEV_1% by smoking status

Table 5 summarizes the findings when lutein/zeaxanthin and vitamins C and E were added separately or simultaneously to the regression models for never, former, and current smokers after adjustment for confounders. When we added variables separately to the models, in never smokers lutein/zeaxanthin and vitamin E were significant correlates of FEV_1 but not vitamin C. No antioxidant variable showed a significant correlation in former smokers. We observed the strongest correlation for all variables in current smokers, but the regression coefficient was not significant for vitamin E. When we added variables simultaneously to the baseline model stratified by smoking, the antioxidant vitamins failed to reach statistical significance. Compared with the model with variables added separately, the coefficient for lutein/zeaxanthin was reduced mainly in current smokers. While the coefficients for vitamin E were similar compared with the other models, we observed the greatest reductions in the regression coefficients for vitamin C in all smoking strata.

TABLE 3. Multiple linear regression coefficients for regression on FEV_1%† and FVC%†, Erie and Niagara counties, New York, 1995–1998‡

Variable (unit)	FEV_1%			FVC%		
	β	SE†	R^2	β	SE	R^2
			Baseline model			
Smoking status (never, former, current)	−2.268***	0.697		−0.786	0.664	
Pack-years of smoking (1 pack-year)	−0.166***	0.022		−0.084***	0.021	
Weight (1 kg)	−0.061**	0.023	0.10	−0.125***	0.022	0.05
Education (degree)	0.487**	0.141		0.398**	0.135	
Eosinophil count (1 cell/μl)	−0.423*	0.206		0.020	0.196	
			Dietary variables entered separately			
α-Carotene (SD†)	0.186	0.429	0.10	−0.157	0.408	0.05
β-Carotene (SD)	0.551	0.430	0.10	0.658	0.408	0.05
Cryptoxanthin (SD)	0.557	0.440	0.10	0.267	0.418	0.05
Lutein/zeaxanthin (SD)	0.997*	0.411	0.11	1.725***	0.389	0.06
Lycopene (SD)	0.264	0.422	0.10	0.317	0.401	0.05
Vitamin C (SD)	1.040*	0.439	0.11	0.845*	0.417	0.05
Vitamin E (SD)	1.601**	0.546	0.11	1.103***	0.520	0.05
Retinol (SD)	0.807	0.555	0.10	0.220	0.528	0.05

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

† FEV_1%, forced expiratory flow in 1 second as percentage of predicted value; FVC%, forced vital capacity as percentage of predicted value; SE, standard error; SD, standard deviation.

‡ All models evaluating dietary intake of antioxidants include the variables of the baseline model (smoking status, total pack-years, weight, education, and eosinophil count) and total daily energy intake. Education is expressed by degree as less than 12 years of school, high school diploma, vocational school, some college, associate degree, bachelor's degree, or graduate degree. The standard deviations for α-carotene, β-carotene, cryptoxanthin, lutein/zeaxanthin, lycopene, vitamin C, vitamin E, and retinol were 436.8 μg/day, 2,197.9 μg/ml, 154.6 μg/day, 1,821.5 μg/day, 2,223.8 μg/day, 72.5 mg/day, 6.9 mg/day, and 677.5 μg/day, respectively. Dietary variables were log transformed to increase normality.

Important antioxidant correlates of FVC% by smoking status

Table 6 shows the regression coefficients for the important dietary variables by smoking status when we added the variables individually or simultaneously to the regression models. The antioxidant variables were significant or borderline significant correlates of lung function in never smokers when we added the variables individually to the baseline model. As for FEV_1%, we did not find significant correlations in former smokers, but in current smokers lutein/zeaxanthin was significantly related to FVC% when all antioxidant variables were added simultaneously to the regression models. In all smoking strata, lutein/zeaxanthin was the strongest correlate that achieved statistical significance in never and current smokers, but vitamins C and E were not statistically significant.

TABLE 4. Multiple linear regression coefficients for regression on FEV_1%* and FVC%*, Erie and Niagara counties, New York, 1995–1998†,‡

Variable (unit)	β	95% confidence interval	p value	R^2
		Dependent variable: FEV_1%		
Lutein/zeaxanthin (SD*)	0.623	−0.303, 1.549	0.187	
Vitamin C (SD)	0.395	−0.624, 1.413	0.447	0.11
Vitamin E (SD)	1.285	0.158, 2.412	0.026	
		Dependent variable: FVC%		
Lutein/zeaxanthin (SD)	1.726	0.849, 2.604	<0.001	
Vitamin C (SD)	−0.244	−1.209, 0.721	0.620	0.06
Vitamin E (SD)	0.739	−0.328, 1.807	0.175	

* FEV_1%, forced expiratory volume in 1 second as percentage of predicted value; FVC%, forced vital capacity as percentage of predicted value; SD, standard deviation.

† Important dietary variables entered simultaneously.

‡ All models evaluating dietary intake of antioxidants include the variables of the baseline model (smoking status, total pack-years, weight, education, and eosinophil count) and total daily energy intake. The standard deviations for lutein/zeaxanthin, vitamin C, and vitamin E were 1,821.5 μg/day, 72.5 mg/day, and 6.9 mg/day, respectively. Dietary variables were log transformed to increase normality.

TABLE 5. Multiple linear regression coefficients for regression on FEV_1%*, Erie and Niagara counties, New York, 1995–1998†,‡

	Variable entered separately			Variables entered simultaneously		
	β	95% confidence interval	p value	β	95% confidence interval	p value
			Never smoker (n = 695) §			
Lutein/zeaxanthin (SD*)	1.091	−0.033, 2.215	0.057	1.022	−0.291, 2.334	0.127
Vitamin C (SD)	0.659	−0.587, 1.906	0.300	−0.296	−1.804, 1.212	0.700
Vitamin E (SD)	1.579	0.008, 3.140	0.049	1.410	−0.257, 3.075	0.097
			Former smoker (n = 700)			
Lutein/zeaxanthin (SD)	0.073	−1.216, 1.361	0.912	−0.065	−1.533, 1.402	0.930
Vitamin C (SD)	0.211	−1.138, 1.559	0.759	0.028	−1.550, 1.606	0.972
Vitamin E (SD)	0.875	−0.718, 2.467	0.281	0.879	−0.789, 2.548	0.301
			Current smoker (n = 221)			
Lutein/zeaxanthin (SD)	2.544	0.142, 4.946	0.038	1.452	−1.217, 4.122	0.285
Vitamin C (SD)	3.049	0.537, 5.560	0.018	2.139	−0.677, 4.955	0.136
Vitamin E (SD)	2.731	−0.859, 6.320	0.135	1.534	−2.165, 5.234	0.415

* FEV_1%, forced expiratory volume in 1 second as percentage of predicted value; SD, standard deviation.
† Important dietary antioxidant vitamin variables.
‡ All models evaluating dietary intake of antioxidants include the variables of the baseline model (total pack-years, weight, education, and eosinophil count) and total daily energy intake. Dietary variables were log transformed to increase normality. The standard deviations for lutein/zeaxanthin, vitamin C, and vitamin E were 1,821.5 μg/day, 72.5 mg/day, and 6.9 mg/day, respectively.
§ Number of subjects.

Other models examined

Adjustment for regular supplemental vitamin use, serum cholesterol, exclusion of eosinophil count, or inclusion of age, height, and vitamin variables after quadratic, cubic, or logarithmic transformation made no substantial difference in the results. We investigated interaction by including the interaction terms of antioxidant vitamin intake, smoking status, and gender, but we did not observe statistically significant interactions. There was also no important interaction among the antioxidant variables. When we stratified the regression analyses by reported daily vitamin supplement intake, we did not observe important differences between users and nonusers for the coefficients of lutein/zeaxanthin.

TABLE 6. Multiple linear regression coefficients for regression on FVC%*, Erie and Niagara counties, New York, 1995–1998†,‡

	Variable entered separately			Variables entered simultaneously		
	β	95% confidence interval	p value	β	95% confidence interval	p value
			Never smoker (n = 695) §			
Lutein/zeaxanthin (SD*)	1.983	0.852, 3.114	0.001	1.928	0.612, 3.243	0.004
Vitamin C (SD)	1.108	−0.152, 2.367	0.085	−0.395	−1.906, 1.116	0.608
Vitamin E (SD)	1.964	0.374, 3.554	0.016	1.551	−0.118, 3.221	0.069
			Former smoker (n = 700)			
Lutein/zeaxanthin (SD)	0.960	−0.251, 2.172	0.120	1.322	−0.054, 2.699	0.060
Vitamin C (SD)	−0.155	−1.425, 1.114	0.810	−0.818	−2.298, 0.663	0.279
Vitamin E (SD)	0.074	−1.432, 1.579	0.923	0.116	−1.449, 1.682	0.884
			Current smoker (n = 221)			
Lutein/zeaxanthin (SD)	2.577	0.530, 4.624	0.014	2.337	0.042, 4.631	0.046
Vitamin C (SD)	1.651	−0.522, 3.824	0.136	0.830	−1.590, 3.251	0.499
Vitamin E (SD)	0.710	−2.382, 3.801	0.651	−0.309	3.489, 2.870	0.848

* FVC%, forced vital capacity as percentage of predicted value; SD, standard deviation.
† Important dietary antioxidant vitamin variables.
‡ All models evaluating dietary intake of antioxidants include the variables of the baseline model (total pack-years, weight, and education) and total daily energy intake. The standard deviations for lutein/zeaxanthin, vitamin C, and vitamin E were 1,821.5 μg/day, 72.5 mg/day, and 6.9 mg/day, respectively. Dietary variables were log transformed to increase normality.
§ Number of subjects.

However, there was a reduction in the coefficients of vitamins C and E in regular vitamin users when the variables were added either individually or simultaneously (data not shown). After addition of supplemental vitamin C and E intakes to dietary intake, the regression coefficients were only slightly larger.

DISCUSSION

In this population-based study we observed that, among the several prevalent carotenoids in the diet, lutein/zeaxanthin had the strongest association with pulmonary function. We also found a positive association between pulmonary function and dietary intakes of vitamin C and vitamin E. When we considered these antioxidant vitamins simultaneously, only vitamin E correlated significantly with FEV_1% and lutein/zeaxanthin with FVC%. Including intakes of supplemental antioxidant vitamins C and E did not significantly alter these results. When we repeated the analysis stratified by smoking status, the associations between antioxidant vitamins and FEV_1% tended to be stronger in the group of current smokers. Lutein/zeaxanthin and vitamin E intakes showed a positive association with FVC% in never smokers, but only lutein/zeaxanthin was associated with FVC% in former and current smokers.

Several previous studies have shown a positive association of dietary β-carotene with pulmonary function (8–10). Until now, however, studies have focused only on dietary β-carotene and not on other carotenoids. We have investigated carotenoids other than β-carotene because of their strong antioxidant function and because they are highly concentrated in human plasma.

Our findings indicate that, among all considered carotenoids, dietary lutein/zeaxanthin has the strongest relation to FEV_1 and FVC%. This finding is somewhat surprising because dietary lycopene and β-carotene intakes are higher than that of lutein/zeaxanthin and because lycopene has been considered to be a more powerful antioxidant than β-cryptoxanthin and lutein/zeaxanthin (11). It has been emphasized, however, that antioxidants' activity measured in vitro, including their relative action compared with that of other carotenoids, may not resemble their activity in complex in vivo conditions (23). For example, in comparison with other carotenoids, a stronger protection against damage of the retina has been ascribed to lutein/zeaxanthin (24, 25), and a negative association with prevalence of angina pectoris and carotid atherosclerosis has been reported for serum β-cryptoxanthin (26). However, there are limited epidemiologic data for carotenoids other than β-carotene and their relation to human disease.

We previously found that cryptoxanthin and lutein/zeaxanthin in serum were positively related to pulmonary function (14). We report now on the relation between dietary antioxidant vitamin intake and pulmonary function. In the current analysis we could confirm the results for lutein/zeaxanthin but not for cryptoxanthin. The lack of an association between dietary cryptoxanthin intake and pulmonary function could be the result of the difficulties associated with accurately measuring cryptoxanthin in the diet. It may be that these limitations are not present for measurement of dietary lutein/zeaxanthin intake or that lutein/zeaxanthin is a stronger antioxidant than β-cryptoxanthin, and we found a positive association in spite of limitations in the dietary measurement of this compound.

The results of this study also confirm previous findings that dietary intake of vitamin C is associated with pulmonary function when vitamin C is considered individually as a dietary antioxidant vitamin (8–10, 27–30). Recently, we have systematically reviewed the relation between antioxidants and pulmonary function (7) and found an approximate pooled effect of a 37-ml increase in FEV_1 associated with an increased intake of 100 mg of daily vitamin C. The corresponding estimate in this study is approximately 40 ml for an increased intake of 100 mg of daily vitamin C and, thus, in agreement with the pooled estimate.

Cigarette smoke contains large concentrations of oxidants (31). As a result one might expect a stronger association of antioxidant vitamins with pulmonary function in smokers if antioxidants could prevent oxidative damage. We failed to observe a statistically significant interaction of serum antioxidants with smoking, but this negative finding should be interpreted with caution. No previous study had sufficient power to detect a statistically significant interaction of vitamin C intake with smoking, but Hu and Cassano (9) observed a stronger correlation of vitamin C with FEV_1 in current smokers in an analysis of the NHANES III data, the largest data set investigated to date. Our study was not sufficiently powered to observe effect modification by smoking, but our results lend further support to the hypothesis that the effect may be stronger in current smokers. The associations between antioxidants and lung function were weak in former smokers. This finding may be a result of a prior change to a healthier lifestyle in smokers with impaired lung function that included smoking cessation and higher intake of dietary antioxidant vitamins. It is also important to note that, similar to our study, previous studies observed an attenuation of the association between pulmonary function and vitamin C when other antioxidants had been taken into account (9, 29). This attenuation appears to result from the correlation of the dietary vitamins C and E intake variables due to common food sources, but there is evidence that they act, at least in part, independently in the lung (32, 33).

The association of vitamin E with lung function has been found with less consistency than that of vitamin C. Our study adds evidence to the epidemiologic studies that found a stronger association of FEV_1 with vitamin E than with vitamin C (34), including NHANES III (9). The stronger association of vitamin E with pulmonary function compared with vitamin C may be a result of random error due to sampling, because other studies did not observe a positive association with vitamin E (10) or found that the association was weakened after taking the effects of vitamin C into account (29). However, the attenuation of an association by another nutrient is often present in the analysis of dietary data, and it is, at least in part, related to the autocorrelation of dietary nutrients. In addition, differences in measurement error between nutrients can result in falsely stronger associations

of the nutrient with lower measurement error. Since dietary vitamin E intake is more difficult to measure and is associated with a greater measurement error than vitamin C intake (35), a stronger association with vitamin C should be observed. Further support for an association of vitamin E with pulmonary function comes from our earlier analysis and the work of others on serum vitamin E and pulmonary function (9, 14, 36).

In previous studies, consideration of supplemental antioxidant intake was restricted to adjusted regression models using dichotomous dummy variables (9, 10). These studies did not report significant changes when the analysis was adjusted for supplemental vitamin use, but they left considerable uncertainty about the effect because of the lack of quantified supplement intake. We calculated the intakes of supplemental vitamins C and E, because these supplements were used regularly in this population. Including information on the intakes of these supplemental vitamins did not significantly alter the results. However, when we stratified by vitamin use, the association between vitamins C and E with pulmonary function tended to be weaker in regular vitamin supplement users for both dietary and total (diet and supplement) intakes. This observation could indicate that long-term users of these antioxidants reach a possible threshold or ceiling effect. The possibility of a ceiling effect is supported by the observation that the majority of supplement users were also in the highest quartile of dietary vitamin intake.

This study has several limitations. The cross-sectional design and the subsequent uncertainty about the cause-effect relation represent a weakness of our study. Longitudinal studies should provide evidence to answer this problem. Another limitation is the limited power to perform subgroup analysis by smoking status. However, even larger studies such as the NHANES III had limited power for this analytical approach (9). Furthermore, the high rate of nonresponders and missing data leaves the possibility for selection bias. Participants excluded because of missing data did not differ from those included in dietary antioxidant or energy intakes, age, height, or weight, but excluded participants had lower lung function, education, and prevalence of never smokers. Because of the possibility for selection bias, our findings can be generalized only with caution. In addition, we cannot exclude that multiple hypothesis testing led to erroneous statistically significant findings.

The strength of this study is the measurement of several dietary carotenoids in relation to lung function, an approach that has not been chosen previously. Because information on the relation of supplemental vitamin intake and pulmonary function is limited, our study adds important information to the current body of evidence. Information about long-term use of supplemental carotenoids is not available. Since less than 5 percent of the participants in this study used supplements containing carotenoids in the month prior to the interview, it is unlikely that carotenoid supplements have been taken regularly and that considering these supplements would have significantly altered the results. Another strength is that there was no important change in the results when we used the NHANES III data as an external prediction equation for FEV_1% and FVC%.

Although it is not resolved completely whether vitamins C and E play a strong role in antioxidant defense in the lung and it is not completely explained why dietary lutein/zeaxanthin shows stronger effects than the other carotenoids, the magnitude of the observed effects on pulmonary function is of clinical significance. To bring the estimates into perspective, a decrease of 1 standard deviation of dietary vitamin E (72.5 mg/day) or lutein/zeaxanthin (1.8 mg/day) is equivalent to the negative effect of approximately 1–2 years of aging on FEV_1 and FVC, respectively.

In summary, we found a positive association of vitamin C, vitamin E, and lutein/zeaxanthin intake with pulmonary function. We identified lutein/zeaxanthin as the dietary carotenoid with the strongest association with pulmonary function. When we considered carotenoids, vitamins C and E, and retinol simultaneously, the individual effects were reduced and vitamin E was most strongly related to FEV_1 and lutein/zeaxanthin with FVC. We also found further evidence that smokers may show stronger associations between dietary antioxidants and lung function. Our findings emphasize that carotenoids may play a role in respiratory health and that studies should include carotenoids other than β-carotene. Further studies are needed to confirm these results, and longitudinal studies could help to clarify whether this association is related to lung development in childhood and adolescents or whether it is the result of an accumulation of protective effects against oxidative damage throughout life. A meta-regression analysis that pools data from all studies could help to answer the question of possible effect modification of smoking on the relation between antioxidant vitamins and lung function.

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REFERENCES

1. Friedman GD, Klatsky AL, Siegelaub AB. Lung function and risk of myocardial infarction and sudden cardiac death. N Engl J Med 1976;294:1071–5.
2. Neas LM, Schwartz J. Pulmonary function levels as predictors of mortality in a national sample of US adults. Am J Epidemiol 1998;147:1011–18.
3. Schünemann HJ, Dorn J, Grant BJ, et al. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest 2000; 118:656–64.
4. Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease. Oxidative Stress Study Group.

Am J Respir Crit Care Med 1997;156:341–57.
5. Schünemann HJ, Muti P, Freudenheim JL, et al. Oxidative stress and lung function. Am J Epidemiol 1997;146:939–48.
6. MacNee W, Rahman I. Oxidants and antioxidants as therapeutic targets in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160(suppl):S58–S65.
7. Schünemann HJ, Freudenheim JL, Grant BJB. Epidemiologic evidence linking antioxidant vitamins to pulmonary function and airway obstruction. Epidemiol Rev 2001;23:248–67.
8. Grievink L, Smit HA, Ocke MC, et al. Dietary intake of antioxidant (pro)-vitamins, respiratory symptoms and pulmonary function: the MORGEN study. Thorax 1998;53:166–71.
9. Hu G, Cassano PA. Antioxidant nutrients and pulmonary function: the Third National Health and Nutrition Examination Survey (NHANES III). Am J Epidemiol 2000;151:975–81.
10. Chen R, Tunstall-Pedoe H, Bolton-Smith C, et al. Association of dietary antioxidants and waist circumference with pulmonary function and airway obstruction. Am J Epidemiol 2001;153:157–63.
11. Sies H, Stahl W. Vitamins E and C, beta-carotene, and other carotenoids as antioxidants. Am J Clin Nutr 1995;62(suppl): 1315S–21S.
12. Palace VP, Khaper N, Qin Q, et al. Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease. Free Radic Biol Med 1999;26:746–61.
13. Grievink L, de Waart FG, Schouten EG, et al. Serum carotenoids, alpha-tocopherol, and lung function among Dutch elderly. Am J Respir Crit Care Med 2000;161:790–5.
14. Schünemann HJ, Grant BJ, Freudenheim JL, et al. The relation of serum levels of antioxidant vitamins C and E, retinol and carotenoids with pulmonary function in the general population. Am J Respir Crit Care Med 2001;163:1246–55.
15. American Thoracic Society. Standardization of spirometry—1994 update. Am J Respir Crit Care Med 1995;152:1107–36.
16. Block G, Hartman AM, Dresser CM, et al. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124:453–69.
17. Block G, Coyle LM, Hartman AM, et al. HHHQ-DIETSYS analysis software, version 3.0. Bethesda, MD: National Cancer Institute, 1993.
18. US Department of Agriculture, Agricultural Research Service. USDA nutrient database for standard reference, release 13. 1999. (Nutrient Data Laboratory Home Page, http://www.nal.usda.gov/fnic/foodcomp).
19. Frette C, Annesi I, Korobaeff M, et al. Blood eosinophilia and FEV_1. Cross-sectional and longitudinal analyses. Am Rev Respir Dis 1991;143:987–92.
20. Hankinson JL, Odencrantz JR, Fedan KB. Spirometry reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 2001;159:179–87.
21. Statistical package for social sciences for Windows, release 9.0. Chicago, IL: SPSS, Inc, 1999.
22. S-PLUS 2000 professional edition for Windows, release 1. Cambridge, MA: MathSoft, Inc, 1999.
23. Britton G. Structure and properties of carotenoids in relation to function. FASEB J 1995;9:1551–8.
24. Schalch W. Carotenoids in the retina: a review of their possible role in preventing damage caused by light and oxygen. In: Emerit I, Chance B, eds. Free radicals and aging. Basel, Switzerland: Birkhauser Verlag, 1992:280–98.
25. Mares-Perlman JA, Fisher AI, Klein R, et al. Lutein and zeaxanthin in the diet and serum and their relation to age-related maculopathy in the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2001;153:424–32.
26. Ford ES, Giles WH. Serum vitamins, carotenoids, and angina pectoris: findings from the National Health and Nutrition Examination Survey III. Ann Epidemiol 2000;10:106–16.
27. Schwartz J, Weiss ST. Dietary factors and their relation to respiratory symptoms. The Second National Health and Nutrition Examination Survey. Am J Epidemiol 1990;132:67–76.
28. Schwartz J, Weiss ST. Relationship between dietary vitamin C intake and pulmonary function in the First National Health and Nutrition Examination Survey (NHANES I). Am J Clin Nutr 1994;59:110–14.
29. Britton JR, Pavord ID, Richards KA, et al. Dietary antioxidant vitamin intake and lung function in the general population. Am J Respir Crit Care Med 1995;151:1383–7.
30. Hu G, Zhang X, Chen J, et al. Dietary vitamin C intake and lung function in rural China. Am J Epidemiol 1998;148:594–9.
31. Pryor WA, Stone K. Oxidants in cigarette smoke: radicals, hydrogen peroxide, peroxynitrate and peroxynitrite. Ann N Y Acad Sci 1993;686:12–28.
32. Neuzil J, Stocker R. Free and albumin-bound bilirubin are efficient co-antioxidants for alpha-tocopherol, inhibiting plasma and low density lipoprotein lipid peroxidation. J Biol Chem 1994;269:16712–19.
33. Cross CE, van der Vliet A, Eiserich JP, et al. Oxidative stress and antioxidants in respiratory tract lining fluids. In: Clerch LB, Massaro DJ, eds. Oxygen, gene expression and cellular function. New York, NY: Marcel Dekker, 1997:367–98.
34. Dow L, Tracey M, Villar A, et al. Does dietary intake of vitamins C and E influence lung function in older people? Am J Respir Crit Care Med 1996;154:1401–4.
35. Willett W. Nutritional epidemiology. 2nd ed. New York, NY: Oxford University Press, Inc, 1998.
36. Grievink L, Smit HA, Veer P, et al. Plasma concentrations of the antioxidants beta-carotene and alpha-tocopherol in relation to lung function. Eur J Clin Nutr 1999;53:813–17.