

Association between lutein intake and lung function in adults: the Rotterdam Study

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Abstract

Lutein, a fat-soluble carotenoid with antioxidant properties, may have an effect on respiratory health. However, the evidence is inconsistent. We aimed to cross-sectionally investigate the association between lutein intake and lung function by measuring forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC) and FEV₁/FVC% in adults (aged 45–79 years). We included 4402 participants from the Rotterdam Study, a prospective cohort study in The Netherlands. Lutein intake was assessed using a validated FFQ. Lung function was assessed using spirometry around the same time point as the dietary assessment. No independent association was found between lutein intake and FEV₁ (–12.17 (95% CI –34.21, 9.87) ml per sd increase in lutein) after adjustment for age, sex, height, cohort effect, ethnicity, education, weight, total daily energy intake, smoking status, physical activity, and intakes of fatty acids, dietary fibre, alcohol, β -carotene, β -cryptoxanthin, lycopene and zeaxanthin. There was also no association between lutein and FVC or FEV₁/FVC%. However, after stratification by smoking status, lutein intake was significantly associated with lower FEV₁/FVC% in current smokers (–1.69 (95% CI –2.93, –0.45)% per sd increase of lutein) independent of other carotenoids. The present study does not support an independent association between lutein intake and lung function in adults. However, future studies should focus on the potential inverse association between high lutein intake and lung function in specific risk groups such as smokers.

Key words: Lutein: Carotenoids: Antioxidants: Lung function: Adults: Elderly

Chronic obstructive pulmonary disease (COPD) is currently the third cause of death worldwide⁽¹⁾. Interestingly, poor lung function is an important predictor of mortality in patients with COPD and in the general population^(2–4).

Several studies have focused on evaluating the impact of nutritional therapy in COPD patients⁽⁵⁾; however, it is unclear how specific dietary components may influence lung function⁽⁶⁾.

Lutein is a carotenoid without vitamin A capacities, but with powerful antioxidant capacities⁽⁷⁾. The main sources of lutein are kale, spinach and collards⁽⁸⁾. Furthermore, lutein is well known for its antioxidant effect in the eye, where it protects the retina from inflammation and oxidative stress⁽⁷⁾. With this in mind, it may be the case that lutein has the same protective function in the lungs; counteracting a retardation in pulmonary function.

It is hypothesised that carotenoids, including lutein, can protect the airways from inflammation-induced damage. Schunemann *et al.* reported in both their studies (cross-sectionally and prospectively) a strong antioxidant effect of lutein (serum and dietary intake) on lung function^(9,10). It has been suggested that inadequate dietary intake of antioxidants is associated with the development of respiratory diseases^(11,12).

The association between lutein intake and respiratory health has recently been reviewed⁽¹³⁾, and very few studies in adult populations have been carried out^(9,10,14–16). However, these studies combined lutein with zeaxanthin and did not extensively adjust for confounders or comprised selected populations (e.g. only in women, young adults or patients with COPD). To date, there are no recommended levels of intake for lutein;

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; RS-I–III, Rotterdam Study cohorts I–III.

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therefore, from a public health perspective, it is important to determine whether recommendations are required. We aimed to cross-sectionally evaluate the effect of lutein intake on lung function as measured by forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC) and the FEV₁/FVC%, in adults from a general population (aged 45–79 years), taking into account socio-demographic, lifestyle and nutritional factors.

Methods

Study design

The present study was conducted with data from the Rotterdam Study, an ongoing, prospective, population-based cohort study since 1990, including adults aged 45 years or older living in the well-defined district Ommoord, a neighbourhood of Rotterdam, The Netherlands⁽¹⁷⁾. The Rotterdam Study was approved by the Medical Ethics Committee of the Erasmus University, and written informed consents were collected from all participants⁽¹⁷⁾. The original aim of the Rotterdam Study was to investigate factors related to frequently occurring diseases in the elderly, as this group is particularly vulnerable to diseases^(17,18). Further information about the objectives and study design of the Rotterdam Study itself is described elsewhere⁽¹⁷⁾.

The baseline visit of the first Rotterdam Study cohort, including 7983 participants aged 55 years or older, was completed between 1990 and 1993 (Rotterdam Study cohort I (RS-I)-visit 1). From 2000 to 2001, the cohort was extended with a second cohort of 3011 individuals, who are now 55 years old or have moved to Ommoord district (RS-II). From 2006 to 2008, a third cohort of 3932 individuals aged 45–54 years living in Ommoord (RS-III) was added⁽¹⁷⁾. Participants were invited for follow-up measurements every 3–4 years.

Study participants

Data from the present study were collected from participants attending the fifth visit of the original cohort (RS-I-visit 5; 2009–2011; *n* 2140), the third visit of the second cohort (RS-II-visit 3; 2011–2012; *n* 1887) and the second visit of the third cohort (RS-III-visit 2; 2012–2013; *n* 3000). We excluded participants for whom dietary intake data were not available (*n* 1337), participants who had an abnormal total energy intake below 2092 kJ (500 kcal) or above 20920 kJ (5000 kcal) (*n* 158) and participants who did not have an interpretable spirometry (*n* 1130). Thus, we included data from 4402 individuals in these analyses. A flow chart is given in Fig. 1.

Dietary intake of lutein

For RS-I-visit 5 (2009–2011), RS-II-visit 3 (2011–2012) and RS-III-visit 1 (2006–2008), self-reported dietary intake was assessed using a FFQ. Participants were asked to fill in a FFQ at home to report their nutritional intake in the past year. The FFQ was a comprehensive, 389-item, semi-quantitative questionnaire based on an existing validated FFQ developed for

Dutch adults^(19,20). The FFQ included questions such as the frequency of consumption of food items over the last month, the amount and type of food item and preparation methods. Portion sizes in g/d were estimated using standardised household measures⁽²¹⁾. Dietary data were converted into nutrient intakes (including daily lutein intake and total energy intake) using the Dutch Food Composition Tables of 2006 and 2011^(22,23).

Lung function

The main outcomes assessed in the present study were the FEV₁, FVC and FEV₁/FVC%. Trained personnel measured lung function using Master Screen[®] PFT Pro (CareFusion) according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines⁽²⁴⁾. To ensure reproducibility, multiple efforts were required. The values of the best acceptable effort were used for analyses. Spirometry tests that did not meet ATS/ERS acceptability and reproducibility criteria were classified as 'not interpretable'.

Confounders

Before the baseline research centre visit, home interviews were conducted by trained interviewers. Thereafter, participants were invited for clinical examination and laboratory tests at the research centre. At the baseline visit of the original cohort (RS-I-visit 1 1990–1993), data of multiple factors were collected. For the present analyses, level of education and ethnicity of the baseline visit were used as proxies for education and ethnicity of the fifth visit (RS-I-visit 5; 2009–2011). Level of education was divided into two groups – low (primary education or less) and high (levels above primary education). Ethnicity of participants was based on the ethnic background of the participants' grandparents, and was divided into Caucasian and non-Caucasian. Physical activity was measured in metabolic equivalent task-h per week, which was a combination of questions on sport, walking, cycling and gardening. Smoking status was divided into three categories – never smoker, former smoker and current smoker. Data on the following confounders used for the analyses were collected from the fifth visit itself (RS-I-visit 5; 2009–2011): age, sex, height, weight, total daily energy intake, physical activity and smoking status. In addition, other potential dietary confounders were collected by the FFQ: total fat intake, ratio of *n*-3:*n*-6 fatty acids (N3:N6), and intakes of fibre, alcohol, β -carotene, β -cryptoxanthin, lycopene and zeaxanthin.

At the baseline visit of the second cohort (RS-II-visit 1; 2000–2001), data on education and ethnicity were collected in the same way as for the baseline visit of the original cohort and were used as proxies for education and ethnicity of the third visit (RS-II-visit 3; 2011–2012). Ethnicity was based on the ethnic background of the participants' parents, and was divided into the same categories as the RS-I-visit 1. The other factors were collected from the third visit itself.

Data on education, ethnicity, physical activity and dietary intake of the first visit of the third cohort (RS-III-visit 1; 2006–2008) were also collected according to the above-mentioned methods and

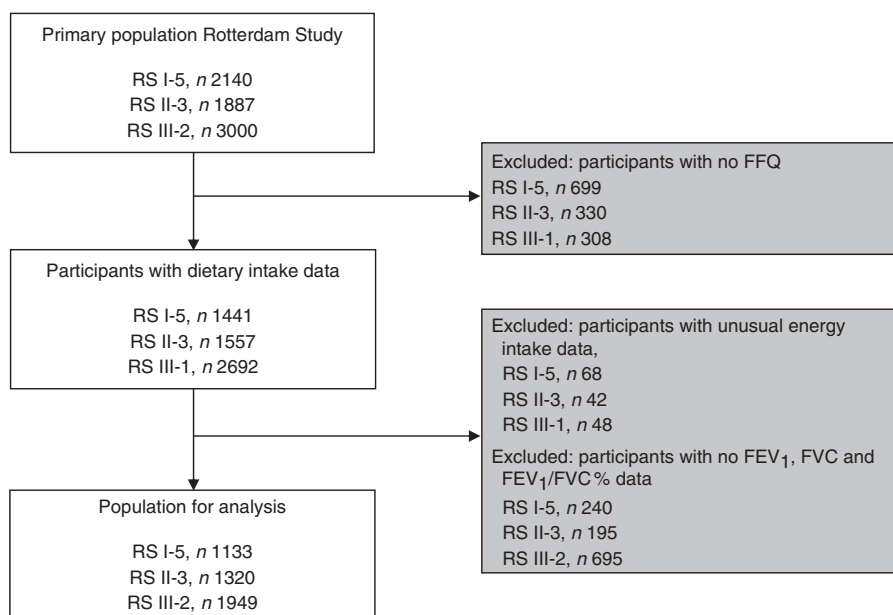


Fig. 1. Flow chart of the participants included in the study (n 4402). RS I–III–1–5, Rotterdam Study cohorts I–III–visits 1–5; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

used as proxies for education, ethnicity and dietary intake data of the second visit (RS-III-visit 2; 2012–2013). The other factors were collected from the second visit itself.

Statistical analysis

We used linear regression analysis to estimate cross-sectionally the effect of 1 SD increase in dietary lutein intake (continuous) on the change in FEV₁ (ml), FVC (ml) and FEV₁/FVC%. We also tested the relationship for non-linearity using natural splines (online Supplementary Fig. S1)⁽²⁵⁾. There was no evidence for a non-linear relationship, but as no recommended daily intake of lutein exists, we decided to categorise dietary lutein intake into four quartiles. As there is no European reference data for lutein intake available, the second quartile (1.9–3.2 mg) was chosen as a reference group, as this quartile was in agreement with the average daily intake of lutein for males (2.0–2.3 mg) and females (1.7–2.0 mg) in the USA⁽²⁶⁾.

Confounders were selected on the basis of published literature and a 10% change in the effect estimate of the association between dietary lutein intake and indices of lung function, as described by Mickey & Greenland⁽²⁷⁾. Lutein and other dietary covariates were adjusted for total energy intake, using the residual method⁽²⁸⁾. Thereafter, analyses were performed with adjustment for social-demographic factors (age, sex, height, cohort, ethnicity and education) in the analyses labelled as model 1. Model 2 was additionally adjusted for lifestyle factors: weight, total daily energy intake, total fat intake, N3:N6, fibre intake, alcohol intake, smoking status and physical activity. To adjust for other carotenoids, model 3 included additional adjustment for intakes of β -carotene, β -cryptoxanthin, lycopene and zeaxanthin. α -Carotene could not be included in this model because of multicollinearity (the correlation between α -carotene and β -carotene was 0.96).

We tested for significant interactions ($P < 0.10$) between lutein and sex, age, BMI (BMI = weight/height²), smoking status, previous diagnosis of lung cancer, asthma and COPD. Subgroup analyses were conducted for smoking and BMI, as a significant effect of BMI on lung volume has been demonstrated⁽²⁹⁾ in addition to an effect modification of smoking on lung function^(30,31). Stratified analysis was conducted by smoking status and BMI strata according to the World Health Organization⁽³²⁾. In addition, the main analyses were repeated with the exclusion of participants with diabetes and/or CVD. Seven confounders contained missing values. In general, missing values were low. The percentages of missing values ranged from 0.02 (height and weight) to 3.4% (ethnicity). To account for potential attrition bias, multiple imputation was used to create ten different possible copies of the original data set, in which the missing values were substituted by imputed values (online Supplementary Table S1). These imputed values were calculated from their predictive distribution based on the observed data⁽³³⁾. Combined results of the created data sets (n 10) were then pooled in a separate pooled data set to account for the uncertainty about the missing values. An outline of the procedure is described in the online Supplementary Table S2.

In addition, the main results are presented as effect estimates and 95% CI for the indices of lung function, and a P value < 0.05 was considered statistically significant. IBM SPSS Statistics for Windows (release 21.0.0.1) was used to perform the analyses.

Results

Table 1 details the study population characteristics, subdivided by cohort. The average age per cohort ranged from 56 to 79 years; women were slightly more represented than men, and the population was almost exclusively Caucasian. The median

Table 1. Characteristics of participants in the Rotterdam Study (*n* 4402)
(Numbers and percentages; mean values and standard deviations; medians and interquartile ranges (IQR))*

	RS-I-visit 5 (<i>n</i> 1133)		RS-II-visit 3 (<i>n</i> 1320)		RS-III-visit 2 (<i>n</i> 1949)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Age (years)						
Mean	79		72		56	
SD	4		5		6	
Female	638	56.3	731	55.4	1130	58.0
Height (cm)						
Mean	166.1		168.3		171.2	
SD	9.1		9.1		9.2	
Weight (kg)						
Mean	75.9		78.0		80.5	
SD	13.4		13.6		15.4	
Caucasian ethnicity	1107	97.7	1265	95.8	1850	94.9
FEV ₁ (litre)						
Mean	2.22		2.48		2.92	
SD	0.65		0.70		0.77	
FEV ₁ (%)						
Mean	103.5		101.8		103.6	
SD	22.9		20.7		17.7	
FVC (litres)						
Mean	2.96		3.26		3.82	
SD	0.82		0.88		0.99	
FEV ₁ /FVC						
Median	76.4		77.1		77.5	
IQR	71.3, 79.9		72.5, 81.0		73.0, 81.3	
Dietary intake						
Lutein intake (mg/d)						
Median	2.09		2.50		3.18	
IQR	1.20, 3.57		1.41, 4.12		1.87, 5.09	
Total energy intake (kJ/d)						
Median	8096		8234		9301	
IQR	6477, 9979		6573, 9920		7724, 11343	
Total energy intake (kcal/d)						
Median	1935		1968		2223	
IQR	1548, 2385		1571, 2371		1846, 2711	
α -Carotene intake (mg/d)						
Median	0.57		0.61		0.82	
IQR	0.23, 1.06		0.25, 1.28		0.36, 1.62	
β -Carotene intake (mg/d)						
Median	3.10		3.46		4.43	
IQR	1.66, 5.19		1.86, 6.15		2.55, 7.38	
β -Cryptoxanthin intake (mg/d)						
Median	0.30		0.28		0.27	
IQR	0.11, 0.68		0.10, 0.56		0.11, 0.50	
Lycopene intake (mg/d)						
Median	0.95		1.25		1.73	
IQR	0.43, 1.89		0.59, 2.38		0.90, 2.92	
Zeaxanthin intake (mg/d)						
Median	0.13		0.13		0.14	
IQR	0.09, 0.18		0.09, 0.18		0.01, 0.18	
Total fat intake (g/d)						
Median	65.4		68.1		77.9	
IQR	50.5, 86.4		51.4, 86.4		60.2, 100.0	
N3:N6 (g/d)						
Median	6.8		6.8		7.1	
IQR	5.9, 7.7		6.0, 7.6		6.3, 7.9	
Dietary fibre intake (g/d)						
Median	24.1		24.3		28.0	
IQR	18.1, 31.5		19.0, 31.1		21.8, 35.8	
Physical activity (MET-h/week)						
Median	30.0		42.9		46.0	
IQR	11.9, 66.9		17.7, 82.3		19.4, 82.1	
Smoking status						
Never	379	33.3	441	33.4	691	35.5
Former	667	59.0	749	56.7	1000	51.3
Current	87	7.7	130	9.9	258	13.2
Education level						
Lower education	575	50.8	647	49.0	817	42.0
Higher education	558	49.2	673	51.0	1132	58.0

Table 1. Continued

	RS-I-visit 5 (n 1133)		RS-II-visit 3 (n 1320)		RS-III-visit 2 (n 1949)	
	n	%	n	%	n	%
Type 2 diabetes mellitus	137	12.1	52	3.9	98	5.0
CVD†	67	0.1	67	5.9	63	3.2
Asthma	61	5.4	75	5.7	102	5.2
COPD	224	19.8	211	16.0	266	13.6
Lung cancer	17	1.5	11	0.8	1	0.1

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; N3:N6, n-3:n-6 fatty acids ratio; MET h/week, metabolic equivalent of task-h per week; COPD, chronic obstructive pulmonary disease.

* Based on imputed data.

† Treatment for narrowed blood vessels, myocardial infarction, stroke, cerebral haemorrhage and cerebrovascular accident.

Table 2. Spearman's correlations of dietary carotenoids (n 4402)

	Lutein	α-Carotene	β-Carotene	β-Cryptoxanthin	Lycopene	Zeaxanthin
Lutein	X	0.55**	0.76**	0.18**	0.19**	0.44**
α-Carotene		X	0.96**	0.17**	0.19**	0.34**
β-Carotene			X	0.19**	0.23**	0.41**
β-Cryptoxanthin				X	0.13**	0.74**
Lycopene					X	0.18**

** $P \leq 0.001$, a P value < 0.05 is considered to be statistical significant.

daily lutein intake was 2.09 mg/d in RS-I-visit 5, 2.50 mg/d in RS-II-visit 3 and 3.12 mg/d in RS-III-visit 1. The median energy intake was 8101 kJ/d (1935 kcal/d) in RS-I-visit 5, 8240 kJ/d (1968 kcal/d) in RS-II-visit 3 and 9307 kJ/d (2223 kcal/d) in RS-III-visit 1. The prevalence of chronic diseases differed among the three cohorts, where 44, 32 and 27% of the participants had diabetes, CVD, COPD, asthma or lung cancer in cohort RS-I-visit 5, RS-II-visit 3 and RS-III-visit 2, respectively. Table 2 shows the Spearman's correlations between the carotenoids. Correlation of lutein with other carotenoids ranged from 0.19 (β-cryptoxanthin) to 0.76 (β-carotene).

Lutein intake and lung function

In comparison with the second quartile, the first and lowest quartile of lutein intake was significantly associated with both a lower FEV₁ and a lower FVC in the first model adjusted for socio-demographic factors (-53.07 (95% CI -94.14, -12.01) ml, -49.34 (95% CI -95.42, -3.25) ml, respectively) (Table 3). After additional adjustment for lifestyle factors (model 2), the associations were attenuated, and thus they were no longer significant. No significant associations were observed between the third and the fourth quartiles of lutein intake and FEV₁, FVC and FEV₁/FVC%, or for the linear associations between lutein and FEV₁, FVC and FEV₁/FVC%. Additional adjustment for carotenoids (model 3) did not have an effect on these results.

Sensitivity analysis

We did not find a significant interaction between lutein and sex, age, lung cancer, asthma or COPD (P value all ≥ 0.133). Although we did not observe a significant interaction for smoking with FEV₁, FVC or FEV₁/FVC% ($P_{\text{interaction}} \geq 0.133$), stratified analyses revealed that lutein was significantly associated with lower FEV₁ and FEV₁/FVC% in smokers after adjusting

for socio-demographic factors and lifestyle factors (-60.08 (95% CI -115.84, -4.31) ml, -1.64 (95% CI -2.63, -0.65)% per SD increase in lutein, respectively) (Tables 4 and 6). After adjustment for other carotenoids, some of the results were attenuated; however, the association remained significant for lutein and FEV₁/FVC (-1.69 (95% CI -2.93, -0.45)% per SD increase of lutein). As compared with the second quartile, the fourth and highest quartile of lutein intake was significantly associated with a lower FEV₁ and a lower FVC in smokers (Tables 4 and 5). Moreover, the association remained significant after full adjustment (model 3: -157.55 ml fourth quartile *v.* second quartile (95% CI -311.32, -3.79)) for FEV₁ and attenuated for FVC. Before adjustment for lifestyle factors, lutein was not significantly associated with FEV₁/FVC%, but the association became significant after adjustment (model 2: -2.79% fourth quartile *v.* second quartile (95% CI -5.15, -0.41)) (Table 6). After full adjustment, this association became borderline significant.

In addition, we observed similar results after stratification by BMI and exclusion of participants with diabetes and/or CVD (data not shown).

Discussion

In a population-based prospective cohort study, we investigated the cross-sectional association between dietary lutein intake and lung function as measured by FEV₁. We observed a weak association between lutein and FEV₁ and FVC in adults aged 45 years and older, after adjustment for socio-demographic factors. However, this was mainly explained by other nutrients and lifestyle factors. Strikingly, we found that lutein intake was associated with lower lung function as measured by FEV₁/FVC% in smokers. To date, there are no dietary recommendations regarding lutein intake; therefore, it is important to clarify to what extent lutein may be related to health outcomes.

Table 3. Association between dietary lutein intake and forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC) and FEV₁/FVC% (*n* 4402) – pooled analysis (β -Coefficients and 95% confidence intervals)

	Model 1†		Model 2‡		Model 3§	
	β	95% CI	β	95% CI	β	95% CI
FEV ₁ (ml)						
Lutein intake (per SD)	0.84	-13.85, 15.53	-5.92	-23.17, 11.33	-12.17	-34.21, 9.87
<i>P</i>		0.911		0.501		0.279
Lutein intake in quartiles						
1st quartile (<i>n</i> 1101)	-53.07	-94.14, -12.01*	-25.60	-66.11, 14.91	-24.72	-65.51, 16.08
2nd quartile (<i>n</i> 1100)		Ref.		Ref.		Ref.
3rd quartile (<i>n</i> 1101)	5.01	-35.95, 45.96	10.31	-29.94, 50.56	9.38	-31.17, 49.94
4th quartile (<i>n</i> 1100)	-25.72	-66.90, 15.45	-20.68	-64.18, 22.82	-24.18	-71.65, 23.30
FVC (ml)						
Lutein intake (per SD)	1.71	-14.78, 18.19	5.02	-14.41, 24.45	-8.11	-32.92, 16.70
<i>P</i>		0.839		0.613		0.522
Lutein intake in quartiles						
1st quartile (<i>n</i> 1101)	-49.34	-95.42, -3.25*	-26.38	-72.01, 19.24	-22.10	-68.03, 23.83
2nd quartile (<i>n</i> 1100)		Ref.		Ref.		Ref.
3rd quartile (<i>n</i> 1101)	4.78	-41.18, 50.75	13.68	-31.65, 59.00	9.39	-36.27, 55.05
4th quartile (<i>n</i> 1100)	-27.48	-73.69, 18.72	-10.57	-59.55, 38.41	-28.52	-81.95, 24.91
FEV ₁ /FVC%						
Lutein intake (per SD)	0.03	-0.19, 0.25	-0.25	-0.50, 0.01	-0.18	-0.51, 0.15
<i>P</i>		0.788		0.059		0.287
Lutein intake in quartiles						
1st quartile (<i>n</i> 1101)	-0.45	-1.06, 0.17	-0.12	-0.72, 0.49	-0.17	-0.78, 0.43
2nd quartile (<i>n</i> 1100)		Ref.		Ref.		Ref.
3rd quartile (<i>n</i> 1101)	0.06	-0.55, 0.67	-0.02	-0.58, 0.61	0.07	-0.53, 0.68
4th quartile (<i>n</i> 1100)	-0.02	-0.64, 0.60	-0.24	-0.88, 0.41	0.02	-0.69, 0.72

Ref., reference values.

* *P* < 0.05.

† Model 1 is adjusted for age, sex, height, ethnicity, cohort and education.

‡ Model 2 is adjusted as for model 1, plus weight, total daily energy intake, total fat intake, *n*-3:*n*-6 fatty acids ratio, fibre intake, alcohol intake, smoking status and physical activity measured in metabolic equivalent of task-h per week.

§ Model 3 was additionally adjusted for daily intakes of β -carotene, β -cryptoxanthin, lycopene and zeaxanthin.

Findings in other studies

Our finding that lutein is not associated with FEV₁ and FVC is in line with a few other observational studies on FEV₁^(9,10,15) and one study on FVC⁽¹⁵⁾. A population-based prospective study found a significant association between lutein/zeaxanthin and FEV₁, FVC and FEV₁/FVC%; however, they investigated the association in adults with chronic airflow limitation⁽¹⁴⁾. A previous longitudinal study found a borderline significant association between lutein/zeaxanthin and a slower decline in FEV₁, and a significant association between lutein/zeaxanthin and FVC. However, this study was conducted in young adults with a mean age of 25 years⁽¹⁶⁾. A borderline significant association between lutein/zeaxanthin blood levels and FVC has been described⁽⁹⁾, and these authors have also demonstrated a significant association between lutein/zeaxanthin intake and FVC⁽¹⁰⁾. In addition, all studies that investigated lutein/zeaxanthin also investigated the association between other carotenoids and/or antioxidant vitamins and lung function. Schunemann *et al.*^(9,10) reported that lutein/zeaxanthin dietary intake and blood levels were strongly related to lung function, although not significant for FEV₁, as compared with other nutrients with antioxidant capacities such as

beta-carotene. This was also reported by Ochs-Balcom *et al.*⁽¹⁴⁾, who demonstrated that lutein/zeaxanthin, measured by dietary intake and blood levels, was strongly related to FEV₁, FVC and FEV₁/FVC%. Dietary lutein intake has been examined by two out of five studies that investigated lung function in adults^(9,10,14-16). A study found a significant positive association between lutein/zeaxanthin and all indices of lung function⁽¹⁴⁾. Moreover, a second study found a significantly positive association between lutein/zeaxanthin and FVC only⁽¹⁰⁾.

Interestingly, subgroup analysis by smoking status in our study revealed that lutein intake was associated with a lower lung function as measured by FEV₁/FVC%. Although this has not been reported before, other studies have documented the potential harmful effects of other carotenoids on lung outcomes. For example, intervention studies suggest that carotenoid supplementation increased lung cancer and mortality in heavy smokers⁽³⁴⁻³⁸⁾. Indeed, the association between lutein intake and FEV₁ in smokers was explained by adjustment for other carotenoids, suggesting that the inverse association between lutein intake and indices of lung function may be explained to a certain extent by other carotenoids.

Table 4. Association between dietary lutein intake and forced expiratory volume in 1 s (FEV₁), stratified by smoking status – pooled analysis (β-Coefficients and 95 % confidence intervals)

	Model 1†		Model 2‡		Model 3§	
	β	95 % CI	β	95 % CI	β	95 % CI
Never/former smokers (n 3927), FEV ₁ (ml)						
Lutein intake (per SD)	2.06	-12.94, 17.06	0.03	-15.92, 15.97	-11.69	-34.68, 11.31
P		0.787		0.998		0.319
Lutein intake in quartiles						
1st quartile (n 959)	-37.23	-79.69, 5.23	-28.09	-70.49, 14.31	-25.93	-68.93, 17.07
2nd quartile (n 998)		Ref.		Ref.		Ref.
3th quartile (n 989)	8.81	-33.20, 50.82	11.20	-30.71, -53.11	9.06	-33.38, 51.50
4th quartile (n 981)	-5.34	-47.65, 36.98	-6.06	-49.42, 37.30	-14.25	-63.94, 35.45
Smokers (n 475), FEV ₁ (ml)						
Lutein intake (per SD)	-46.29	-97.05, 4.47	-60.08	-115.84, -4.31*	-52.38	-124.49, 19.72
P		0.074		0.035		0.154
Lutein intake in quartiles						
1 st quartile (n 142)	-61.79	-190.47, 66.89	-41.19	-171.29, 88.92	-41.87	-173.31, 88.57
2nd quartile (n 102)		Ref.		Ref.		Ref.
3th quartile (n 112)	-20.75	-155.10, 113.60	-24.42	-159.77, 110.93	-20.38	-158.22, 117.46
4th quartile (n 119)	-166.85	-300.48, -33.21*	-178.52	-317.17, -39.88*	-157.55	-311.32, -3.79*

Ref., reference values.

* P < 0.05 (P_{interaction} = 0.13).

† Model 1 is adjusted for age, sex, height, ethnicity, cohort and education.

‡ Model 2 is adjusted as for model 1, plus weight, total daily energy intake, total fat intake, n-3:n-6 fatty acids ratio, fibre intake, alcohol intake and physical activity measured in metabolic equivalent of task-h per week.

§ Model 3 was additionally adjusted for daily intakes of β-carotene, β-cryptoxanthin, lycopene and zeaxanthin.

Table 5. Association between dietary lutein intake and forced vital capacity (FVC), stratified by smoking status – pooled analysis (β-Coefficients and 95 % confidence intervals)

	Model 1†		Model 2‡		Model 3§	
	β	95 % CI	β	95 % CI	β	95 % CI
Never/former smokers (n 3927), FVC (ml)						
Lutein intake (per SD)	2.80	-14.43, 20.03	6.18	-14.29, 26.64	-11.75	-38.08, 14.58
P		0.750		0.554		0.382
Lutein intake in quartiles						
1st quartile (n 959)	-36.91	-85.68, 11.86	-24.61	-73.12, 23.90	-19.21	-68.07, 29.66
2nd quartile (n 998)		Ref.		Ref.		Ref.
3th quartile (n 989)	3.66	-44.59, 51.90	9.47	-38.41, 57.36	4.17	-44.06, 52.40
4th quartile (n 981)	-10.21	-58.81, 38.39	-0.85	-52.78, 51.09	-23.58	-80.32, 33.16
Smokers (n 475), FVC (ml)						
Lutein intake (per SD)	-28.58	-82.14, 24.98	-24.58	-89.27, 40.11	-1.54	-78.43, 75.36
P		0.296		0.456		0.969
Lutein intake in quartiles						
1st quartile (n 142)	-75.91	-211.54, 59.71	-58.30	-195.07, 78.47	-58.63	-195.96, 78.70
2nd quartile (n 102)		Ref.		Ref.		Ref.
3th quartile (n 112)	17.09	-124.50, 158.68	19.79	-122.60, 162.16	26.57	-117.37, 170.52
4th quartile (n 119)	-154.77	-295.62, -13.92*	-138.51	-288.90, 11.89 [‡]	-108.90	-270.75, 52.95

Ref., reference values.

P_{interaction} = 0.549, * P < 0.05, ‡ P = 0.071.

† Model 1 is adjusted for age, sex, height, ethnicity, cohort and education.

‡ Model 2 is adjusted as for model 1, plus weight, total daily energy intake, total fat intake, n-3:n-6 fatty acids ratio, fibre intake, alcohol intake and physical activity measured in metabolic equivalent of task-h per week.

§ Model 3 was additionally adjusted for daily intakes of β-carotene, β-cryptoxanthin, lycopene and zeaxanthin.

Mechanisms

The belief that relates lutein intake with improved respiratory health is based mainly on counteracting oxidative stress.

Antioxidants are known to act against reactive oxygen species (ROS), which can be divided into exogenous oxidants (e.g. cigarette smoke) and endogenous oxidants (i.e. produced by inflammatory cells)^(39,40). Oxidative stress, an imbalance

Table 6. Association between dietary lutein intake and forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC%), stratified by smoking status – pooled analysis (β -Coefficients and 95% confidence intervals)

	Model 1†		Model 2‡		Model 3§	
	β	95% CI	β	95% CI	β	95% CI
Never/former smokers (<i>n</i> 3927), FEV ₁ /FVC%						
Lutein intake (per SD)	0.04	-0.18, 0.26	-0.14	-0.40, 0.12	-0.08	-0.42, 0.26
<i>P</i>		0.726		0.297		0.646
Lutein intake in quartiles						
1st quartile (<i>n</i> 959)	-0.26	-0.88, 0.36	-26.0	-0.88, 0.37	-0.31	-0.94, 0.32
2nd quartile (<i>n</i> 998)		Ref.		Ref.		Ref.
3th quartile (<i>n</i> 989)	0.24	-0.37, 0.85	0.18	-0.44, 0.76	0.23	-0.39, 0.85
4th quartile (<i>n</i> 981)	0.20	-0.42, 0.82	-0.02	-0.68, 0.65	-0.22	-0.51, 0.95
Smokers (<i>n</i> 475), FEV ₁ /FVC%						
Lutein intake (per SD)	-0.63	-1.51, 0.26	-1.64	-2.63, -0.65	-1.69	-2.93, -0.45
<i>P</i>		0.168		0.002		0.008
Lutein intake in quartiles						
1st quartile (<i>n</i> 142)	-0.22	-2.49, 2.04	0.29	-1.92, 2.51	0.22	-2.01, 2.45
2nd quartile (<i>n</i> 102)		Ref.		Ref.		Ref.
3th quartile (<i>n</i> 112)	-1.39	-3.76, 0.98	-1.84	-4.15, 0.46	-1.76	-4.10, 0.58
4th quartile (<i>n</i> 119)	-1.39	-3.68, 0.90	-2.79	-5.15, -0.41*	-2.57	-3.91, -1.22 [‡]

Ref., reference values.

*P*_{interaction} = 0.033, * *P* < 0.05, † *P* = 0.056.

† Model 1 is adjusted for age, sex, height, ethnicity, cohort and education.

‡ Model 2 is adjusted as for model 1, plus weight, total daily energy intake, total fat intake, *n*-3:*n*-6 fatty acids ratio, fibre intake, alcohol intake and physical activity measured in metabolic equivalent of task-h per week.

§ Model 3 was additionally adjusted for daily intake of β -carotene, β -cryptoxanthin, lycopene and zeaxanthin.

between antioxidant capacity and ROS^(41,42), is suggested to be associated with worsening of lung function. For instance, an association between increased markers of oxidative stress (i.e. malondialdehyde or oxidised LDL and decreased lung function in COPD patients has been found^(43,44). However, our results are not in line with this hypothesis. On the basis of this mechanism, it can be suggested that the function of lutein (as an antioxidant) depends on the level of exposure to smoking (as an oxidant). For that reason, we performed stratified analyses by smoking status, as it has been proposed that a high intake of carotenoids may reduce their protective function against ROS, particularly in smokers and may even enhance smoke-induced oxidative stress⁽⁴⁵⁾. A possible explanation for this lost function is that cigarette smoke modifies the chemical composition of these nutrients, turning antioxidants into pro-oxidants⁽⁴⁶⁾. Hence, further studies on the potentially harmful effects of dietary lutein intake in smokers are required.

Methodological considerations

Several important strengths of our study can be acknowledged. In comparison with previous studies, we have a large population-based sample size, and were able to adjust for a wide range of confounders including lifestyle and dietary factors as well as intakes of other carotenoids, which were found to be very important.

However, some limitations also need to be taken into account. First, our study had an observational cross-sectional design, which prevents final conclusions about the causality of

the observed associations. We found that other dietary and lifestyle factors largely explained the observed association. With this in mind, it may be important to study overall dietary patterns in relation to lung function as this takes the inter-correlation between dietary factors into account⁽⁴⁷⁾. Indeed, several dietary patterns have been found to be associated with lung function⁽⁴⁸⁻⁵⁴⁾. Second, we only had information on dietary intake of lutein and not on blood levels. It may be argued that the blood levels of lutein give a better reflection of lutein status in the human body. For example, when studying blood levels, unmeasured factors such as genetic factors can be better taken into account⁽⁵⁵⁾. In contrast, when high oxidative stress is present, such as in COPD, blood levels of antioxidants may decrease because of an increased demand, which leads to lower blood levels of antioxidants as a consequence, such as lutein⁽⁵⁶⁾. Hence, reverse causality might be present, as it remains unknown whether individuals with, for example, COPD have low blood levels of antioxidants as a consequence of the disease (e.g. physiologically or due to altered dietary intake), or whether low blood levels contribute to the development of the disease. Although our results were not different after excluding participants with chronic diseases, reverse causation might still partly explain the findings. Third, we used a FFQ for dietary assessment of lutein, which is subject to measurement error. To account for potential systematic measurement error, we adjusted lutein intake for total energy intake⁽²⁸⁾. However, non-differential misclassification may still be present, which may have led to bias towards the null⁽⁵⁷⁾. Fourth, selection bias or survival bias may be present, as we selected participants for this study on the basis of available information on their dietary intakes and lung function.

Individuals with lower lung function or at a severe stage of chronic disease might not have visited the research centre, and therefore may have been excluded from the present study. This exclusion could have underestimated our association. However, the socio-demographic characteristics (e.g. age, sex, height, body weight, ethnicity and smoking status) of the included participants in our study did not differ from the total population of the Rotterdam Study⁽⁵⁸⁾.

In conclusion, we investigated the cross-sectional association between dietary lutein intake and lung function in a large, population-based, prospective cohort study. Although we observed some associations between lutein intake and lung function, the majority of these disappeared after adjustment for other nutrients and lifestyle factors. This suggests that a combination of healthy dietary and lifestyle factors might contribute to an improved lung function instead of lutein intake alone. Future studies in the general population should focus on whole diet to identify patterns in foods linked to specific nutrients that are associated with lung function. Interestingly, we observed that higher lutein intake was associated with a lower lung function in smokers. This finding supports previous evidence on the adverse effect of high intakes of antioxidants in smokers. However, to date, there is no dietary recommendation for lutein, which is urgently needed in the clinical setting, as harmful effects might manifest when a high dose is taken by particular risk groups. Future studies should also be aware of the potential inverse association between high lutein intake and specific risk groups such as smokers. To date, the effect of high doses of nutrients that are included in nutritional supplements for the general population or risk groups is poorly studied. A trial by Omenn *et al.*⁽³⁸⁾ investigated the protective effect of high doses of vitamin A and β -carotene on lung cancer, which were discontinued when the incident risk of lung cancer was shown to be higher in the treatment group as compared with the control group. Some trials supported their findings, and some other research groups did not⁽⁵⁹⁾. In addition, some risk groups might benefit from a nutrition supplement and others may not⁽⁵⁹⁾. For example, (pre) pregnant women are advised to take folate supplementation to avoid spina bifida; however, a high dose of folate increased the risk of adenomas in a trial investigating colorectal adenomas⁽⁶⁰⁾. These examples demonstrate that more research is needed to give a public health recommendation on nutritional supplements.

Supplementary material

For supplementary material/s referred to in this article, please visit <https://doi.org/10.1017/S0007114517000319>

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