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Research article

Associations of serum carotenoids with asthma and mortality in the US adults

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ABSTRACT

Objective: This study was to investigate the association between serum carotenoid levels and the prevalence of asthma, as well as the relationship between serum carotenoid levels and the risk of mortality among individuals with asthma.

Methods: Data on five serum carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene) were obtained from the National Health and Nutrition Examination Survey (NHANES) 2001–2006. Mortality data was extracted from the pertinent mortality records within the NHANES database, up to December 31, 2019. Logistic regression analysis was employed to investigate the association between serum carotenoid concentrations and asthma prevalence. Cox proportional hazards models were used to investigate the connection between serum carotenoids and mortality rates in asthma individuals.

Results: Among the study population, 1569 (12.63 %) individuals were diagnosed with asthma, while 25.01 % of asthma patients died within a median follow-up duration of 15.5 (13.8–17.3) years. After controlling for all other variables, greater serum levels of certain carotenoids, such asα-carotene, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin, were found to be substantially linked with a decreased prevalence of asthma. Furthermore, persons with asthma who had greater levels of serum carotenoids in the fourth quartile had a significantly lower risk of all-cause death compared to those in the first quartile. Specifically, the presence of α-carotene, β-cryptoxanthin, and lutein/zeaxanthin was associated with reductions in all-cause mortality by 45 % (HR = 0.55 [0.36–0.84], $P_{trend} = 0.002$), 38 % (HR = 0.62 [0.42–0.92], $P_{trend} = 0.004$), and 45 % (HR = 0.55 [0.41–0.73], $P_{trend}<0.001$), respectively. The above relationships are mostly linear and remain robust in sensitivity analyses.

Conclusions: Our findings indicate that higher serum carotenoids are related with a reduced likelihood of mortality in asthmatic individuals.

1. Introduction

Asthma is a chronic respiratory disease characterized by airway inflammation and constriction, leading to breathing difficulties [1]. It affects millions of individuals worldwide, posing significant public health challenges [2–4]. One of the primary concerns related to asthma is the risk of exacerbations, commonly referred to as asthma attacks [5]. During an attack, symptoms worsen significantly, further compromising the individual's ability to breathe [6,7]. Severe attacks can be life-threatening and may require immediate

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medical attention. The etiology of asthma is intricate, influenced by a myriad of factors ranging from genetic predisposition to environmental triggers [8,9]. Beyond these primary influences, inflammation and autoimmunity emerge as pivotal factors contributing to the intricate tapestry of asthma pathogenesis [10]. Genetic susceptibility sets the stage for an individual's responsiveness to environmental triggers, such as allergens and pollutants, further amplifying the intricate nature of this respiratory condition.

Carotenoids are a group of natural chemicals found in plants that provide a multitude of nutritional and health benefits [11–13]. Carotenoid research has gained significance as individuals increasingly prioritize health and pay attention to their nutritional requirements [14]. First and foremost, carotenoids are precursors of vitamin A, playing a role in various physiological functions, including vision, immune response, and reproduction [15]. Furthermore, carotenoids exhibit potent antioxidant effects, inhibiting the generation of free radicals and lipid peroxidation, which in turn contributes to the stability of cell membranes and metabolic well-being [16]. Carotenoids have been linked to both the growth inhibition and prevention of cancer, eye disorders, and diabetes in numerous studies [17,18]. A cross-sectional study yielded results indicating an association between higher dietary intake of carotenoids and a lower prevalence of asthma among adults [19]. Moreover, two separate studies conducted on pediatric populations also demonstrated analogous outcomes, further strengthening the observed relationship [20,21]. These collective research efforts reinforce the potential significance of carotenoid intake in relation to asthma prevalence.

Furthermore, given the paucity of research on the relationship between serum carotenoids and mortality rates, it is critical to look into these relationships in asthma at the population level [22,23]. Our study aims to elucidate the potential connections between serum carotenoid levels and mortality in the adult asthma population of the United States. This investigation holds the potential to not only enhance our understanding of the role of diet and nutrition in respiratory health but also to contribute to the broader discourse on overall well-being. To comprehensively assess the intricate interplay between serum carotenoid levels, asthma prevalence, and mortality risk, we have meticulously considered potential confounding variables in our analysis. The insights gleaned from these comprehensive analyses promise to provide invaluable insights into the complex interactions between blood carotenoid levels and the associated health outcomes.

2. Materials and methods

2.1. Study population

The National Health and Nutrition Examination Survey (NHANES) is a program of studies conducted by the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC) in the United States. The NHANES collects data on various aspects of health and nutrition among the civilian, non-institutionalized population [24]. Through NHANES, researchers and policymakers gain valuable insights into the prevalence, risk factors, and impact of various health conditions and disparities across different population subgroups [25]. The survey covers a wide range of health topics, including chronic diseases, infectious diseases, mental health, dietary patterns, physical activity, and environmental exposures. The research protocols were approved by the NCHS Research Ethics Review Board, and all participants provided informed permission.

Data was obtained from the NHANES over three cycle years (including 2001–2002, 2003–2004, and 2005–2006). Participants with incomplete asthma assessment data (n = 1573), participants lacking information on the five serum carotenoids (n = 7758), individuals below the age of 20 (n = 8999), and pregnant women (n = 754) were eliminated. This exclusion process resulted in a final total of 12,425 eligible participants, comprising 10,856 participants without asthma and 1569 asthmatic individuals. Furthermore, we excluded two asthmatic patients who had failed to follow-up, for a total of 1567 asthmatic participants in the survival analysis (Fig. S1).

2.2. Assessment of serum carotenoids

The concentrations of five carotenoid molecules circulating in the bloodstream, namely α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene, were measured using high performance liquid chromatography with multiwavelength photodiode-array absorbance detection. Previous works discussed the precise estimation process in detail [26,27]. The concentrations of five serum carotenoids were added to yield the total serum carotenoid concentration.

2.3. Assessment of asthma and mortality

Participants were classified as having asthma if they met any of the following requirements: 1) previously diagnosed with asthma [19], 2) using antiasthmatic medication, or 3) taking medications such as selective phosphodiesterase-4 inhibitors, mast cell stabilizers, leukotriene modifiers, or inhaled corticosteroids, were under 40 years old, and had no history of smoking, chronic bronchitis, or emphysema [28,29]. As of December 31, 2019, mortality is calculated by comparing National Death Index (NDI) records with data from the study population's death certificates to identify those who passed away during the study [30].

2.4. Covariates

Age, gender, race/ethnicity, education level, total energy intake, dietary total carotenoids, and carotenoid supplement use were all acquired using questionnaires and laboratory tests.

The poverty income ratio (PIR) is computed by dividing the revenue of a household by the poverty level applicable to the size and

composition of the family [31]. The resulting ratio provides insights into how far below or above the poverty line a household's income falls (≤1.0, 1.1–3.0, or >3.0). The NHANES assessed participants' smoking status by asking them about their past and present smoking habits and recording relevant information (including age of smoking initiation, daily cigarette consumption, and whether they had tried to quit) [27]. Participants were categorized into three groups based on their smoking history: never smokers (those who had smoked no more than 100 cigarettes), former smokers (those who had smoked over 100 cigarettes but had quit smoking), and current smokers (those who continued to smoke) [26,27]. Drinking status was classified into three categories: non-drinkers, low-to moderate-level drinkers (men consuming <2 drinks/day and women consuming <1 drink/day), and heavy drinkers (men consuming ≥2 drinks/day and women consuming ≥1 drink/day) [26]. Physical activity levels were divided into three groups: inactive (no leisure-time physical activity), insufficiently active (engaging in moderate activity 1–5 times per week with MET 3–6 or vigorous activity 1–3 times per week with MET >6), and active (individuals with higher levels of moderate or vigorous activity than the

Table 1
Characteristics of adult participants in NHANES 2001–2006.

Characteristics	Total	Quartiles of serum total carotenoids levels, μg/dL				*P* value
		<47.64	47.64–65.29	65.30–89.30	>89.30	
Participants, N	12425	3106	3107	3103	3109	
Age, years	46.52 (0.33)	46.06 (0.43)	44.96 (0.40)	45.55 (0.49)	49.72 (0.42)	<0.001
Male, %	6308 (50.77)	1676 (50.34)	1617 (50.85)	1603 (50.58)	1412 (43.43)	<0.001
Race/ethnicity, %						0.007
Mexican American	2511 (20.21)	500 (5.55)	601 (6.91)	687 (8.70)	723 (8.71)	
Other Hispanic	431 (3.47)	97 (4.14)	117 (4.92)	108 (4.01)	109 (4.30)	
Non-Hispanic White	6534 (52.59)	1754 (75.20)	1634 (72.83)	1577 (71.42)	1569 (71.03)	
Non-Hispanic Black	2485 (20)	665 (11.24)	641 (10.51)	609 (10.51)	570 (10.00)	
Other race	464 (3.73)	90 (3.87)	114 (4.83)	122 (5.35)	138 (5.96)	
Education level, %						<0.001
Below high school	3623 (29.16)	1061 (23.56)	907 (18.41)	862 (16.97)	793 (13.72)	
High school	3018 (24.29)	866 (31.17)	799 (27.86)	743 (24.53)	610 (19.31)	
Above high school	5784 (46.55)	1179 (45.27)	1401 (53.73)	1498 (58.50)	1706 (66.97)	
Family PIR, %						<0.001
≤1.0	2168 (17.45)	677 (16.79)	585 (13.09)	516 (11.59)	390 (8.00)	
1.1–3.0	5259 (42.33)	1484 (43.55)	1312 (37.20)	1277 (34.79)	1186 (30.18)	
>3.0	4998 (40.23)	945 (39.66)	1210 (49.70)	1310 (53.62)	1533 (61.82)	
Smoking status, %						<0.001
Never smoker	6239 (50.21)	1181 (38.18)	1463 (46.86)	1679 (53.02)	1916 (62.59)	
Former smoker	3321 (26.73)	789 (22.17)	806 (24.07)	819 (25.79)	907 (28.37)	
Current smoker	2865 (23.06)	1136 (39.65)	838 (29.06)	605 (21.19)	286 (9.04)	
Drinking status, %						<0.001
Nondrinker	2913 (23.44)	708 (20.51)	713 (19.39)	726 (20.11)	766 (20.31)	
Low-to-moderate drinker	8477 (68.23)	2044 (67.63)	2114 (70.17)	2183 (72.66)	2136 (71.62)	
Heavy drinker	1035 (8.33)	354 (11.86)	280 (10.44)	194 (7.23)	207 (8.07)	
Physical activity, %						<0.001
Inactive	3477 (27.98)	1024 (27.38)	877 (21.64)	808 (19.46)	768 (17.68)	
Insufficiently active	6090 (49.01)	1425 (52.19)	1548 (56.18)	1539 (56.04)	1578 (56.37)	
Active	2858 (23)	657 (20.43)	682 (22.18)	756 (24.50)	763 (25.95)	
Total energy intake, kcal/day	2047.00 (1500.00,2769.00)	2028.00 (1458.00,2799.00)	2069.00 (1500.00,2789.00)	2099.00 (1525.00,2794.00)	2003.00 (1513.00,2689.00)	0.081
Dietary total carotenoids, μg/day	5552.00 (1941.00,13121.00)	3256.00 (999.00, 8772.00)	4693.00 (1729.00,11916.00)	6313.00 (2481.00,13470.00)	8959.00 (3822.00,18579.00)	<0.001
Carotenoid supplement use, %	3512 (28.27)	604 (21.56)	744 (25.77)	936 (32.80)	1228 (44.36)	<0.001
Self-reported hypertension, %	4142 (33.34)	1205 (34.03)	1011 (27.89)	961 (26.90)	965 (26.12)	<0.001
Self-reported diabetes, %	1302 (10.48)	451 (10.98)	333 (7.36)	264 (6.23)	254 (5.13)	<0.001
Asthma, %	1569 (12.63)	440 (15.57)	402 (14.25)	381 (13.91)	346 (12.20)	0.031

Normally distributed continuous variables are described as means ± SEs, and continuous variables without a normal distribution are presented as medians [interquartile ranges]. Categorical variables are presented as numbers (percentages). N reflect the study sample while percentages reflect the survey-weighted data. PIR, poverty income ratio.

aforementioned) [32,33]. To gather additional information, we employed self-reported questionnaires to assess the prevalence of hypertension, diabetes, and the use of carotenoid supplements among the participants. Additionally, the intake levels of the five dietary carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene) were summed to derive the total dietary carotenoid intake. The relevant full questionnaire information for our study is available at the following URL: https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/questionnaires.aspx?Cycle=2005-2006. Laboratory testing includes the detection of nutritional biomarkers (serum iron, vitamin A, vitamin E, and vitamin C levels) and inflammatory markers (white blood cell, neutrophil, and lymphocyte levels). For detailed laboratory testing methods, please refer to the following website: https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/labmethods.aspx?Cycle=2005-2006.

2.5. Statistical analysis

Normally distributed continuous variables are described as means ± SEs, and continuous variables without a normal distribution are presented as medians (interquartile ranges [IQR]). Comparative analyses were conducted employing Student's t-test for normally distributed variables and the Mann-Whitney *U* test for those deviating from normal distribution. Categorical variables were represented numerically (as percentages), and their comparisons were executed through the application of the chi-square test. The correlation coefficients between serum and dietary carotenoids were calculated using pairwise Spearman correlation analysis. A natural logarithm (ln) transformation was applied to the serum carotenoid levels with skewed distributions to approximate a normal distribution. Based on the IQR of carotenoid intake, the respondents were divided into four separate categories of intake, using participants in the lowest intake group as the reference.

We conducted logistic regression analysis to explore the association between blood carotenoids and asthma prevalence in the adult population of the United States. The logistic regression full model was adjusted for age, sex, race/ethnicity, education level, family PIR, smoking status, drinking status, total energy intakes, physical activity, carotenoid supplement use, total dietary carotenoid intakes, self-reported hypertension, and self-reported diabetes. We utilized Cox proportional hazards models to investigate the connection between serum carotenoids and mortality rates among participants with asthma. The COX regression full model was adjusted for age, sex, race/ethnicity, education level, family PIR, smoking status, drinking status, total energy intakes, physical activity, carotenoid supplement use, total dietary carotenoid intakes, self-reported hypertension, self-reported diabetes, anti-asthma medication use. To investigate potential non-linear associations between serum carotenoid and asthma prevalence or mortality risk, we implemented restricted cubic spline (RCS) regressions with three nodes. RCS regressions allow us to flexibly model the relationship using cubic splines while considering potential non-linearities and capturing complex patterns. The non-linearity *P*-values were computed using likelihood ratio tests. *P*-values below the significance level are interpreted as indicating statistically significant non-linear associations.

We also performed some sensitivity analyses. First, to minimize the possibility of reverse-causality bias, after eliminating persons who died within the first two years of follow-up, we ran one Cox regression analysis. Second, after eliminating patients with a history of cancer, we ran another Cox regression analysis. Finally, we took into account dietary variables, nutritional indicators, and inflammatory markers. Finally, we looked at the relationship between dietary carotenoid intake and overall mortality in persons with asthma. R software (version 4.2.0) was used for statistical analyses, and a two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of the study participants

This study involved 10,856 participants without asthma and 1569 asthmatic patients in total. Table 1 displays the general characteristics of the study participants. The participants had a mean age of 46.52 (0.33) years old, 6308 (50.77 %) of participants were male. Participants with higher serum total carotenoids were more likely to be old female, have higher levels of education, and have more household income. They had lower proportions of current smokers and heavy drinker and were more physically active. These participants had higher dietary total carotenoids and frequently used carotenoid supplements, and had a lower self-reported prevalence of hypertension, diabetes, and asthma. In addition, Table S1 also presents baseline characteristics of participants with and without asthma.

3.2. Distribution and concentration of serum carotenoids

Table S2 listed the distribution of serum carotenoids among adults with asthma. The mean total serum carotenoids, α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, lycopene was 61.94, 2.50, 11.93, 6.90, 13.10, and 22.80 μg/dL, respectively. In addition, we also analysed the distribution of participants' dietary carotenoid intake, intake of other dietary elements, serum nutritional biomarkers, and inflammatory markers. Figure S2. showed the Spearman correlation coefficients among serum and dietary carotenoids. From low ($r = 0.12$ for dietary lutein/zeaxanthin and lycopene) to high ($r = 0.76$ for serum α-carotene and β-carotene), the Spearman correlation between serum and dietary carotenoids varied.

3.3. Association between serum carotenoids and asthma

Higher total serum carotenoids were substantially related to a decreased prevalence of asthma, both in the unadjusted and multivariable models (Table 2). The highest quartile of α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin concentrations

associated with low asthma prevalence in unadjusted models, but this relationship was not found for Lycopene. In model 3, compared with the first quantile, the fourth quantile of α-carotene (OR = 0.70 [0.59–0.83], P_{trend} = 0.002), β-carotene (OR = 0.73 [0.59–0.91], P_{trend} = 0.012), β-cryptoxanthin (OR = 0.80 [0.65–0.98], P_{trend} = 0.064), and lutein/zeaxanthin (OR = 0.75 [0.62–0.91], P_{trend} = 0.006) were inversely associated with asthma prevalence. Fig. 1 showed that there was a linear associations of serum total carotenoid, α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene with asthma prevalence (all *P* for nonlinearity>0.05).

3.4. Association between serum carotenoids and all-cause mortality

In the prospective cohort study with a median follow-up of 15.5 (13.8–17.3) years, a total of 1567 participants with asthma were observed, and among them, 392 experienced all-cause mortality (Table 3). All-cause deaths occurred in asthmatics who were old female, had lower education levels and household income, smoked and drank alcohol more frequently, and were less physically active. These participants had lower serum total carotenoid levels and dietary carotenoid intake, a higher prevalence of self-reported hypertension and diabetes, and a higher frequency of anti-asthma medication use.

Cox regression analysis of the association between serum carotenoids and all-cause mortality among adults with asthma was shown in Table 4. Both crude and multivariate corrected models found a significant relationship between higher serum total carotenoids and a lower likelihood of all-cause death in asthmatics. In model 1, all five serum carotenoids showed a protective association with all-cause mortality in asthmatics. However, with further adjustment for confounding variables in Models 2 and 3, serum β-carotene and Lycopene were not associated with the risk of all-cause mortality in asthmatics. In models 3, α-carotene, β-cryptoxanthin, and lutein/zeaxanthin reduced all-cause mortality in asthmatics by 45 % (HR = 0.55 [0.36–0.84], P_{trend} = 0.002), 38 % (HR = 0.62 [0.42–0.92], P_{trend} = 0.004), and 45 % (HR = 0.55 [0.41–0.73], P_{trend}<0.001), respectively. Fig. 2 showed that serum total carotenoid, α-carotene, β-cryptoxanthin and asthma all-cause mortality are linearly and negatively correlated (*P* for nonlinearity = 0.382, 0.593, and 0.534, respectively), and lutein/zeaxanthin and asthma all-cause mortality are non-linearly and negatively correlated (*P* for nonlinearity = 0.006), with inflection points of 19.06 μg/dL.

Table 2
OR (95 % CI) of the prevalence of asthma according to quartiles of serum carotenoids concentrations among adults in NHANES 2001–2006.

	Serum carotenoids (μg/dL)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}
Total serum carotenoids					
Range					
Crude	1 [Reference]	0.90 (0.75–1.08)	0.88 (0.72–1.06)	0.75 (0.65–0.88)	0.001
Model 1	1 [Reference]	0.90 (0.75–1.09)	0.90 (0.73–1.10)	0.79 (0.68–0.92)	0.010
Model 2	1 [Reference]	0.92 (0.76–1.12)	0.91 (0.74–1.11)	0.80 (0.67–0.94)	0.022
α-Carotene					
Range	<1.51	1.51–3.00	3.01–5.19	>5.19	
Crude	1 [Reference]	0.69 (0.58–0.81)	0.82 (0.72–0.95)	0.70 (0.60–0.81)	<0.001
Model 1	1 [Reference]	0.71 (0.60–0.83)	0.87 (0.75–1.01)	0.71 (0.60–0.82)	0.001
Model 2	1 [Reference]	0.69 (0.58–0.82)	0.85 (0.74–0.99)	0.70 (0.59–0.83)	0.002
β-Carotene					
Range	<8.01	8.01–14.19	14.20–24.99	>24.99	
Crude	1 [Reference]	0.81 (0.69–0.95)	0.80 (0.68–0.94)	0.73 (0.62–0.86)	<0.001
Model 1	1 [Reference]	0.82 (0.70–0.96)	0.82 (0.68–0.99)	0.74 (0.61–0.89)	0.005
Model 2	1 [Reference]	0.82 (0.70–0.97)	0.82 (0.67–1.00)	0.73 (0.59–0.91)	0.012
β-Cryptoxanthin					
Range	<5.00	5.00–7.99	8.00–12.69	>12.69	
Crude	1 [Reference]	0.89 (0.73–1.07)	0.89 (0.75–1.05)	0.69 (0.57–0.82)	<0.001
Model 1	1 [Reference]	0.89 (0.73–1.07)	0.92 (0.78–1.10)	0.78 (0.64–0.94)	0.028
Model 2	1 [Reference]	0.90 (0.74–1.09)	0.93 (0.78–1.12)	0.80 (0.65–0.98)	0.064
Lutein/zeaxanthin					
Range	<14.01	14.01–23.00	23.01–35.99	>35.99	
Crude	1 [Reference]	0.84 (0.71–0.99)	0.79 (0.67–0.95)	0.67 (0.57–0.80)	<0.001
Model 1	1 [Reference]	0.88 (0.75–1.04)	0.86 (0.72–1.03)	0.75 (0.62–0.90)	0.004
Model 2	1 [Reference]	0.90 (0.76–1.06)	0.86 (0.72–1.04)	0.75 (0.62–0.91)	0.006
Lycopene					
Range	<12.60	12.60–17.99	18.00–25.20	>25.20	
Crude	1 [Reference]	1.12 (0.92–1.37)	1.16 (0.95–1.43)	1.08 (0.88–1.32)	0.503
Model 1	1 [Reference]	1.04 (0.85–1.28)	1.04 (0.84–1.29)	0.97 (0.79–1.20)	0.695
Model 2	1 [Reference]	1.05 (0.85–1.30)	1.06 (0.85–1.31)	0.99 (0.80–1.23)	0.880

Model 1 was adjusted for age (continuous), sex (male or female), and race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black or Other).

Model 2 was apdjusted as model 1 plus education level (below high school, high school, or above high school), family poverty income ratio (≤1.0, 1.1–3.0, or >3.0), smoking status (never smoker, former smoker, or current smoker), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), total energy intakes (ln-transformed), physical activity (inactive, insufficiently active, or active), carotenoid supplement use (yes or no), total dietary carotenoid intakes (ln-transformed), self-reported hypertension (yes or no), and self-reported diabetes (yes or no).

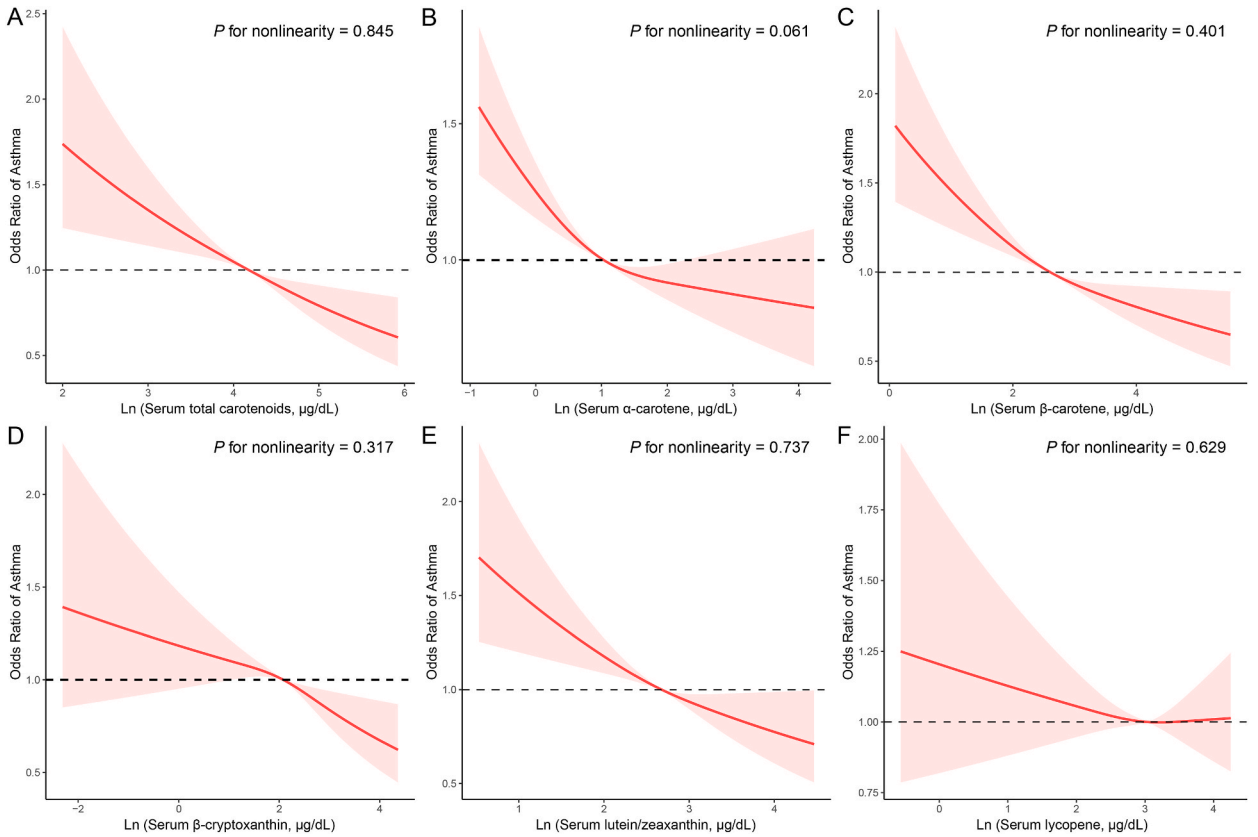

Fig. 1. The exposure-response associations of serum carotenoids and the prevalence of asthma by restricted cubic spline (RCS). Model was adjusted for age (continuous), sex (male or female), race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black or Other), education level (below high school, high school, or above high school), family poverty income ratio (≤1.0, 1.1–3.0, or >3.0), smoking status (never smoker, former smoker, or current smoker), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), total energy intakes (ln-transformed), physical activity (inactive, insufficiently active, or active), carotenoid supplement use (yes or no), total dietary carotenoid intakes (ln-transformed), self-reported hypertension (yes or no), and self-reported diabetes (yes or no).

3.5. Sensitivity analyses

Our investigation revealed that the association mentioned earlier persisted even after excluding participants who passed away within two years of follow-up (Table S3). Furthermore, upon excluding participants with prior malignancy diagnoses, negative correlations were observed between serum total carotenoids, α-carotene, lutein/zeaxanthin, and asthma-related all-cause mortality (Table S4). Moreover, the consistency of our study's findings was maintained even after additional adjustments for dietary variables, nutritional indicators, and inflammatory markers (Table S5). Notably, no significant connection was found between dietary carotenoids intake and the risk of all-cause mortality (Table S6).

4. Discussion

This study utilized extensive cohort data from the 2001–2006 NHANES project to investigate the associations between serum carotenoid concentrations, asthma prevalence, and all-cause mortality in US adults. The findings revealed a noteworthy connection between reduced asthma frequency in adults and higher serum levels of total carotenoids, as well as specific carotenoids like α-carotene, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin. Moreover, elevated serum carotenoid levels (including total carotenoids, α-carotene, β-cryptoxanthin, and lutein/zeaxanthin) were independently associated with a decreased risk of all-cause mortality in individuals with asthma, even after considering all relevant covariates. The robustness of the relationship between serum carotenoid concentrations and mortality in individuals with asthma was further confirmed in sensitivity analysis.

Due to its antioxidant properties and potential health benefits, carotenoids play a vital role in promoting the well-being of individuals [34]. A substantial amount of research has explored the relationship between carotenoids and chronic diseases, providing insights into their impact on disease prevention and progression. One major area of concern is cardiovascular disease (CVD). According to epidemiological findings, increased carotenoid intake or blood levels, particularly lycopene, may be related with a lower prevalence of CVD [35,36]. Certain types of cancer have also been extensively studied in relation to carotenoid intake [37]. For example, diets rich

Table 3
Baseline characteristics of adults with asthma in NHANES 2001–2006.

Variables	Total (n = 1567)	All-cause mortality		*P* value
		No (n = 1175)	Yes (n = 392)	
Age, years	44.51 (0.47)	40.65 (0.46)	63.73 (0.96)	<0.001
Male, %	691 (44.1)	515 (42.80)	176 (39.39)	0.287
Race/ethnicity, %				0.395
Mexican American	176 (11.23)	147 (3.98)	29 (1.79)	
Other Hispanic	60 (3.83)	49 (5.01)	11 (4.56)	
Non-Hispanic White	917 (58.52)	662 (75.76)	255 (78.76)	
Non-Hispanic Black	353 (22.53)	267 (10.62)	86 (11.27)	
Other race	61 (3.89)	50 (4.62)	11 (3.62)	
Education level, %				<0.001
Below high school	355 (22.65)	210 (11.70)	145 (27.96)	
High school	339 (21.63)	251 (22.73)	88 (23.38)	
Above high school	873 (55.71)	714 (65.58)	159 (48.67)	
Family PIR, %				<0.001
≤1.0	294 (18.76)	206 (13.12)	88 (21.08)	
1.1–3.0	619 (39.5)	421 (32.30)	198 (45.81)	
>3.0	654 (41.74)	548 (54.58)	106 (33.12)	
Smoking status, %				<0.001
Never smoker	728 (46.46)	604 (50.85)	124 (30.07)	
Former smoker	466 (29.74)	291 (24.48)	175 (41.72)	
Current smoker	373 (23.8)	280 (24.68)	93 (28.21)	
Drinking status, %				<0.001
Nondrinker	341 (21.76)	230 (16.42)	111 (27.90)	
Low-to-moderate drinker	1085 (69.24)	837 (73.74)	248 (61.66)	
Heavy drinker	141 (9)	108 (9.84)	33 (10.44)	
Physical activity, %				<0.001
Inactive	429 (27.38)	247 (18.82)	182 (40.39)	
Insufficiently active	774 (49.39)	641 (57.44)	133 (37.64)	
Active	364 (23.23)	287 (23.74)	77 (21.97)	
Total energy intake, kcal/day	2072.00 (1517.00,2865.00)	2162.00 (1604.00,2967.00)	1657.00 (1282.00,2212.00)	<0.001
Dietary total carotenoids, μg/day	5825.00 (1932.00,12251.00)	6009.00 (1951.00,12845.00)	4418.00 (1592.00,10151.00)	0.004
Serum total carotenoids, μg/dL	61.94 (45.30,83.00)	63.15 (46.58,82.60)	56.40 (40.79,85.44)	0.027
Carotenoid supplement use, %	454 (28.97)	318 (30.17)	136 (36.11)	0.100
Self-reported hypertension, %	604 (38.54)	364 (26.58)	240 (57.09)	<0.001
Self-reported diabetes, %	172 (10.98)	88 (5.72)	84 (18.85)	<0.001
Anti-asthma medication use, %	246 (15.7)	142 (12.73)	104 (28.01)	<0.001

Normally distributed continuous variables are described as means ± SEs, and continuous variables without a normal distribution are presented as medians [interquartile ranges]. Categorical variables are presented as numbers (percentages). N reflect the study sample while percentages reflect the survey-weighted data. HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

in carotenoids have been associated with a lower incidence of Head and neck cancer (HNC), lung cancer, and breast cancer [38–40]. In addition, lutein and zeaxanthin have shown potential protective effects against age-related macular degeneration (AMD) [41]. Our study also found that higher serum total carotenoids, α-carotene, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin were associated with a lower prevalence of asthma in adults.

Some studies have discovered a link between carotenoids and the likelihood of developing chronic diseases, as well as a link between carotenoids and mortality. They have found that those with greater carotenoids concentrations in their blood have a reduced likelihood of cardiovascular events, as well as reduced CVD and deaths from all causes [26,42]. Xu et al. found that increasing the intake of total dietary carotenoids improved the prognosis of stroke patients [43]. In addition, lower cancer mortality rates were also observed in individuals with higher carotenoid levels (α-carotene, and β-carotene) [44]. Higher carotenoids concentrations have been linked to enhanced lung function and lower mortality in individuals with chronic obstructive pulmonary disease (COPD), indicating the importance of carotenoids in respiratory disease management [45,46]. Furthermore, we observed that the usage of carotenoid supplements was more frequent among participants who experienced mortality; however, it is worth highlighting that this disparity did not reach statistical significance. It is also crucial to emphasize that we identified statistically significant disparities in baseline serum carotenoid levels and dietary carotenoid intake between the mortality group and the non-mortality group. These findings carry clinical significance, indicating a potential association between lower baseline serum carotenoid levels and reduced dietary carotenoid intake with an elevated risk of mortality. These distinctions are not only statistically meaningful but also clinically relevant, potentially suggesting that factors beyond supplement usage could be contributing to the observed outcomes.

Although the precise methods by which carotenoids exert their protective effects are not entirely understood, it is believed that their anti-inflammatory and antioxidant qualities are of utmost importance. Carotenoids are powerful antioxidants that aid in the fight against oxidative stress [47,48]. Asthma is characterized by chronic inflammation and an elevated production of reactive oxygen species (ROS). These free radicals are neutralized by carotenoids, avoiding cell death and decreasing inflammation in the airways. By controlling the generation and activity of inflammatory mediators, carotenoids may modify the immune system's response [49,50]. In asthmatics, this regulation promotes a balanced immune response and prevents over-inflammation. Some carotenoids function as

Table 4
HRs (95 % CIs) of all-cause mortality according to quartiles of serum carotenoids concentrations among adults with asthma in NHANES 2001–2006.

	Serum carotenoids (μg/dL)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}
Serum total carotenoids					
Range	<45.26	45.26–62.32	62.33–85.10	>85.10	
No. deaths/total	120/392	100/392	65/391	107/392	
Model 1	1 [Reference]	0.68 (0.50,0.91)	0.39 (0.28,0.56)	0.44 (0.32,0.60)	<0.001
Model 2	1 [Reference]	0.81 (0.59,1.11)	0.50 (0.34,0.74)	0.69 (0.47,0.97)	0.011
Model 3	1 [Reference]	0.81 (0.59,1.11)	0.50 (0.34,0.74)	0.69 (0.47,0.96)	0.011
α-Carotene					
Range	<1.30	1.30–2.40	2.41–4.60	>4.60	
No. deaths/total	106/413	95/372	104/396	87/386	
Model 1	1 [Reference]	0.62 (0.43,0.88)	0.42 (0.32,0.56)	0.33 (0.22,0.50)	<0.001
Model 2	1 [Reference]	0.80 (0.55,1.16)	0.58 (0.40,0.84)	0.55 (0.36,0.84)	0.001
Model 3	1 [Reference]	0.78 (0.54,1.13)	0.57 (0.39,0.83)	0.55 (0.36,0.84)	0.002
β-Carotene					
Range	<7.20	7.20–12.49	12.50–22.25	>22.25	
No. deaths/total	87/395	72/389	107/391	126/392	
Model 1	1 [Reference]	0.74 (0.47,1.18)	0.60 (0.42,0.84)	0.51 (0.36,0.72)	<0.001
Model 2	1 [Reference]	0.93 (0.60,1.46)	0.85 (0.60,1.22)	0.89 (0.61,1.28)	0.450
Model 3	1 [Reference]	0.91 (0.58,1.44)	0.86 (0.60,1.23)	0.88 (0.61,1.27)	0.449
β-Cryptoxanthin					
Range	<4.60	4.61–7.24	7.25–11.20	>11.20	
No. deaths/total	121/397	82/387	105/392	84/391	
Model 1	1 [Reference]	0.71 (0.54,0.95)	0.64 (0.48,0.86)	0.43 (0.30,0.63)	<0.001
Model 2	1 [Reference]	0.89 (0.66,1.20)	0.75 (0.55,1.03)	0.62 (0.42,0.92)	0.004
Model 3	1 [Reference]	0.88 (0.65,1.19)	0.75 (0.55,1.03)	0.62 (0.42,0.92)	0.004
Lutein/zeaxanthin					
Range	<9.60	9.60–13.60	13.61–19.00	>19.00	
No. deaths/total	105/394	92/391	92/391	103/391	
Model 1	1 [Reference]	0.56 (0.41,0.74)	0.42 (0.29,0.62)	0.41 (0.32,0.53)	<0.001
Model 2	1 [Reference]	0.55 (0.41,0.74)	0.51 (0.34,0.76)	0.55 (0.41,0.74)	<0.001
Model 3	1 [Reference]	0.55 (0.40,0.74)	0.50 (0.34,0.75)	0.55 (0.41,0.73)	<0.001
Lycopene					
Range	<14.66	14.66–21.44	21.45–29.00	>29.00	
No. deaths/total	174/392	84/392	75/393	59/390	
Model 1	1 [Reference]	0.52 (0.35,0.76)	0.60 (0.43,0.84)	0.53 (0.35,0.81)	0.004
Model 2	1 [Reference]	0.61 (0.42,0.88)	0.70 (0.51,0.96)	0.72 (0.49,1.05)	0.097
Model 3	1 [Reference]	0.62 (0.43,0.90)	0.72 (0.52,0.98)	0.71 (0.49,1.03)	0.088

Model 1 was adjusted for age (continuous), sex (male or female), and race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black or Other).
Model 2 was adjusted as model 1 plus education level (below high school, high school, or above high school), family poverty income ratio (≤1.0, 1.1–3.0, or >3.0), smoking status (never smoker, former smoker, or current smoker), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), total energy intakes (ln-transformed), physical activity (inactive, insufficiently active, or active), carotenoid supplement use (yes or no), total dietary carotenoid intakes (ln-transformed), self-reported hypertension (yes or no), and self-reported diabetes (yes or no).
Model 3 was adjusted as model 2 plus anti-asthma medication use (yes or no).

nuclear receptor ligands, such as retinoic acid receptors (RARs), which are essential for controlling the expression of genes [51,52]. Carotenoids exert their anti-inflammatory and immunomodulatory actions by activating these receptors, which lessens the severity of asthma symptoms.

This study pioneers an investigation into the correlation between blood carotenoid levels and mortality rates within the asthma community. Several strengths of this research can be highlighted. Firstly, the utilization of the NHANES project's extensive sample dataset enhances the generalizability of the findings, allowing for more accurate conclusions regarding the adults in the United States. Secondly, the accuracy and reliability of the results are ensured by the researchers' implementation of established laboratory techniques for analyzing serum carotenoid levels. Furthermore, our study demonstrates a comprehensive approach by extensively adjusting for various confounding variables. Factors such as dietary variables, nutritional indicators, and inflammatory markers were taken into account, increasing the validity of the study's findings. This study fills an important knowledge gap by exploring the potential link between carotenoid status and susceptibility to mortality in asthma patients. A potential link between antioxidant status, as reflected by carotenoid levels, and health outcomes in asthma individuals was revealed. Therefore, these results could highlight a potential avenue for improving outcomes in asthma management by focusing on dietary or supplemental strategies to enhance carotenoid intake.

Nevertheless, this study does possess certain limitations. Firstly, due to its observational design, establishing a cause-and-effect relationship becomes challenging. The inability to determine whether the observed associations are a result of carotenoid levels or other underlying factors is a notable drawback. Secondly, measuring blood carotenoids at a specific point in time might not accurately represent the effects of continuous exposure to these substances. Longitudinal studies incorporating multiple measurements over time

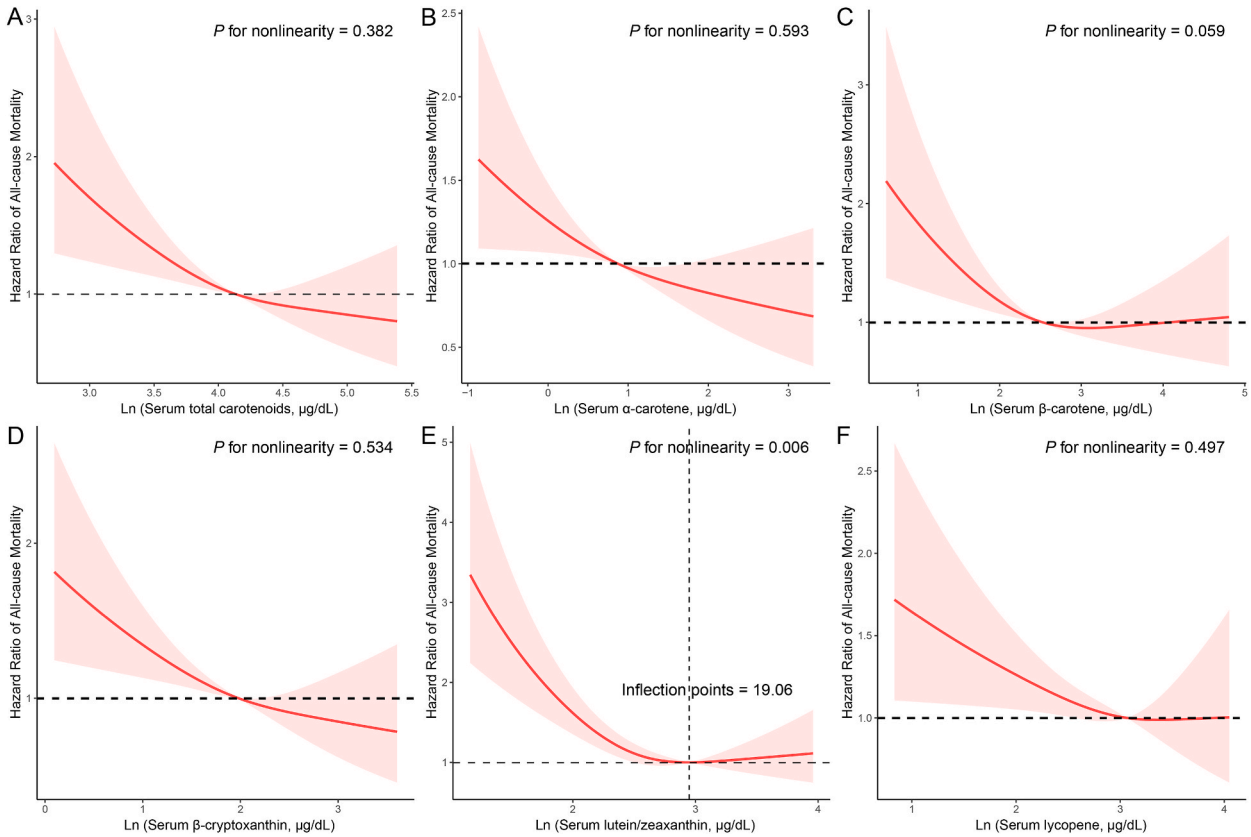

Fig. 2. The exposure-response associations of serum carotenoids and all-cause mortality among adults with asthma by restricted cubic spline (RCS). Model was adjusted for age (continuous), sex (male or female), race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black or Other), education level (below high school, high school, or above high school), family poverty income ratio (≤1.0, 1.1–3.0, or >3.0), smoking status (never smoker, former smoker, or current smoker), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), total energy intakes (ln-transformed), physical activity (inactive, insufficiently active, or active), carotenoid supplement use (yes or no), total dietary carotenoid intakes (ln-transformed), self-reported hypertension (yes or no), self-reported diabetes (yes or no), and anti-asthma medication use (yes or no).

would provide more robust evidence. Thirdly, the study relied on participants' self-reported medical histories to identify asthma cases. This methodology introduces the possibility of misclassification or recall bias, which may affect the accuracy and consistency of the study results. Lastly, despite our efforts to control for various confounding variables, there remains a possibility of residual confounding influencing the observed associations. This could be due to unmeasured or inadequately measured variables that might still exert an influence on the outcomes we have investigated. In conclusion, this study's pioneering examination of the interplay between blood carotenoids and mortality rates among individuals with asthma brings valuable insights. However, acknowledging the study's limitations and emphasizing the need for cross-validation through international studies will bolster the overall impact and credibility of these findings.

5. Conclusion

This study using extensive cohort data from the NHANES project demonstrated a significant association between higher serum carotenoid concentrations and reduced asthma prevalence in US adults. Additionally, elevated serum carotenoid levels were independently linked to a lower risk of all-cause mortality in individuals with asthma, even after accounting for relevant covariates. The findings were further validated through sensitivity analysis. Future research should explore the underlying mechanisms of carotenoids' impact on asthma and mortality, potentially leading to targeted interventions and improved public health strategies.

Ethical approval and consent to participate

All participants provided written informed consent and study procedures were approved by the National Center for Health Statistics Research Ethics Review Board.

Consent to publication

The manuscript is approved by all authors for publication.

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Data availability

NHANES data described in this manuscript are available at https://wwwn.cdc.gov/nchs/nhanes/.

CRediT authorship contribution statement

Guidong Zhang: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Xiaocong Li:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Xiaohe Zheng:** Writing – review & editing, Supervision, Project administration, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24992.

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