British Journal of Nutrition (2023), 130, 1932–1941 doi:10.1017/S0007114523000806

Inverse correlations between serum carotenoids and respiratory morbidity and mortality: the Third National Health and Nutrition Examination Survey

Ruiming Yang[1]†, Ziteng Cao[1]†, Xin Liu[1]†, Mengjie Xiao[1], Mengyao Li[1], Yunyan Chen[1], Luyao Chen[1], Changhao Sun[1], Xia Chu[1], Qiang Ren[2] and Wei Wei[1,3]*

[1]*Department of Nutrition and Food Hygiene, The National Key Discipline, School of Public Health, Harbin Medical University, Harbin, People's Republic of China*

[2]*Department of Respiratory Medicine, The First Affiliated Hospital of Harbin Medical University, Harbin, People's Republic of China*

[3]*Department of Pharmacology, College of Pharmacy Key Laboratory of Cardiovascular Research, Ministry of Education, Harbin Medical University, Harbin, People's Republic of China*

(Submitted 26 October 2022 – Final revision received 3 March 2023 – Accepted 14 March 2023 – First published online 11 April 2023)

Abstract

The objective was to evaluate the association between serum carotenoid levels and respiratory morbidity and mortality in a nationally representative sample of US adults. We assessed the association of serum carotenoid levels with respiratory morbidity and mortality using logistic regression and proportional hazards regression models. Meanwhile, a series of confounders were controlled in regression models and restricted cubic spline, which included age, sex, race, marriage, education, income, drinking, smoking, regular exercise, BMI, daily energy intake, vitamin E, vitamin C, fruit intake, vegetable intake, diabetes, hypertension, asthma, emphysema and chronic bronchitis. Compared with participants in the lowest tertiles, participants in the highest tertiles of serum total carotenoids, *β*-cryptoxanthin and lutein/zeaxanthin levels had a significantly lower prevalence of emphysema ($OR_{total\ carotenoids} = 0{\cdot}61$, 95% CI: 0·41–0·89, $OR_{\beta\text{-cryptoxanthin}} = 0{\cdot}67$, 95% CI: 0·49–0·92), chronic bronchitis ($OR_{\beta\text{-cryptoxanthin}} = 0{\cdot}66$, 95% CI: 0·50–0·87) and asthma (Q2: $OR_{lutein/zeaxanthin} = 0{\cdot}78$, 95% CI: 0·62–0·97); participants in the highest tertiles of total carotenoids, *α*-carotene, lutein/zeaxanthin and lycopene had a lower risk of respiratory mortality (hazard ratio $(HR)_{total\ carotenoids} = 0{\cdot}62$, 95% CI: 0·42–0·90, $HR_{\alpha\text{-carotene}} = 0{\cdot}54$, 95% CI: 0·36–0·82, $HR_{lutein/zeaxanthin} = 0{\cdot}48$, 95% CI: 0·33–0·71, $HR_{lycopene} = 0{\cdot}66$, 95% CI: 0·45–0·96) than those in the lowest tertiles. Higher serum total carotenoids and *β*-cryptoxanthin levels is associated with decreased prevalence of emphysema and chronic bronchitis, and higher serum total carotenoids, *α*-carotene, lutein/zeaxanthin and lycopene levels had a lower mortality of respiratory disease.

Key words: **Antioxidant: Serum carotenoids: Respiratory disease: Morbidity: Mortality**

Oxidative stress refers to a state of imbalance between oxidative and antioxidant effects in the body[1,2], which involves an overproduction of reactive oxygen species or dysfunction of the antioxidant defence system, resulting in macromolecular damage and disruption of redox signalling and cellular control[3], which in turn leads to inflammatory infiltration of neutrophils and production of a large number of oxidative intermediates[1–4]. Oxidative stress plays an important role in many clinical conditions, and antioxidant therapy can have a positive effect on these diseases[5]. Carotenoids are a class of natural pigments that are widely distributed in yellow, orange and red fruits and vegetables. *α*-carotene, *β*-carotene, *β*-cryptoxanthin, lutein/zeaxanthin and lycopene are all natural antioxidants[6], and they play an active antioxidant role in these diseases[6–10]. In addition, carotenoids are associated with the expression of superoxide dismutase, catalase and glutathione peroxidase and activate the body's own antioxidant defence system by interacting with transcription factors[11]. Carotenoids also have powerful anti-cancer properties and have positive effects on the human body by participating in physiological activities such as intercellular signalling conduction, immune system regulation and inhibiting cell proliferation[12,13]. Moreover, lungs have abundant blood flowing through and are constantly exposed to high levels of oxygen, and they are prone to inhaling harmful substances, which makes

Abbreviations: HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; RCS, restricted cubic spline.

* **Corresponding author:** Wei Wei, email 102594@hrbmu.edu.cn

† These authors contributed equally to this work

them highly susceptible to oxidative stress and developing lung diseases[14,15]. The AlphaTocopherol, Beta-Carotene Cancer Prevention (ATBC) and Beta-Carotene and Retinol Efficacy Trial (CARET) studies showed an increased risk of lung cancer rate when smokers or asbestos workers were supplemented with β-carotene[16]. Oxidative stress induces airway hyperresponsiveness and neutrophilic inflammation, leading to cell death and chronic bronchial inflammation and emphysema[17]. It can also further cause cellular and molecular damage to DNA, proteins and lipids, making asthma worse[18]. Currently, a large number of studies have shown that carotenoids have positive effects on the human body[6,11,19–21], but there are some studies with inconsistent results[16,22,23]. Despite the increasing interest in studying the role of serum carotenoids in respiratory health, population-based studies examining the relationship between serum carotenoid levels and respiratory mortality are limited[24,25]. To further explore the connection, this study used data from the Third National Health and Nutrition Examination Survey (NHANES III), including data from over 18 000 participants, to investigate whether levels of serum α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin and lycopene are associated with respiratory morbidity and mortality among American adults.

Method

Study population

The data used in this study came from the NHANES III, a total of 39 695 individuals aged 2 months and older. The study was conducted in two phases from 1988 to 1994. Phase I (1988–1991) and Phase II (1991–1994) were nationally representative samples, respectively. During the 6-year sample survey, 33 994 samplers were interviewed and 30 818 were inspected, with an overall inspection response rate of 78 %. We limited the study population to subjects ≥ 20 years of age at the time of the examination. Of the 18 805 subjects, 15 534 (82·61 %) had serum carotenoid levels available. Among them, we excluded 7650 patients who were missing data on smoking. The cohort analysis presented in this study was thus based on 7884 NHANES III participants.

Serum carotenoid measurements

Serum carotenoid levels are useful biomarkers of the total dietary intake of vegetables and fruits. Serum concentrations of α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin and lycopene are measured by using HPLC. The median inter-assay coefficients of variation were 9·4 % forα-carotene, 7·0 % for β-carotene, 8·7 % for β-cryptoxanthin, 11·0% for lutein/zeaxanthin and 7·7% for lycopene[26].

Main outcomes

The main outcome variables were asthma, emphysema, chronic bronchitis and mortality of disease specific and all cause. The participants were considered to have asthma, emphysema and chronic bronchitis if they separately answered yes to the questions 'Has a doctor or other health professional ever told you that you had asthma/emphysema/chronic bronchitis?'. These questions were included in the part of the medical conditions in the NHANES, and the participants' conditions were based on the medical history record of their clinicians or medical departments.

The mortality of all-cause and respiratory diseases was determined by the National Death Index, which is widely used to identify deaths. Causes of death were determined by using the International Classification of Diseases Tenth Revision (ICD-10) codes. Deaths that occurred before 1999 were originally coded by using a previous version of the classification code (i.e. ICD-9) and now use the ICD-10 code recorded by the National Center for Health Statistics. Chronic lower respiratory disease mortality was defined as death from asthma (J45–J46), emphysema (J43), bronchitis (chronic or other; J40–J42) or other chronic lower respiratory disease (J44 and J47).

Covariates

The participants were interviewed in NHANES III to obtain information on age (years), sex (men or women), race (White, Black, Hispanic or other), annual household income and education (less than high school, high school graduate, or college or more). Drinking condition was assessed by using the question, 'Had you had drinks for at least 12 times in the last 12 months?'. The response was yes or no. The exercise was assessed by using the question, 'Have you participated in exercise in the past month?' The response was yes or no. Smoking-related variable (Do you smoke cigarettes now?). The response was yes, no or blank but applicable. The BMI was calculated by dividing the weight in kilograms by the height in metres squared. The BMI was categorised into three groups (< 18·5, 18·5–24·9 and ≤ 25·1 kg/m^2). Energetic intake (kcal/d) was measured by using a single 24-h diet recall. Marriage (married – spouse in the household, married – spouse not in the household, living as married in the household, widowed in the household, divorced in the household, separated in the household, never married, blank but applicable, Don't know). Diabetic condition, 'Ever been told you have sugar/diabetes?'. High blood pressure condition, 'Doctor ever told you had hypertension/HBP?'. Asthma condition, 'Doctor ever told you had asthma?'. Emphysema condition, 'Doctor ever told you had emphysema?'. Chronic bronchitis condition, 'Doctor ever told you had chronic bronchitis?'.

Statistical analysis

The baseline characteristics in terms of demographics, lifestyle and biochemical indices were presented as mean (standard deviation) and numbers (percentage). The serum levels of α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin and lycopene were categorised into tertiles. General linear models and a χ^2 test were used to compare the differences for baseline characteristics by tertiles of α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin and lycopene, respectively. Logistic regression models were performed to evaluate the OR and 95 % CI for the association of α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin and lycopene with the prevalence of asthma, emphysema and chronic bronchitis. Cox proportional hazards models were performed to evaluate the association of α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin and lycopene with mortality of all-cause and chronic lower

respiratory diseases. In these Cox models, follow-up began at time 0 at study entry and continued until the event of interest (death from chronic lower respiratory disease) or censored event (death from other causes or death on 31 December 2015), the event that occurred first prevailed. Due to the NHANES data being cross-sectional, covariates were measured when participants were first enrolled and therefore did not change in these models. Restricted cubic spline (RCS) was used to visualise the dose–response association of the significant association found in the logistic regression or Cox proportional hazards models by setting 4 knots at the 5th, 25th, 75th and 95th percentiles.

We also controlled a series of confounders, including age, sex, race, marriage, education level, regular exercise, drinking, smoking, BMI, annual family income, energetic intake, vitamin E intake, vitamin C intake, fruit intake, vegetable intake, diabetes, hypertension, asthma, emphysema and chronic bronchitis in all models. All statistical analyses were conducted by R 4.2.2, and *P*-values < 0·05 were considered statistically significant.

Sensitive analysis

Three sensitivity analyses were performed. The first analysis excluded the participants whose follow-up duration was less than 2 years, to examine whether the severe illness would influence the results. The second analysis excluded the participants who had the extreme values in *α*-carotene, *β*-carotene, *β*-cryptoxanthin, lutein/zeaxanthin and lycopene to examine the stability of the results. The third analysis evaluated whether age (age > 45 years old), BMI (< 25 and ≥ 25 kg/m^2) and smoking status had a modification effect on these relationships.

Results

Baseline characteristics

Table 1 shows the differences in the baseline characteristics in terms of demographic, anthropometric, lifestyle and biochemical indicators across tertiles of baseline *α*-carotene, *β*-carotene, *β*-cryptoxanthin, lutein/zeaxanthin and lycopene. Participants with higher *α*-carotene were more likely to be non-Hispanic white with higher levels of education, income and fruit intake, and a lower percentage of smoking rate, drinking rate and low levels of BMI (all the $P < 0{\cdot}05$). Meanwhile, participants with higher *β*-carotene were older and more likely to be non-Hispanic white and at higher levels of education and income, as well as a higher prevalence of hypertension with a lower percentage of smoking rate, drinking rate and low levels of BMI (all the $P < 0{\cdot}05$). Reversely, participants with higher *β*-cryptoxanthin were younger and more likely to be men with high levels of BMI and fruit intake, and low levels of education and income as well as a lower prevalence of chronic bronchitis (all the $P < 0{\cdot}05$). Meanwhile, participants with higher lutein/zeaxanthin were men and high levels of BMI, smoking rate and drinking rate as well as a higher prevalence of hypertension with a lower percentage of smoking rate and drinking rate (all the $P < 0{\cdot}05$). Similarly, participants with higher lycopene were younger and more likely to be men with higher levels of BMI, income, smoking rate and drinking rate, and a lower prevalence of hypertension, fruit intake, vegetable intake and emphysema (all the $P < 0{\cdot}05$). Table 2 shows the concentration range of carotenoids in serum.

Association between serum total carotenoids and respiratory morbidity, all-cause and disease-specific mortalities

Table 3 shows that emphysema morbidity was significantly associated with serum total carotenoid levels (OR = 0·61, 95 % CI 0·41, 89). The hazard ratio (HR) and 95 % CI for the association of tertiles of serum *α*-carotene with mortality of all cause and respiratory disease are presented in Table 4. Compared with the lowest tertile of serum*α*-carotene, the participants in the highest tertile had lower mortality of all-cause (HR = 0·62, 95 % CI 0·42, 0·90) and respiratory diseases (HR = 0·74, 95 % CI 0·67, 0·81) in Table 4. Due to the inverse association of tertiles of total carotenoids with the prevalence of all-cause and respiratory diseases, the RCS was used to flexibly model for visualising the above association, which is presented in Fig. 1. Meanwhile, sensitivity analyses were performed, and none of them affected the above results.

Association between serum α-carotene and respiratory morbidity, all-cause and disease-specific mortalities

Respiratory morbidity was not associated with serum*α*-carotene levels (Table 3). Compared with the lowest tertile of serum*α*-carotene, the participants in the highest tertile had lower mortality of all-cause (HR = 0·76, 95 % CI 0·69, 0·84) and respiratory diseases (HR = 0·54, 95 % CI 0·36, 0·82) in Table 4. RCS curve results are shown in Fig. 1. Similarly, sensitivity analyses were performed, and none of them affected the above results.

Association between serum β-carotene and respiratory morbidity, all-cause and disease-specific mortalities

Respiratory morbidity was not associated with serum *β*-carotene levels (Table 3). Compared with the lowest tertile of serum *β*-carotene, the participants in the highest tertile had lower mortality of all cause (HR = 0·82, 95 % CI 0·74, 0·91). And no significant association between serum carotenoids and respiratory disease mortality was observed (HR = 0·71, 95 % CI 0·48, 1·05) in Table 4. RCS curve results are shown in Fig. 1. Similarly, sensitivity analyses were performed, and none of them affected the above results.

Association between serum β-cryptoxanthin and respiratory morbidity, all-cause and disease-specific mortalities

Table 3 shows that emphysema and chronic bronchitis morbidity were significantly associated with serum *β*-cryptoxanthin levels ($OR_{emphysema}$ = 0·67, 95 % CI 0·49, 92; $OR_{chronic\ bronchitis}$ = 0·66, 95 % CI 0·50, 0·87). Compared with the lowest tertile of serum *β*-cryptoxanthin, the participants in the highest tertile had lower mortality of all-cause and respiratory diseases (HR = 0·83, 95 % CI 0·75, 0·91) in Table 4. RCS curve results are shown in

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Table 1. Characteristics of study participants according to tertiles of total carotenoids, α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin and lycopene (Numbers and percentages; mean values and standard deviations)

Characteristics	α-carotene (μg/l)							β-carotene (μg/l)							β-cryptoxanthin (μg/l)						
	T1		T2		T3		*P*	T1		T2		T3		*P*	T1		T2		T3		*P*
	n	%	*n*	%	*n*	%		*n*	%	*n*	%	*n*	%		*n*	%	*n*	%	*n*	%	
Age (years)																					
Mean	45·4		51·27		54·9		< 0·001	44·2		49·4		56·9		< 0·001	50·4		48·4		50·9		< 0·001
SD	17·9		18·4		17·6			17·4		18·2		17·3			18·6		18·1		18·2		
Men	1937	62·2	1458	60·2	1302	55·5	< 0·001	1807	66·2	1551	58·6	1339	53·5	< 0·001	2062	60·1	1246	58·7	1389	59·6	0·555
Non-Hispanic white	1236	39·7	1151	47·5	1283	54·7	< 0·001	1073	39·3	1246	47·1	1351	53·9	< 0·001	1865	54·4	996	46·9	809	34·7	< 0·001
BMI (kg/m^2)																					
Mean	27·2		27·0		26·3		< 0·001	27·4		27·0		26·2		< 0·001	27·0		26·9		26·7		< 0·001
SD	6·1		5·4		4·7			6·0		5·4		4·9			6·0		5·3		4·9		
Regular exercise	2095	67·2	1642	67·8	1746	74·4	< 0·001	1875	68·7	1825	68·9	1783	71·2	0·097	2318	67·6	1539	72·5	1626	69·8	0·001
College graduate or above	554	17·8	620	25·6	834	35·5	< 0·001	542	19·8	668	25·2	798	31·9	< 0·001	766	22·3	575	27·1	667	28·6	< 0·001
Annual household income, > 50 000	250	8·0	315	13·0	428	18·2	< 0·001	253	9·3	335	12·7	405	16·2	< 0·001	378	11·0	307	4·5	308	13·2	< 0·001
Energy content (kcal/d)																					
Mean	2288·9		2117·5		2055·4		< 0·001	2350·3		2144·4		1988·7		< 0·001	2150		2219·1		2142·7		< 0·001
SD	1211·7		1049·9		925·5			1206·7		1072·8		922·6			1105·3		1109·1		1041·2		
Current smoking	2058	66·0	1130	46·7	725	30·9	< 0·001	1743	63·8	1338	50·5	832	33·2	< 0·001	2027	59·1	1027	48·4	859	36·9	< 0·001
Current drinking	1757	56·4	1254	51·8	1146	48·8	< 0·001	1719	62·9	1339	50·6	1099	43·9	< 0·001	1811	52·8	1162	54·7	1184	50·8	0·018
Current married (spouse in household)	1583	50·8	1487	61·4	1533	65·3	< 0·001	1461	53·5	1573	59·4	1569	62·6	< 0·001	1899	55·4	1266	59·6	1438	61·7	< 0·001
Current diabetes	230	7·4	236	9·7	230	9·8	< 0·001	227	8·3	223	8·4	246	9·8	0·15	265	7·7	177	8·3	254	10·9	< 0·001
Current hypertension	840	27·0	709	29·3	698	29·8	0·155	711	26·0	727	27·5	809	32·3	< 0·001	1011	29·5	589	27·7	647	27·8	0·609
Current asthma	264	8·5	183	7·6	162	6·9	0·178	203	7·4	199	7·5	207	8·3	0·495	284	8·3	167	7·9	158	6·8	0·215
Current emphysema	100	3·2	100	4·1	89	3·8	0·315	79	2·9	93	3·5	117	4·7	0·011	158	4·6	61	2·9	70	3·0	0·003
Current chronic bronchitis	226	7·3	184	7·6	159	6·8	0·603	185	6·8	184	6·9	200	8·0	0·271	294	8·6	157	7·4	118	5·1	< 0·001
	Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD	
Vitamin C (μg/l)	0·46	0·42	0·67	0·42	0·86	0·45	< 0·001	0·47	0·40	0·63	0·43	0·84	0·47	< 0·001	0·50	0·45	0·67	0·42	0·83	0·42	< 0·001
Vitamin E (μg/l)	989	383	1160	427	1355	596	< 0·001	992	373	1128	437	1347	568	< 0·001	1030	385	1164	460	1316	601	< 0·001
Fruits intake (times/month)	14	17	21	23	27	23	< 0·001	16	18	20	23	25	22	< 0·001	16	18	20	19	27	26	< 0·001
Vegetables intake (times/month)	16	14	19	15	24	16	< 0·001	17	15	18	14	22	16	< 0·001	18	15	19	15	20	16	< 0·001

Characteristics	lutein/zeaxanthin (μg/l)							Lycopene (μg/l)						
	T1		T2		T3		*P*	T1		T2		T3		*P*
	n	%	*n*	%	*n*	%		*n*	%	*n*	%	*n*	%	
Age (years)														
Mean	47·4		49·2		53·5		< 0·001	57·6		47·7		44·0		< 0·001
SD	19·0		18·3		17·3			18·3		17·7		16·2		
Men	1501	55·5	1566	60·2	1630	63·2	< 0·001	1687	60·8	1509	56·8	1501	61·3	0·001
Non-Hispanic white	1488	55·0	1190	45·8	992	38·5	< 0·001	1241	44·7	1213	45·6	1216	49·7	< 0·001
BMI (kg/m²)														
Mean	27·1		26·8		26·7		< 0·001	26·8		27·0		26·9		< 0·001
SD	6·2		5·3		4·8			5·7		5·6		5·1		
Regular exercise	1853	68·5	1850	71·2	1780	69·0	0·085	1682	60·6	1889	71·0	1912	78·1	< 0·001
College graduate or above	612	22·6	684	26·3	712	27·6	< 0·001	544	19·6	690	25·9	774	31·6	< 0·001

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Table 1. (*Continued*)

Characteristics	lutein/zeaxanthin (μg/l)							Lycopene (μg/l)						
	T1		T2		T3		*P*	T1		T2		T3		*P*
	n	%	*n*	%	*n*	%		*n*	%	*n*	%	*n*	%	
Annual household income, > 50 000 (%)	287	10·6	335	12·9	371	14·4	< 0·001	235	8·5	351	13·2	407	16·6	< 0·001
Energy content (kcal/d)														
Mean	2194·2		2199·7		2105·1		< 0·001	1980·1		2176·1		2358·2		< 0·001
SD	1143·9		1080·3		1033·0			1020·9		1096·1		1115·4		
Current smoking	1599	59·1	1286	49·5	1028	39·9	< 0·001	1305	47·0	1343	50·5	1265	51·7	0·002
Current drinking	1451	53·6	1369	52·7	1337	51·9	0·496	1166	42·0	1495	56·2	1496	61·1	< 0·001
Current married (spouse in household)	1495	55·2	1527	58·7	1581	61·3	< 0·001	1550	55·8	1577	59·3	1476	60·3	< 0·001
Current diabetes	216	8·0	213	8·2	267	10·4	0·003	341	12·3	211	7·9	144	5·9	< 0·001
Current hypertension	716	26·5	717	27·6	814	31·6	< 0·001	934	33·6	704	26·5	609	24·9	< 0·001
Current asthma	243	9·0	181	7·0	185	7·2	0·025	205	7·4	214	8·0	190	7·8	0·613
Current emphysema	108	4·0	96	3·7	85	3·3	0·593	159	5·7	80	3·0	50	2·0	< 0·001
Current chronic bronchitis	224	8·3	192	7·4	153	5·9	0·012	229	8·2	179	6·7	161	6·6	0·068
	Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD	
Vitamin C (mg/l)	0·54	0·45	0·65	0·45	0·74	0·45	< 0·001	0·61	0·48	0·65	0·45	0·66	0·43	< 0·001
Vitamin E (μg/l)	998	391	1142	447	1319	572	< 0·001	1103	470	1148	495	1208	509	< 0·001
Fruits intake (times/month)	16	18	20	20	24	25	< 0·001	21	20	21	23	19	20	0·002
Vegetables intake (times/month)	18	14	19	15	20	16	< 0·001	19	16	19	15	19	15	0·140

Continuous variables are presented as mean values and standard deviations. Categorical variables are presented as numbers and percentages.

Table 2. Concentrations of carotenoids in the serum of the study participants (*n* 7884)
(Mean values and standard deviations)

Variables	Serum concentration (μg/l)	
	Mean	SD
Total carotenoids	79·94	36·70
α-carotene	3·93	4·08
β-carotene	19·01	19·38
β-cryptoxanthin	9·38	7·32
Lutein/zeaxanthin	22·55	13·32
Lycopene	21·07	11·33

Continuous variables are presented as mean values and standard deviations.

Fig. 1. Meanwhile, sensitivity analyses were performed, and none of them affected the above results.

Association between serum lutein/zeaxanthin and respiratory morbidity, all-cause and disease-specific mortalities

Table 3 shows that asthma morbidity was associated with serum lutein/zeaxanthin levels (Q2: OR = 0·78, 95 % CI 0·62, 0·97). Compared with the lowest tertile of serum lutein/zeaxanthin, the participants in the highest tertile had lower mortality of all-cause (HR = 0·83, 95 % CI 0·76, 0·91) and respiratory diseases (HR = 0·48, 95 % CI 0·33, 0·71) in Table 4. RCS curve results are shown in Fig. 1. Similarly, sensitivity analyses were performed, and none of them affected the above results.

Association between serum lycopene and respiratory morbidity, all-cause and disease-specific mortalities

Respiratory morbidity was not associated with serum lycopene levels (Table 3). Compared with the lowest tertile of serum lycopene, the participants in the highest tertile had lower mortality of all-cause (HR = 0·75, 95 % CI 0·68, 0·83) and respiratory diseases (HR = 0·66, 95 % CI 0·45, 0·96) in Table 4. RCS curve results are shown in Fig. 1. Meanwhile, sensitivity analyses were performed, and none of them affected the above results.

Discussion

This study examined the association of total carotenoids, *α*-carotene, *β*-carotene, *β*-cryptoxanthin, lutein/zeaxanthin and lycopene with the prevalence of asthma, emphysema and chronic bronchitis, and mortality of all-cause and respiratory diseases. This study found that participants with higher total carotenoids and *β*-cryptoxanthin levels had a lower prevalence of emphysema and chronic bronchitis, and higher total carotenoids, *α*-carotene, lutein/zeaxanthin and lycopene levels had lower mortality of respiratory disease[27,28].

Carotenoids are coloured pigments synthesised by plants, fungi or bacteria. Carotenoids are important markers of fruit and vegetable intake but are also associated with polyphenol, dietary fibre intake[29–31]. Lutein/zeaxanthin may be mainly found in maize foods, while lycopene is mainly found in tomato sauce and many fast foods, and the distribution of foods will also affect their intake[32]. They have potent anti-cancer properties,

Table 3. OR and 95 % CI for the association of total carotenoids, α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin and lycopene with the prevalence of asthma, emphysema and chronic bronchitis
(Odds ratios and 95 % confidence intervals)

		Model 1			Model 2			Model 3		
Subgroup	Cases/*n*	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*
Asthma										
Total carotenoids										
Q1	213/2643	Ref		0·56	Ref		0·833	Ref		0·795
Q2	198/2628	0·92	0·75, 1·13		0·99	0·79, 1·25		1·00	0·80, 1·26	
Q3	198/2613	0·94	0·76, 1·16		1·03	0·80, 1·32		1·03	0·81, 1·33	
α-carotene										
Q1	264/3116	Ref		0·027	Ref		0·138	Ref		0·147
Q2	183/2422	0·91	0·74, 1·12		0·99	0·79, 1·25		1·00	0·79, 1·25	
Q3	162/2346	0·78	0·62, 0·97		0·82	0·63, 1·07		0·82	0·63, 1·07	
β-carotene										
Q1	203/2731	Ref		0·834	Ref		0·423	Ref		0·400
Q2	199/2648	0·96	0·78, 1·19		1·04	0·83, 1·31		1·05	0·83, 1·32	
Q3	207/2505	1·02	0·82, 1·27		1·11	0·86, 1·44		1·12	0·86, 1·45	
β-cryptoxanthin										
Q1	284/3429	Ref		0·850	Ref		0·413	Ref		0·402
Q2	167/2124	1·00	0·82, 1·23		1·05	0·84, 1·32		1·06	0·84, 1·32	
Q3	158/2331	0·98	0·79, 1·21		1·11	0·86, 1·44		1·12	0·86, 1·44	
Lutein/zeaxanthin										
Q1	243/2706	Ref		0·055	Ref		0·067	Ref		0·076
Q2	181/2600	0·78	0·64, 0·96		0·77	0·61, 0·97		0·78	0·62, 0·97	
Q3	185/2578	0·81	0·66, 1·00		0·80	0·63, 1·02		0·80	0·63, 1·02	
Lycopene										
Q1	205/2776	Ref		0·956	Ref		0·289	Ref		0·281
Q2	214/2659	1·07	0·87, 1·32		1·19	0·95, 1·50		1·19	0·95, 1·50	
Q3	190/2449	1·01	0·81, 1·25		1·14	0·89, 1·46		1·14	0·90, 1·46	
Emphysema										
Total carotenoids										
Q1	123/2643	Ref		0·004	Ref		0·008	Ref		0·011
Q2	82/2628	0·72	0·53, 0·97		0·80	0·56, 1·13		0·82	0·57, 1·16	
Q3	84/2613	0·65	0·48, 0·87		0·60	0·40, 0·87		0·61	0·41, 0·89	
α-carotene										
Q1	100/3116	Ref		0·099	Ref		0·289	Ref		0·356
Q2	100/2422	0·98	0·73, 1·32		1·12	0·79, 1·60		1·15	0·81, 1·65	
Q3	89/2346	0·77	0·56, 1·05		0·80	0·53, 1·21		0·82	0·54, 1·25	
β-carotene										
Q1	79/2371	Ref		0·380	Ref		0·760	Ref		0·807
Q2	93/2648	0·88	0·64, 1·21		0·98	0·67, 1·43		1·05	0·76, 1·47	
Q3	117/2505	0·87	0·64, 1·19		0·94	0·63, 1·40		0·92	0·66, 1·28	
β-cryptoxanthin										
Q1	158/3429	Ref		0·119	Ref		0·004	Ref		0·004
Q2	61/2124	0·72	0·52, 0·98		0·72	0·50, 1·02		0·91	0·67, 1·24	
Q3	70/2331	0·78	0·57, 1·06		0·54	0·36, 0·82		0·67	0·49, 0·92	
Lutein/zeaxanthin										
Q1	108/2706	Ref		0·036	Ref		0·130	Ref		0·160
Q2	96/2600	0·90	0·67, 1·21		1·12	0·79, 1·58		0·71	0·49, 1·02	
Q3	85/2578	0·72	0·53, 0·98		0·74	0·51, 1·09		0·55	0·36, 0·82	
Lycopene										
Q1	159/2776	Ref		0·006	Ref		0·091	Ref		0·092
Q2	80/2659	0·77	0·57, 1·02		0·91	0·65, 1·27		0·91	0·64, 1·27	
Q3	50/2449	0·62	0·43, 0·87		0·71	0·47, 1·05		0·71	0·47, 1·05	
Chronic bronchitis										
Total carotenoids										
Q1	211/2643	Ref		0·022	Ref		0·178	Ref		0·222
Q2	194/2628	0·96	0·78, 1·18		1·04	0·82, 1·31		1·07	0·84, 1·35	
Q3	164/2613	0·77	0·62, 0·96		0·83	0·64, 1·09		0·85	0·65, 1·11	
α-carotene										
Q1	226/3116	Ref		0·043	Ref		0·148	Ref		0·171
Q2	184/2422	0·97	0·78, 1·20		1·01	0·80, 1·28		1·02	0·80, 1·29	
Q3	159/2346	0·79	0·62, 0·99		0·81	0·61, 1·08		0·82	0·62, 1·09	
β-carotene										
Q1	185/2731	Ref		0·198	Ref		0·410	Ref		0·515
Q2	184/2648	0·87	0·70, 1·08		0·96	0·75, 1·22		0·97	0·76, 1·24	
Q3	200/2505	0·86	0·69, 1·08		0·89	0·68, 1·17		0·91	0·70, 1·20	

Table 3. (*Continued*)

Subgroup	Cases/*n*	Model 1			Model 2			Model 3		
		OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*
β-cryptoxanthin										
Q1	294/3429	Ref		0·001	Ref		0·004	Ref		0·004
Q2	157/2124	0·93	0·76, 1·15		0·88	0·70, 1·11		0·88	0·69, 1·11	
Q3	118/2331	0·68	0·54, 0·86		0·66	0·50, 0·87		0·66	0·50, 0·87	
Lutein/zeaxanthin										
Q1	224/2706	Ref		0·017	Ref		0·180	Ref		0·211
Q2	192/2600	0·96	0·78, 1·18		1·04	0·83, 1·32		1·05	0·84, 1·33	
Q3	153/2578	0·76	0·61, 0·95		0·84	0·65, 1·08		0·85	0·65, 1·10	
Lycopene										
Q1	229/2776	Ref		0·475	Ref		0·937	Ref		0·939
Q2	179/2659	0·87	0·70, 1·08		0·93	0·74, 1·18		0·93	0·74, 1·18	
Q3	161/2449	0·92	0·73, 1·15		0·99	0·77, 1·27		0·99	0·77, 1·28	

Data are odds ratios and 95 % confidence intervals.
Model 1 was adjusted for age, sex, race, marriage and education.
Model 2 was model 1 with additional adjustments for sport, drink, smoke, BMI, income, energy, vitamin E, vitamin C, fruit intake and vegetable intake.
Model 3 was model 2 with additional adjustments for diabetes, hypertension, asthma, emphysema and chronic bronchitis.

intercellular signalling conduction and are involved in antioxidant activities *in vivo* as well as immune system regulation[12,13,33]. These could explain the relationship between serum carotenoids and respiratory disease morbidity and mortality observed in this study. Among them, serum carotenoids have been shown to reduce lung disease damage through antioxidant activity[34,35]. In a study of mice with lung injury, different doses of lycopene were administered by gavage, and the results showed that lycopene had a protective effect on lung injury and could reduce lipid peroxidation and DNA damage, increased SOD, CAT and GSH activity, minimising redox processes[36].

The study found that participants with higher total carotenoids and *α*-carotene levels had a lower mortality of respiratory disease. This is consistent with recent reports[27,37], but no association was found in people whose BMI was higher than 25 ($P = 0{\cdot}516$). This may be due to the aggravation of oxidative stress caused by obesity, which makes the protective effect of serum carotenoids not obvious[38–40]. And no association was found in current smokers ($P_{\alpha\text{-carotene}} = 0{\cdot}525$), while there is no doubt that smoking does damage to the lungs, and it will greatly affect the relationship between the association[41]. Participants with higher total carotenoids had a lower prevalence of emphysema, but no association was found in sensitivity analyses stratified by smoking ($P_{\text{current smokers}} = 0{\cdot}141$, $P_{\text{Never/former smokers}} = 0{\cdot}118$), and the underlying mechanism is unclear.

Participants with higher *β*-cryptoxanthin had a lower prevalence of emphysema and chronic bronchitis. In an experiment investigating the effects of nicotine on mice, *β*-cryptoxanthin (BCX) was found to inhibit nicotine-induced emphysema and lung tumourigenesis[42]. The association between *β*-cryptoxanthin and chronic bronchitis was also observed in non-smokers, consistent with recent studies[37], but no association was found in current smokers ($P_{\text{emphysema}} = 0{\cdot}188$, $P_{\text{chronic bronchitis}} = 0{\cdot}162$), while smoking has an indelible effect on the lungs and increases oxidative stress in the lungs, this may nullify the protective effects of carotenoids[41]. Interestingly, although the main results of this study did not find an association between *β*-carotene and respiratory disease morbidity and mortality, a positive association between carotene and asthma was found in smokers. In a clinical trial study, *β*-carotene was found to be positively associated with lung function[37], and in an epidemiological study, *β*-carotene supplementation was also found to increase the risk of lung disease[43], which is consistent with the results reported above.

This study found that participants with higher lutein/zeaxanthin levels had lower mortality of respiratory disease. In a study of forced expiratory volume in 1 s and forced vital capacity with several carotenoids, lutein/zeaxanthin was found to play an important role in respiratory health, which supports the above results[44]. Similarly, this study found that the relationship between lutein/zeaxanthin and death from respiratory disease was also observed in a sensitivity analysis stratified by smoking and BMI, demonstrating the robustness of the results. Moreover, the association between lutein/zeaxanthin and respiratory disease mortality remained significant in persons older than 45 years. Participants with higher lutein/zeaxanthin had a lower prevalence of asthma (Q2: OR = 0·78, 95 % CI 0·62, 0·97)), this relationship can also be seen in the sensitivity analysis, which is consistent with recent research[37,41].

Finally, this study found that participants with higher lycopene levels had lower mortalities of respiratory disease. In a study of ferrets exposed to tobacco carcinogens and cigarette smoke, with or without low and high doses of lycopene, lycopene was found to significantly inhibit both tobacco carcinogens and cigarette smoke-induced total accumulation of cholesterol and increases the mRNA expression of key genes related to reverse cholesterol transport (PPARα, LXRα and ATP-binding cassette transporters ABCA1 and ABCG1) in the lung[45]. In a case–control study, where lutein was inversely associated with IL-6, lycopene was negatively associated with SAT, *β*-carotene was positively associated with a Mediterranean-style diet and COPD patients may particularly need a lycopene-rich diet, which is consistent with previous research findings[36,46]. However, no

Table 4. HR and 95 % CI for the association of total carotenoids, α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin and lycopene with all-cause and disease-specific mortalities
(Hazard ratios and 95 % confidence intervals)

		Model 1			Model 2			Model 3		
Subgroup	Cases/*n*	HR	95 % CI	*P*	HR	95 % CI	*P*	HR	95 % CI	*P*
Respiratory disease Mortality										
Total carotenoids										
Q1	111/2643	Ref		< 0·001	Ref		0·010	Ref		0·013
Q2	71/2628	0·60	0·44, 0·81		0·69	0·49, 0·98		0·70	0·50, 0·99	
Q3	71/2613	0·49	0·36, 0·67		0·61	0·42, 0·89		0·62	0·42, 0·90	
α-carotene										
Q1	102/3116	Ref		< 0·001	Ref		0·003	Ref		0·004
Q2	88/2422	0·81	0·60, 1·08		0·79	0·57, 1·11		0·79	0·57, 1·11	
Q3	63/2346	0·47	0·33, 0·65		0·54	0·35, 0·81		0·54	0·36, 0·82	
β-carotene										
Q1	80/2731	Ref		0·003	Ref		0·081	Ref		0·083
Q2	84/2648	0·76	0·56, 1·05		0·77	0·54, 1·11		0·77	0·53, 1·11	
Q3	89/2505	0·61	0·44, 0·84		0·70	0·47, 1·04		0·71	0·48, 1·05	
β-cryptoxanthin										
Q1	131/3429	Ref		0·002	Ref		0·193	Ref		0·208
Q2	71/2124	0·90	0·67, 1·20		1·04	0·75, 1·46		1·05	0·75, 1·47	
Q3	51/2331	0·59	0·42, 0·83		0·76	0·50, 1·15		0·77	0·50, 1·16	
Lutein/zeaxanthin										
Q1	112/2706	Ref		< 0·001	Ref		< 0·001	Ref		< 0·001
Q2	82/2600	0·67	0·5, 0·89		0·8	0·57, 1·11		0·80	0·58, 1·12	
Q3	59/2578	0·41	0·3, 0·57		0·48	0·32, 0·7		0·48	0·33, 0·71	
Lycopene										
Q1	129/2776	Ref		0·003	Ref		0·026	Ref		0·027
Q2	70/2659	0·66	0·49, 0·89		0·72	0·51, 1·01		0·71	0·51, 1·00	
Q3	54/2449	0·60	0·43, 0·84		0·65	0·45, 0·95		0·66	0·45, 0·96	
All-cause mortality										
Total carotenoids										
Q1	1462/2643	Ref		< 0·001	Ref		< 0·001	Ref		< 0·001
Q2	1187/2628	0·75	0·69, 0·81		0·77	0·70, 0·84		0·77	0·71, 0·84	
Q3	1314/2613	0·68	0·63, 0·73		0·74	0·68, 0·82		0·74	0·67, 0·81	
α-carotene										
Q1	1502/3116	Ref		< 0·001	Ref		< 0·001	Ref		< 0·001
Q2	1232/2422	0·82	0·76, 0·89		0·85	0·78, 0·93		0·85	0·78, 0·93	
Q3	1226/2346	0·70	0·64, 0·75		0·77	0·69, 0·85		0·76	0·69, 0·84	
β-carotene										
Q1	1228/2731	Ref		< 0·001	Ref		< 0·001	Ref		< 0·001
Q2	1259/2648	0·78	0·72, 0·85		0·80	0·73, 0·88		0·82	0·75, 0·90	
Q3	1473/2505	0·73	0·67, 0·79		0·81	0·73, 0·89		0·82	0·74, 0·91	
β-cryptoxanthin										
Q1	1889/3429	Ref		< 0·001	Ref		< 0·001	Ref		< 0·001
Q2	985/2124	0·84	0·77, 0·90		0·85	0·78, 0·93		0·84	0·77, 0·92	
Q3	1086/2331	0·77	0·71, 0·83		0·84	0·76, 0·92		0·83	0·75, 0·91	
Lutein/zeaxanthin										
Q1	1333/2706	Ref		< 0·001	Ref		< 0·001	Ref		< 0·001
Q2	1233/2600	0·79	0·73, 0·86		0·84	0·77, 0·92		0·84	0·77, 0·92	
Q3		0·74	0·69, 0·80		0·83	0·76, 0·91		0·83	0·76, 0·91	
Lycopene										
Q1	1851/2776	Ref		< 0·001	Ref		< 0·001	Ref		< 0·001
Q2	1228/2659	0·82	0·76, 0·88		0·84	0·78, 0·92		0·85	0·78, 0·92	
Q3	881/2449	0·71	0·65, 0·77		0·76	0·69, 0·83		0·75	0·68, 0·83	

Data are hazard ratios and 95 % confidence intervals.
Model 1 was adjusted for age, sex, race, marriage and education.
Model 2 was model 1 with additional adjustments for sport, drink, smoke, BMI, income, energy, vitamin E, vitamin C, fruit intake and vegetable intake.
Model 3 was model 2 with additional adjustments for diabetes, hypertension, asthma, emphysema and chronic bronchitis.

association was found between β-cryptoxanthin and respiratory disease mortality among those with a BMI of less than 25 ($P = 0{\cdot}066$), and the underlying mechanism is unclear.

An important limitation of this study is that serum carotenoid levels were measured when participants first joined the study, which was too long since follow-up outcomes to address the effects of changes in participants' serum carotenoid levels. Furthermore, the self-reported data are somewhat biased and not entirely correct. In addition, this study was observational. Although we have adjusted for most known confounding factors, we cannot exclude the possibility that unmeasured variables may have influenced our results. Finally, the NHANES III-linked

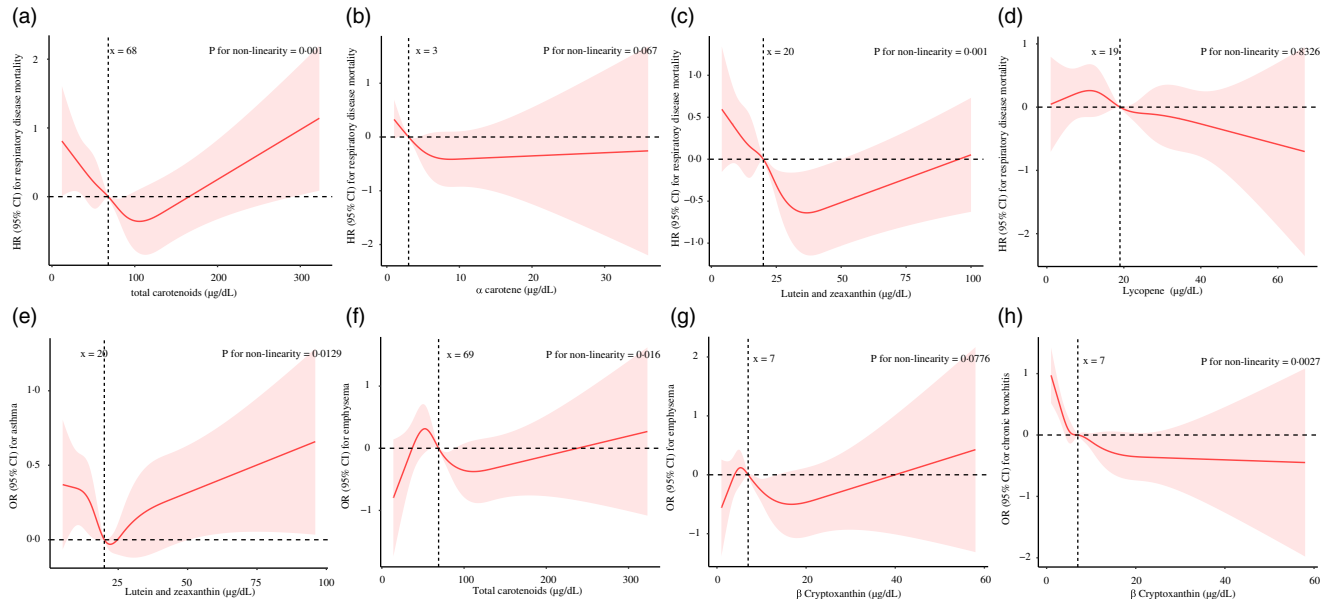

Fig. 1. RCS analysis between serum carotenoids levels and respiratory disease morbidity and mortality. (a) RCS analysis of the relationship between total carotenoids and respiratory disease mortality. (b) RCS analysis of the relationship between α-carotene and respiratory disease mortality. (c) RCS analysis of the relationship between lutein and zeaxanthin and respiratory disease mortality. (d) RCS analysis of the relationship between lycopene and respiratory disease mortality. (e) RCS analysis of the relationship between lutein and zeaxanthin and the prevalence of asthma. (f) RCS analysis of the relationship between total carotenoids and the prevalence of emphysema. (g) RCS analysis of the relationship between β-cryptoxanthin and the prevalence of emphysema. (h) RCS analysis of the relationship between β-cryptoxanthin and the prevalence of chronic bronchitis. RCS, restricted cubic spline.

mortality profile is constructed by the cause of death through the National Mortality Index, in which there may be errors in the classification of the cause of death. In conclusion, the results of the present study show that participants with higher serum total carotenoids and β-cryptoxanthin levels are associated with a decreased prevalence of emphysema and chronic bronchitis, and higher serum total carotenoids, α-carotene, lutein/zeaxanthin and lycopene levels had a lower mortality of respiratory disease.

Conclusions

Higher serum total carotenoids and β-cryptoxanthin levels are associated with a decreased prevalence of emphysema and chronic bronchitis, and higher serum total carotenoids, α-carotene, lutein/zeaxanthin and lycopene levels had a lower mortality of respiratory disease. These findings indicate that serum carotenoids can be considered a supplementary treatment for people with respiratory diseases.

Acknowledgements

The authors thank the participants and staff of the National Health and Nutrition Examination Survey from 1988 to 1994 for their valuable contributions.

This research was supported by funds from HMU Marshal Initiative Funding (HMUMIF-21013 to Wei Wei).

Q. R. and W. W. and X. C. conceived the study conceptualization. W. W. provided the data. R. Y. and Z. C. and X.L. did the formal analysis. R. Y. and M. L. and M. X. did the visualization. R. Y. and Y. C. and L. C. wrote the original draft. All authors provided critical revisions of the draft and approved the submitted draft. Q. R. and W. W. are the guarantor of this work and are responsible for the integrity of the data and the accuracy of the data analysis.

The authors did not have any competing interests to declare.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114523000806

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