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Association between dietary carotenoid intakes and the risk of asthma in adults: a cross-sectional study of NHANES, 2007–2012

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ABSTRACT

Objective To investigate the association between dietary carotenoid intake and asthma using data from a nationally representative sample of US adults.

Design Cross-section study.

Setting The National Health and Nutrition Examination Survey 2007–2012.

Participants A total of 13 039 participants aged 20–80 years (current asthma n=1784, non-current asthma n=11 255) were included in this study.

Primary and secondary outcome measures Asthma was defined by self-report questionnaires. Weighted logistic regression analyses and the smooth curve fittings were performed to explore the association between total carotenoid intake, dietary carotenoid subgenera, including (α-carotene, β-carotene, β-cryptoxanthin, lutein with zeaxanthin and lycopene) and the risk of asthma.

Results The ORs with 95% CIs of dietary α-carotene, dietary β-carotene, dietary β-cryptoxanthin, total lutein with zeaxanthin, total lycopene, dietary carotenoid and total carotenoid intake for individuals with current asthma after adjusting the confounders in model 3 were 0.80 (0.67 to 0.95), 0.67 (0.57 to 0.79), 0.68 (0.55 to 0.85), 0.77 (0.61 to 0.98), 0.71 (0.57 to 0.87), 0.75 (0.59 to 0.96) and 0.61 (0.48 to 0.76) in the highest versus lowest quartile, respectively. The smooth curve fittings suggested a non-linear relationship between total carotenoid intake and the risk of current asthma.

Conclusions Higher intake of a-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein with zeaxanthin and total carotenoid were associated with lower odds of having current asthma in the US adults. This is a cross-sectional study and no causal relationship can be drawn, so caution is needed to interpret the results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study used a larger and nationally representative sample of the US adult population.
⇒ This study first showed the linear and non-linear relationship between carotenoids' intakes and the risk of asthma.
⇒ This study controlled more confounding factors.
⇒ This study was limited by its cross-sectional design, and no causal relationship could be drawn.
⇒ There might be some bias, because the definition of asthma and dietary carotenoid intake was obtained from self-reports.

INTRODUCTION

Asthma is a common airway inflammatory disease in adults and children affecting approximately 3.58 million people worldwide.[1] Due to environmental and lifestyle changes, the incidence of asthma has increased over the past few decades, with an additional 100 million asthma diagnoses expected by 2025.[2] Due to frequent exacerbations, hospitalisations and comorbidity management, asthma increases healthcare costs and this causes a poor quality of life for patients. Therefore, identifying the modifiable risk factors for the incidence and morbidity of this disease is necessary to decrease the disease burden of asthma.

Chronic airway inflammation and airway hyper-responsiveness are asthma's main pathological features. Increasing evidence showed that oxidative stress is involved in the pathophysiological mechanism of asthma and implicated in the inflammation and severity of asthma.[3–5] Dietary epidemiological evidence suggests that Western diets, characterised by high intake of saturated fats and simple sugars, are related to an increased incidence of asthma.[6 7] While Mediterranean diets, characterised by an intake of plant-based foods (mainly vegetables and fruits), may reduce the risk of asthma through its antioxidant and anti-inflammatory effects.[8]

Carotenoids, widely found in fruits, vegetables and seaweed species, have anti-inflammatory and antioxidative stress effects and have proved to be related to hypertension, non-alcoholic fatty liver disease, cancer and other chronic diseases.[9–13] A few previous studies have reported the correlation between carotenoids and asthma. The result from a cross-sectional study of 68 535 women

indicated that increased intakes of carotene, tomatoes and carotenoid-rich vegetables were related to a lower risk of asthma.[14] Two small-sample randomised controlled studies showed that lower carotenoid intakes were associated with a higher risk of asthma, and modifying the dietary intake of carotenoids can affect clinical outcomes in patients with asthma.[15 16] Also, dietary and serum carotenoids have also been associated with improved lung function in other studies.[17 18] Conversely, from a meta-analysis of five cross-sectional studies, there was no association between higher dietary intake of β-carotene and asthma and forced expiratory volume in 1 s.[19] However, the results were controversial. Most of those studies only focused on the association between dietary carotenoids and asthma, and few evaluated the effect of supplementary carotenoids. Besides, the associations with age, gender and other individual characteristics are not well described and analysed. Therefore, in this study, we aimed to explore the relationship between all kinds of dietary carotenoid intake and asthma using data from the National Health and Nutrition Examination Survey (NHANES) (2007–2012), which provided a representative sample of the US population.

MATERIALS AND METHODS

Data source

This was a cross-sectional study. All the data used for analysis were freely available and obtained from NHANES 2007–2012, which were conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC).[20]

Participants

This study included adults older than 20 years from three independent cross-sectional waves (including 2007–2008, 2009–2010 and 2011–2012). Individuals who did not participate in the asthma survey or did not have the reliable two 24-hour dietary recall data were excluded. Additionally, participants with missing data on body mass index (BMI), asthma, carotenoids and total energy intake and those with extreme total energy intake (female: <600 or >6000 kcal/day; male: <800 or >8000 kcal/day) were excluded from our study population.

Asthma

The asthma information was collected using a self-administered questionnaire, completed at the clinic visit. Individuals with current asthma were defined as affirmative responses to both of the following questions: 'Has a doctor or other health professionals ever told you that you have asthma?' and 'In the past 12 months (have you/has SP) had wheezing or whistling in (your/his/her) chest?'. Control subjects were defined as participants without current asthma who answered 'NO' to either question.

Dietary carotenoid intake

In every NHANES cycle, two 24-hour dietary recall interviews, which recorded the detailed dietary information about the participants, were used to estimate various nutrients and total energy intake. The first diet recall interview was conducted in person in the Mobile Examination Center, recording the type and amount of all food and beverages consumed 24 hours before the interview. The second was conducted by telephone 3–10 days later. Each participant reported the detailed information about the types and amounts of individual food. They used a set of measuring guides (various glasses, bowls, mugs, drink boxes, bottles, etc) to estimate the amounts of food. The dietary recall's examination protocol and data collection methods are fully documented in the NHANES dietary interviewers' procedure manuals.[21] Data for carotenoid and other nutrients examined were from the US Department of Agriculture Food and Nutrient Database for Dietary Studies database for NHANES.[22] The food and drinks nutrient values were calculated using 'what are we eating in the United States'.[23 24]

In this study, the dietary intakes of a-carotene, β-carotene, β-cryptoxanthin, lycopene and lutein with zeaxanthin were calculated by averaging over the two recall periods. In each NHANES cycle, the supplement intakes of lycopene and lutein with zeaxanthin were also collected during the same two 24 hours. For this study, the intakes from supplements were also averaged over 2 days, and the intakes of total lycopene and lutein with zeaxanthin were calculated as the sum of dietary and supplement intakes. The dietary carotenoid intake was the sum of the intakes of dietary a-carotene, dietary β-carotene, dietary β-cryptoxanthin, dietary lycopene and dietary lutein with zeaxanthin. The total carotenoid intake was the sum of the dietary and supplement carotenoid intakes. Total carotenoid intakes were adjusted by weight (mg/kg per day) and categorised into quartiles.

C reactive protein

Serum C reactive protein (CRP), a biomarker of systemic inflammation, was measured and quantified using latex-enhanced nephelometry.[25] The minimum limit of detection was 0.02 mg/dL. For this study, serum CRP levels were available from two of the NHANES cycles (2007–2008 and 2009–2010).

Other covariates

For this analysis, the following covariates were collected: age, gender, ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black and other/multiracial), marital status (married, living with partner, divorced, widowed, never married and separated), education level (less than high school, high school or more than high school), poverty income ratio which was used to reflect family income, BMI, smoking status, asthma medication, total energy, total fat and dietary fibre. These covariates were selected based on the previous literature.[17 18 26–30]

Table 1 Characteristics of the study population by quartile of total carotenoids (diet and supplement) intake levels

Total carotenoids (Diet and supplement)	Quartile 1 <41.43 (μg/kg per day)	Quartile 2 ≥41.46–<86.75 (μg/kg per day)	Quartile 3 ≥86.75–<165.58 (μg/kg per day)	Quartile 4 ≥165.59 (μg/kg per day)	P value
	n=3260	n=3259	n=3260	n=3260	
Age (continuous)	50.23±17.61	49.58±17.70	49.79±17.47	49.53±17.93	0.822
Age					0.881
<40	1021 (31.32%)	1078 (33.08%)	1071 (32.85%)	1135 (34.82%)	
≥40–<60	1111 (34.08%)	1093 (33.54%)	1109 (34.02%)	1046 (32.09%)	
≥60	1128 (34.60%)	1088 (33.38%)	1080 (33.13%)	1079 (33.10%)	
Gender					0.196
Male	1614 (49.51%)	1659 (50.91%)	1585 (48.62%)	1547 (47.45%)	
Female	1646 (50.49%)	1600 (49.09%)	1675 (51.38%)	1713 (52.55%)	
Race/ethnicity					**<0.001**
Mexican American	440 (13.50%)	525 (16.11%)	550 (16.87%)	426 (13.07%)	
Other Hispanic	324 (9.94%)	330 (10.13%)	320 (9.82%)	315 (9.66%)	
Non-Hispanic white	1442 (44.23%)	1540 (47.25%)	1545 (47.39%)	1608 (49.33%)	
Non-Hispanic black	898 (27.55%)	652 (20.01%)	568 (17.42%)	571 (17.52%)	
Other/Multiracial	156 (4.79%)	212 (6.51%)	277 (8.50%)	340 (10.43%)	
Education level					0.773
Less than high school	1041 (31.93%)	863 (26.48%)	741 (22.73%)	640 (19.63%)	
High school	831 (25.49%)	765 (23.47%)	731 (22.42%)	638 (19.57%)	
More than high school	1386 (42.52%)	1625 (49.86%)	1786 (54.79%)	1976 (60.61%)	
Missing	2 (0.06%)	6 (0.18%)	2 (0.06%)	6 (0.18%)	
Marital status (%)					0.717
Married	1578 (48.42%)	1747 (53.65%)	1800 (55.21%)	1765 (54.19%)	
Widowed	284 (8.71%)	248 (7.62%)	263 (8.07%)	247 (7.58%)	
Divorced	403 (12.37%)	332 (10.20%)	333 (10.21%)	318 (9.76%)	
Separated	111 (3.41%)	125 (3.84%)	97 (2.98%)	89 (2.73%)	
Never married	641 (19.67%)	555 (17.05%)	520 (15.95%)	597 (18.33%)	
Living with partner	1578 (48.42%)	1747 (53.65%)	1800 (55.21%)	1765 (54.19%)	
Family income (poverty income ratio, PIR)	2.22±1.53	2.48±1.63	2.68±1.64	2.80±1.68	**<0.001**
Body mass index (kg/m^2)	31.10±7.77	29.71±6.55	28.78±6.44	26.78±5.47	**<0.001**
CRP (2007–2010) (mg/dL)	0.40±0.42	0.33±0.37	0.31±0.36	0.27±0.35	**<0.001**
Smoking status					**<0.001**
Never	1620 (49.69%)	1726 (52.96%)	1858 (56.99%)	1902 (58.34%)	
Current	790 (24.23%)	861 (26.42%)	833 (25.55%)	820 (25.15%)	
Former	850 (26.07%)	670 (20.56%)	567 (17.39%)	537 (16.47%)	
Missing	0 (0.00%)	2 (0.06%)	2 (0.06%)	1 (0.03%)	
Current asthma	595 (18.25%)	431 (13.22%)	414 (12.70%)	344 (10.55%)	**<0.001**
Total energy (kcal/day)	1859.78±668.36	2044.24±742.70	2133.78±762.11	2272.14±852.48	**<0.001**
Dietary fibre (g)	12.62±6.72	15.81±7.55	18.29±8.04	22.06±9.93	**<0.001**
Total fat (g)	69.51±31.86	76.98±34.75	79.50±35.46	82.98±39.53	**<0.001**
Asthma medication	25 (0.77%)	18 (0.55%)	36 (1.10%)	36 (1.10%)	0.063

Mean±SD for continuous variables: p value was calculated by weighted linear regression model; per cent for categorical variables. P value was calculated by weighted χ^2 test.
Significant values are highlighted in bold.
CRP, C reactive protein.

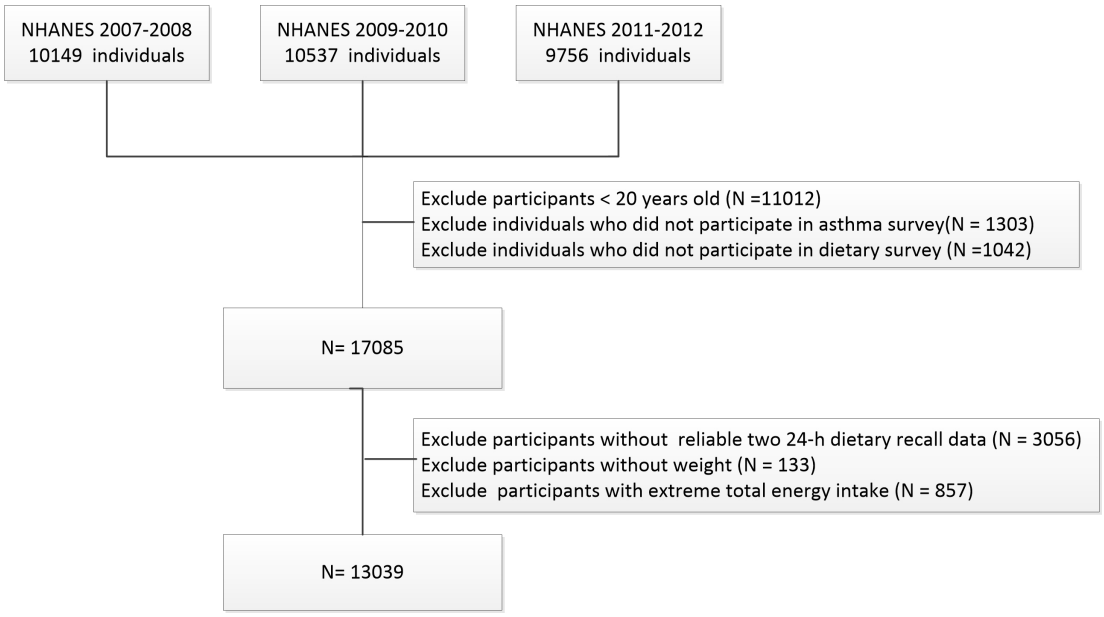

Figure 1 Flow chart of the current study. NHANES, National Health and Nutrition Examination Survey.

Smoking status included never smoking, former smoking defined as 'smoked at least 100 cigarettes in a lifetime but does not currently smoke' and current smoking defined as 'smoked at least 100 cigarettes in a lifetime and currently smokes'. Asthma medication was obtained through a questionnaire in which participants were asked: 'if they had taken any prescribed medications in the past month'. The asthma medication included inhaled corticosteroids, leukotriene modifiers, long-acting beta agonists, combination inhalers and methylxanthines. Total energy, total fat and dietary fibre were also obtained from the average of two 24-hour dietary recall interviews.

Statistical analysis

We used the Strengthening the Reporting of Observational Studies in Epidemiology cross-sectional checklist when writing our report.[31] In this study, percentages were used to present the categorical variables, while mean±SD or medians (IQR) were used to present the continuous variables. All the variables were compared among different groups using the weighted χ^2 tests when they were categorical variables, and the weighted linear regression models when they were continuous variables.[32 33]

In each model, a weight suggested by the CDC was used to consider the oversampling of minority and thus provide an accurate estimate of effects for the population. Weighted multivariate logistic regression models were used to explore the relationships between dietary carotenoid intake and current asthma. For this study, three sequential models (model 1: non-adjusted model; model 2: adjusted for age, gender and race; model 3: adjusted for all covariates) were used to control potential confounders. Then, a generalised additive model and the smooth curve fittings were used to evaluate the non-linearity of dietary carotenoid intake and current asthma after adjustment for similar covariates in the model 3. Additionally, subgroup and interaction analyses of the relationship between total carotenoid intake and the risk of current asthma have been conducted to determine whether each subgroup's results were stable.

The EmpowerStats software (www.empowerstats.com V.R.3.4.3) and the statistical software package R were used to process and analyse all our data. A two-tailed p value <0.05 was considered statistically significant.

Participants and public involvement

Participants were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Participants' characteristics

A total of 13 039 participants were included in this study. The characteristics of the study population are shown in table 1 and the flowchart of study cohort selection is shown in figure 1. The average age of the study participants was 49.78±17.68 years, and 49.12% of participants were male. Subjects with a higher dietary total carotenoid intake were more likely to be non-Hispanic white and other/multiracial. They had lower BMIs, lower smoking prevalence, lower serum CRP and lower prevalence of current asthma compared with those with a lower dietary total carotenoid intake (p<0.001). Additionally, participants in the higher total carotenoid intake groups had higher family income, higher energy, higher fat and dietary fibre intake than lower carotenoid intake groups (p<0.001).

Approximately, 1784 (13.68%) were classified as having current asthma based on a self-administered questionnaire. Intake of all kinds of carotenoids in participants with current asthma was lower than those without current

Table 2 Weighted ORs and 95% CIs for current asthma according to quartiles of carotenoids intakes

	Cut-off (μg/kg per day)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	P value for trend
α-carotene (diet)					
Quartile 1	<0.34	Referent	Referent	Referent	0.087
Quartile 2	≥0.34–<1.26	**0.70 (0.60 to 0.81)**	**0.70 (0.60 to 0.81)**	**0.79 (0.67 to 0.93)**	
Quartile 3	≥1.26–<6.29	**0.76 (0.64 to 0.89)**	**0.75 (0.64 to 0.88)**	0.91 (0.75 to 1.11)	
Quartile 4	≥6.29	**0.57 (0.51 to 0.68)**	**0.58 (0.50 to 0.67)**	**0.80 (0.67 to 0.95)**	
β-carotene (diet)					
Quartile 1	<5.66	Referent	Referent	Referent	**<0.001**
Quartile 2	≥5.66–<14.54	**0.73 (0.59 to 0.91)**	**0.73 (0.59 to 0.90)**	**0.77 (0.63 to 0.96)**	
Quartile 3	≥14.54–<36.58	**0.65 (0.52 to 0.80)**	**0.64 (0.51 to 0.79)**	**0.77 (0.60 to 0.98)**	
Quartile 4	≥36.58	**0.49 (0.42 to 0.58)**	**0.47 (0.40 to 0.55)**	**0.67 (0.57 to 0.79)**	
β-cryptoxanthin (diet)					
Quartile 1	<0.18	Referent	Referent	Referent	**<0.001**
Quartile 2	≥0.18–<0.55	**0.82 (0.69 to 0.98)**	**0.82 (0.69 to 0.99)**	0.87 (0.71 to 1.07)	
Quartile 3	≥0.55–<1.34	**0.69 (0.59 to 0.81)**	**0.69 (0.59 to 0.81)**	**0.77 (0.64 to 0.92)**	
Quartile 4	≥1.34	**0.58 (0.49 to 0.70)**	**0.59 (0.49 to 0.71)**	**0.68 (0.55 to 0.85)**	
Lycopene (diet)					
Quartile 1	<9.75	Referent	Referent	Referent	**0.018**
Quartile 2	≥9.75–<33.03	0.82 (0.63 to 1.07)	0.84 (0.65 to 1.10)	0.93 (0.72 to 1.20)	
Quartile 3	≥33.03–<84.82	**0.69 (0.57 to 0.82)**	**0.71 (0.59 to 0.86)**	**0.80 (0.66 to 0.97)**	
Quartile 4	≥84.82	**0.69 (0.55 to 0.86)**	**0.71 (0.57 to 0.89)**	**0.78 (0.62 to 0.99)**	
Lutein with zeaxanthin (diet)					
Quartile 1	<5.56	Referent	Referent	Referent	**0.002**
Quartile 2	≥5.56–<10.15	**0.72 (0.62 to 0.84)**	**0.73 (0.62 to 0.85)**	**0.80 (0.67 to 0.95)**	
Quartile 3	≥10.15–<20.02	**0.69 (0.57 to 0.84)**	**0.69 (0.57 to 0.84)**	**0.75 (0.61 to 0.92)**	
Quartile 4	≥20.03	**0.56 (0.48 to 0.66)**	**0.54 (0.46 to 0.64)**	**0.70 (0.57 to 0.86)**	
Total carotene (diet)					
Quartile 1	<40.25	Referent	Referent	Referent	**0.016**
Quartile 2	≥40.25–<84.70	**0.75 (0.62 to 0.90)**	**0.76 (0.63 to 0.92)**	0.87 (0.70 to 1.07)	
Quartile 3	≥84.70–<162.07	**0.64 (0.53 to 0.77)**	**0.65 (0.54 to 0.78)**	**0.80 (0.66 to 0.98)**	
Quartile 4	≥162.07	**0.53 (0.44 to 0.63)**	**0.53 (0.44 to 0.63)**	**0.75 (0.59 to 0.96)**	
Total lycopene (diet and supplement)					
Quartile 1	<10.64	Referent	Referent	Referent	**0.017**
Quartile 2	≥10.64–<34.09	0.84 (0.65 to 1.10)	0.86 (0.66 to 1.12)	0.94 (0.73 to 1.22)	
Quartile 3	≥34.09–<85.93	**0.70 (0.59 to 0.82)**	**0.72 (0.61 to 0.86)**	**0.80 (0.67 to 0.97)**	
Quartile 4	≥85.93	**0.69 (0.55 to 0.86)**	**0.71 (0.57 to 0.89)**	**0.77 (0.61 to 0.98)**	
Total lutein with zeaxanthin (diet and supplement)					
Quartile 1	<5.87	Referent	Referent	Referent	**0.002**
Quartile 2	≥5.87–<10.78	**0.77 (0.64 to 0.91)**	**0.77 (0.64 to 0.92)**	0.83 (0.68 to 1.01)	
Quartile 3	≥10.79–<21.23	**0.66 (0.54 to 0.81)**	**0.65 (0.53 to 0.80)**	**0.73 (0.58 to 0.91)**	
Quartile 4	≥21.24	**0.56 (0.48 to 0.66)**	**0.53 (0.45 to 0.64)**	**0.71 (0.57 to 0.87)**	
Total carotene (diet and supplement)					
Quartile 1	<41.43	Referent	Referent	Referent	**<0.001**
Quartile 2	≥41.46–<86.75	**0.69 (0.57 to 0.84)**	**0.70 (0.57 to 0.85)**	**0.78 (0.65 to 0.95)**	
Quartile 3	≥86.75–<165.58	**0.64 (0.54 to 0.76)**	**0.64 (0.54 to 0.77)**	**0.77 (0.63 to 0.94)**	

Continued

Table 2 Continued

	Cut-off (μg/kg per day)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	P value for trend
Quartile 4	≥165.59	**0.51 (0.43 to 0.61)**	**0.51 (0.42 to 0.61)**	**0.61 (0.48 to 0.76)**	

Significant values are highlighted in bold.
Model 1: non-adjusted model.
Model 2: adjusted for age (continuous), gender, race (non-Hispanic white, black, Mexican American, other Hispanic, other race/ethnicity).
Model 3: adjusted for age (continuous), gender, race (non-Hispanic white, black, Mexican American, other Hispanic or other race/ethnicity), education (less than high school, high school, more than high school or mission), marital status (married, widowed, divorced, separated, never married or living with partner), family Income (continuous), smoking status (never, current or former), intake energy (continuous), total fat (continuous), dietary fibre (continuous) and asthma medication.

asthma. Subjects with current asthma also had higher BMI and CRP levels, and lower dietary fibre intake (online supplemental table S1).

Association between dietary carotenoid intakes and the risk of current asthma

The weighted ORs with 95% CIs of asthma by quartiles of dietary carotenoids and their total are shown in table 2. In model 1 without adjustment, there were significant negative associations between different kinds of dietary carotenoid intakes and asthma (OR with 95% CI in the highest vs lowest quartiles: dietary α-carotene, 0.57 (0.51 to 0.68); dietary β-carotene, 0.49 (0.42 to 0.58); dietary β-cryptoxanthin, 0.58 (0.49 to 0.70); dietary lycopene, 0.69 (0.55 to 0.86); dietary lutein with zeaxanthin, 0.56 (0.48 to 0.66); dietary carotenoid, 0.53 (0.44 to 0.63); total lycopene, 0.69 (0.55 to 0.86); total lutein with zeaxanthin, 0.56 (0.48 to 0.66) and total carotenoid, 0.51 (0.43 to 0.61), respectively). After adjusting age, gender and race in model 2 and after adjusting all the confounding factors in model 3, the results remained stable and statistically significant. The trend test also showed significant associations between intake of all other carotenoids except for dietary α-carotene as well as the risk of current asthma.

Additionally, weighted generalised additive models and smooth curve fittings were used to visually assess the relationships between the intakes of all carotenoids and the risk of current asthma, which are presented in figure 2. The results showed that the intakes of all carotenoids were negatively associated with the risk of current asthma in the adjusted models.

Furthermore, the relationship between the supplement carotenoid intakes and the risk of asthma was analysed (online supplemental table S2). In this study, there were 1905 and 1724 participants, received supplement lycopene and supplement lutein/zeaxanthin, respectively. A total of 2099 participants received supplement carotenoid. Participants with current asthma had lower supplement carotenoid intakes than participants without current asthma (3.51±38.52 μg/kg per day vs 3.56±35.12 μg/kg per day, p<0.001). After adjusting for all the confounding factors, participants with supplement carotenoid intakes had a lower risk of asthma (OR 95% CI 0.76 (0.60 to 0.96), p=0.030).

Subgroup analyses

According to age and gender, the stratified analyses were performed to further analyse the relationship of total carotenoid intake and the risk of current asthma in each subgroup, shown in table 3. In stratified analyses according to age, all levels of total carotenoid intake were significantly and negatively associated with the risk of asthma across all age groups in model 1 (unadjusted model). In model 3, which adjusted for all confounders, the risk of asthma was still significantly lower in the third and fourth versus the first quartile analysis among participants aged 40–59 years. Stratified according to gender, females had a significant association between all levels of total carotenoid intake and a decreased risk of current asthma in all the models. In male, the third quartile of total carotenoid intake was associated with decreased risk of asthma in model 1 and model 2. Additionally, for the highest quartile of total carotenoid intakes, there was a significant association with decreased risk of asthma in all three models. The interaction analyses indicated that age and gender insignificantly affected these associations (p value for interaction >0.05).

The subgroup analyses for the relationship between total carotenoid intake and the risk of asthma stratified according to race and smoking status are shown in online supplemental tables S3 and S4. The results showed that in different subgroups, the relationship between the highest quartile of total carotenoid intake and the decreased risk of current asthma stably existed after careful adjustments, except for other Hispanic and other/multiracial participants. The interaction terms in these stratified analyses were insignificant.

Association between dietary carotenoid intake and serum CRP

Figure 3 shows the distribution of serum CRP levels according to quartile of total carotenoid intake in total subjects, non-current subjects with asthma and current subjects with asthma. The results suggested that CRP levels were lower for subjects with a higher dietary total

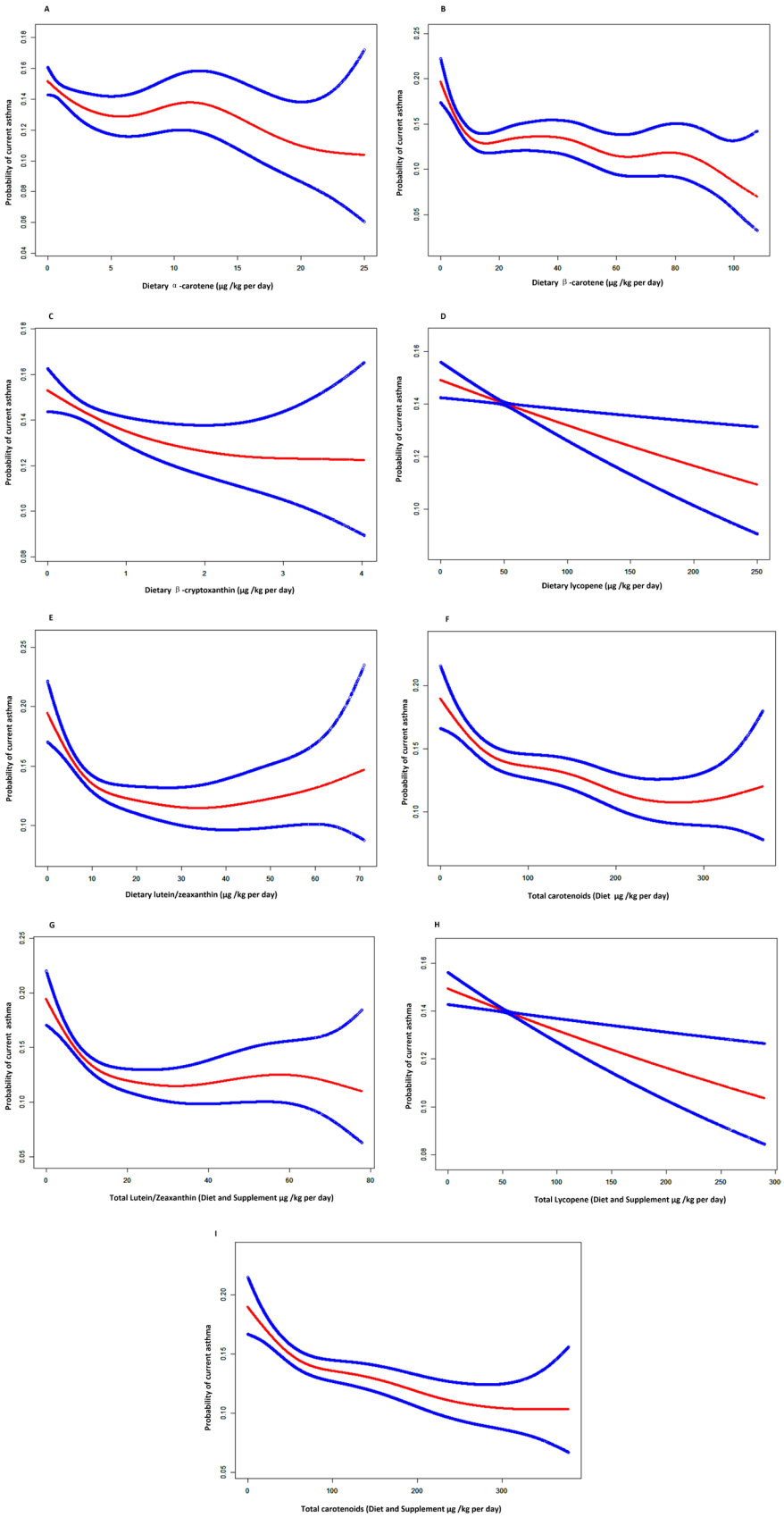

Figure 2 The adjusted smoothed plots between carotenoid intakes and current asthma based on two-piece-wise regression model. (A–I) The non-linear or linear relationships between α-carotene, β-carotene, β-cryptoxanthin, dietary lycopene, dietary lutein with zeaxanthin, dietary carotenoid intakes, total lutein with zeaxanthin, total lycopene and total carotenoid intakes. Adjusted for age, gender, race, education, marital status, family income, smoking status, intake energy, total fat, dietary fibre and asthma medication. The red and blue line represent the estimated values and their corresponding 95% CIs.

Table 3 Weighted ORs (95% CIs) for current asthma according to quartiles of total carotenoids intake, stratified by age and gender

Total carotenoid (diet and supplement)	Model 1	Model 2	Model 3	P value for interaction
	OR 95% CI, p value	OR 95% CI, p value	OR 95% CI, p value	
Age				0.634
20–39 years old				
Quartile 1	Referent	Referent	Referent	
Quartile 2	**0.68 (0.50 to 0.93), 0.021**	**0.68 (0.50 to 0.94), 0.022**	0.79 (0.56 to 1.12), 0.197	
Quartile 3	**0.66 (0.48 to 0.91), 0.016**	**0.67 (0.49 to 0.92), 0.017**	0.79 (0.55 to 1.12), 0.201	
Quartile 4	**0.55 (0.41 to 0.75), <0.001**	**0.55 (0.40 to 0.75), <0.001**	0.66 (0.44 to 1.00), 0.064	
40–59 years old				
Quartile 1	Referent	Referent	Referent	
Quartile 2	**0.71 (0.52 to 0.99), 0.047**	0.72 (0.52 to 1.01), 0.066	0.78 (0.56 to 1.07), 0.136	
Quartile 3	**0.58 (0.45 to 0.77), <0.001**	**0.59 (0.45 to 0.78), <0.001**	**0.71 (0.53 to 0.95), 0.031**	
Quartile 4	**0.44 (0.33 to 0.59), <0.001**	**0.44 (0.32 to 0.59), <0.001**	**0.49 (0.34 to 0.70), <0.001**	
≥60 years old				
Quartile 1	Referent	Referent	Referent	
Quartile 2	**0.67 (0.53 to 0.86), 0.003**	**0.67 (0.53 to 0.87), 0.004**	0.80 (0.61 to 1.06), 0.131	
Quartile 3	**0.71 (0.52 to 0.97), 0.037**	**0.71 (0.52 to 0.97), 0.039**	0.88 (0.61 to 1.26), 0.495	
Quartile 4	**0.61 (0.45 to 0.82), 0.002**	**0.60 (0.46 to 0.81), 0.002**	0.77 (0.52 to 1.13), 0.195	
Gender				0.1703
Male				
Quartile 1	Referent	Referent	Referent	
Quartile 2	0.72 (0.52 to 1.01), 0.061	0.73 (0.52 to 1.01), 0.067	0.83 (0.59 to 1.18), 0.312	
Quartile 3	**0.74 (0.56 to 0.97), 0.037**	**0.75 (0.57 to 0.98), 0.044**	0.88 (0.64 to 1.20), 0.438	
Quartile 4	**0.57 (0.42 to 0.77), <0.001**	**0.58 (0.43 to 0.77), <0.001**	**0.67 (0.45 to 0.96), 0.039**	
Female				
Quartile 1	Referent	Referent	Referent	
Quartile 2	**0.67 (0.52 to 0.87), 0.004**	**0.68 (0.53 to 0.88), 0.005**	**0.74 (0.58 to 0.95), 0.027**	
Quartile 3	**0.56 (0.45 to 0.70), <0.001**	**0.57 (0.45 to 0.71), <0.001**	**0.67 (0.55 to 0.86), <0.001**	
Quartile 4	**0.46 (0.36 to 0.61), <0.001**	**0.46 (0.35 to 0.61), <0.001**	**0.56 (0.41 to 0.75), <0.001**	

Each subgroup analyses adjusted for all other variables except its own.
Significant values are highlighted in bold.
Model 1: non-adjusted model.
Model 2: adjusted for age (continuous), gender, race (non-Hispanic white, black, Mexican American, other Hispanic, other race/ethnicity).
Model 3: adjusted for age (continuous), gender, education (less than high school, high school, more than high school or mission), marital status (married, widowed, divorced, separated, never married or living with partner), family Income (continuous), smoking status (never, current or former), intake energy (continuous), total fat (continuous), dietary fibre (continuous) and asthma medication.

carotenoid intake than those with a lower dietary total carotenoid intake. Among the total subjects with different grades of total carotenoid intake, CRP levels varied significantly (medium (Q1–Q3)), quartile 1: 0.26 (0.11–0.58), quartile 2: 0.20 (0.08–0.46), quartile 3: 0.18 (0.07–0.41), quartile 4: 0.14 (0.06–0.34), respectively (p<0.001). Additionally, the results were similar among subjects with current asthma or without current asthma.

DISCUSSION

In this cross-sectional analysis, we used data from three waves of the NHANES (2007–2012) to investigate the relationship between dietary intakes of carotenoids (including α-carotene, β-carotene, β-cryptoxanthin, lutein with zeaxanthin, lycopene, dietary carotenoid and total carotenoid) and the risk of current asthma. To our knowledge, this is the first study to comprehensively examine the associations between different kinds of carotenoid intakes and the risk of current asthma, focusing on the general population. It was found that all carotenoid intakes were associated with lower odds of having current asthma. After adjusting for age, sex, race and other potential confounding factors, these relationships remained significant. The results of generalised additive models and smooth curve fittings showed non-linear relationships between α-carotene, β-carotene, β-cryptoxanthin, lutein with zeaxanthin, total carotenoid intake and the risk of current asthma, as well as a linear relationship

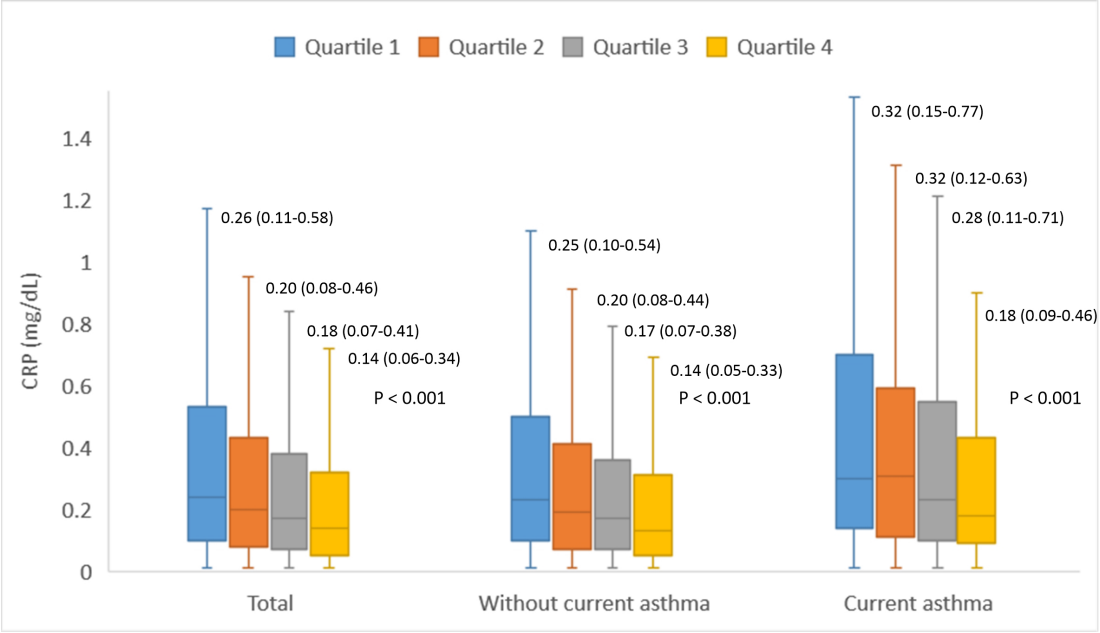

Figure 3 Levels of serum CRP according to quartile of total carotenoid intake. Boxplot shows the median (bar), the first and third quartiles (box) and the 1 s and 99th percentiles (whiskers) for each group. Data are presented as medians (Q1–Q3). P value was calculated by weighted linear regression model. CRP, C reactive protein.

between lycopene intake and the risk of current asthma. In the stratified analysis, a stronger association was found between total carotenoid intake and the risk of asthma in the age group of 40–59 years old, and in non-Hispanic white, black and Mexican American adults. Additionally, the CRP levels were lower in subjects with a higher carotenoid intake than in those with lower carotenoid intake.

Asthma is a chronic disease characterised by airway inflammation and airway hyper-responsiveness. Physiological damage caused by oxidative stress through reactive oxygen species (ROS) attack plays an important role in the chronic inflammation of asthma.[34] ROS increases the vagal tone by decreasing β-adrenaline function, resulting in airway hyper-responsiveness.[35] ROS induces the contraction of airway smooth muscles by increasing acetylcholine and promotes the histamine release from mast cells and the mucus secretion from airway epithelial cells.[36 37] Additionally, excessive ROS production may cause an imbalance of respiratory antioxidants/oxidants, leading to the emergence and persistence of pulmonary fibrosis induced by transforming growth factor-β1.[38] So, pulmonary and systemic oxidative stress increases the inflammatory response associated with asthma and allergies.[39] Carotenoids as diet-derived antioxidants have antioxidant effects and can lower ROS activities, thereby reducing airway inflammation and improving lung function in patients with asthma. Previous studies have shown that β-carotene can scavenge the highly reactive free radical superoxide anions and donate an electron to reduce free radical molecules, preventing oxidative damage.[8 40] Additionally, lycopene suppresses Th2 responses, reduce eosinophilic infiltrates the lungs, and ovalbumin-induced airway inflammation in an animal model of allergic asthma.[41 42] In our study, the results showed that total carotenoid intake was negatively associated with CRP levels in the peripheral blood of participants. CRP can be significantly elevated in the airways and peripheral blood of patients with asthma from previous study.[43] Therefore, we hypothesise that carotenoids may promote asthma prevention through general anti-inflammatory and antioxidant capabilities.

Several meta-analyses have suggested that fruit and vegetable consumption may reduce the risk of asthma due to their antioxidant effects.[27 28] There are also some studies suggesting that the Mediterranean diet that is rich in vegetables and fruits, correlated negatively with the risk of asthma compared with the Western diet.[6 7] As vegetables and fruits are the main sources of carotenoids, these studies indirectly suggested that carotenoid intakes reduce asthma risk. Two previous studies on serum antioxidant levels and asthma risk using NHANES (1988–1994) among children and adults, respectively, showed that low serum carotenoid levels increased the risk of asthma in children, but there were no differences of serum carotenoid levels in adults.[30 44]

Another result from a large E3N study of 68 535 French women showed that increased consumption of tomatoes, carrots and leafy vegetables (rich in carotenoids) was associated with a lower risk of asthma in women.[14] Recently, a cross-sectional observational study of 158 adolescents found that obese asthmatics had the lowest serum total carotenoid levels compared with healthy weight asthmatics and healthy weight controls. They speculated that carotenoids might have a protective effect on metabolic health and lung function in obese asthmatic patients.[45] Results from both a randomised controlled[46] and a case–controlled study[29] showed that dietary supplementation or adequate intake of lycopene-rich foods may be beneficial in subjects with asthma, improving lung function and decreasing serum CRP

levels in patients with asthma. Contrastly, a meta-analysis,[19] which included five observational studies, suggested that high dietary β-carotene intake was not associated with the risk of asthma and lung function. However, all five studies included only β-carotene, without other types of carotene consumption, and two studies lacked adjustment for the potentially important confounding factors.

In subgroup analysis, although the associations between the carotenoid intake and the risk of asthma were stronger in the 40–59 age group, in non-Hispanic white, black and Mexican American groups, the results of the interaction were not significant. In the NHANES database, the prevalence of asthma and serum carotenoid levels varied among race groups, and their relationships with race varied.[47 48] It is unclear why the associations were different among races. We speculate that the variability may be due to other potentially confounding factors which are difficult to assess (eg, exercise and dietary patterns). Also, the potential mechanism why the association between carotenoids and asthma would be stronger in the 40–59 age is unclear. This could be a chance finding, and more research is needed to explain the relationship.

Our study used a larger and nationally representative NHANES database to investigate the association between the intake of multiple carotenoids singly and in combination and the risk of asthma. We also adjusted for more potential confounders than previous studies, including modifications of lumped dietary fibre and fatty acids, which are reported to be associated with the risk of asthma.[26 49] Additionally, a generalised additive model and smooth curve fitting were used to show the linear and non-linear relationship between the intake of carotenoids and the risk of current asthma. These are improvements on previous studies.

This study had some limitations. First, in the NHANES database, the carotenoid data were derived from two 24-hour food recalls collected after asthma diagnosis. We lacked dietary intake data before asthma diagnosis. Whether carotenoid intake increased the asthma risk or whether carotenoid intake was altered by disease after asthma onset was unclear. Therefore, we could not establish a causal relationship between carotenoid intake and asthma risk. Prospective studies are also needed and are able to establish a causal relationship between carotenoid intake and asthma risk, and the molecular and physiological mechanisms behind it need to be further studied and clarified. Second, the average carotenoid intakes in this study were calculated using two 24-hour dietary recalls, so there may be recall bias. Additionally, we used a self-reported scale instead of lung function to identify participants with asthma, which may lead to misclassification. Third, although we found CRP levels were lower in subjects with higher total carotenoid intake, the difference in the absolute CRP value was very small among all four quartiles, and this may only have a very minor biological impact. Additionally, we lacked the information on active infection and medication, which can alter CRP levels and affect the result's accuracy. Therefore, it may be necessary to investigate the relationship between other inflammatory factors and carotenoid intake in the future in order to speculate on the underlying mechanisms. Fourth, we lacked the data of participants' serum or skin carotenoid levels to further analyse whether serum carotenoids were associated with asthma risk. Fifth, there was the possibility of disease-related modification of consumption, which could not be tested and might affect the accuracy of the results. Sixth, although we adjusted some confounding factors, there were still some potentially unknown confounding factors that may affect our results.

CONCLUSION

In conclusion, our investigation indicates that in a sample of US adults, higher intakes of a-carotene, β-carotene, β-cryptoxanthin, lutein with zeaxanthin, lycopene or total of them were associated with lower risk of current asthma and lower systemic inflammation. The relationship needs to be further validated in other prospective studies and the mechanisms behind these associations need to be further investigated. These findings may help people reduce the asthma risk and get the disease better controlled by changing their lifestyle and diet factors.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants but the data were obetained from NHANES, and NHANES approved by the National Center for Health Statistics Research Ethics Review Board under Continuation of Protocol. The data were obetained from NHANES and all subjects signed the informed consent during the recruitment period.

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Data availability statement Data are available in a public, open access repository. Data are available in a public, open access repository. Open access data are available on the NHANES website. https://www.cdc.gov/nchs/nhanes/index.htm.

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