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The associations between serum carotenoids and hyperuricemia among U.S. National Health and Nutrition Examination Survey

Hong He[1†], Ping Li[2†], Haokun Huang[3], Yanlin Zeng[1], Min Zhang[1], Zhibing Chen[4], Shiqi Huang[3], Fangfang Zeng[3] and Hui Ge[1*]

Abstract

Background Hyperuricemia is a risk factor for various metabolic disorders. We aimed to investigate the association between serum carotenoid levels and hyperuricemia using data from the National Health and Nutrition Examination Survey (NHANES).

Methods We conducted a cross-sectional analysis utilizing data from three specific NHANES cycles (2003–2004, 2005–2006, 2017–2018), containing the most complete serum carotenoid data from 12,253 participants aged 20 years and older. Serum carotenoids were quantified using high-performance liquid chromatography, while hyperuricemia was defined as serum uric acid levels ≥ 416 μmol/L (7.0 mg/dL) in men and ≥ 357 μmol/L (6.0 mg/dL) in women. Multivariable logistic regression models were employed to assess the relationship between carotenoids and hyperuricemia.

Results The mean age of participants was 50.1 ± 18.7 years, with a hyperuricemia prevalence of 20.5%. Higher serum carotenoids were associated with a lower prevalence of hyperuricemia, with each 1-unit increase in total carotenoids being inversely associated with hyperuricemia (odds ratio [OR] = 0.77, 95% confidence interval [CI]: 0.72–0.82) in multivariable analyses. Compared to participants with the lowest quartile, reduced ORs for hyperuricemia odds were observed for those with the highest quartile for total carotenoids (0.55 [0.47–0.64]), α-carotene (0.60 [0.52–0.71]), β-carotene (0.56 [0.48–0.65]), β-cryptoxanthin (0.58 [0.49–0.67]), trans-lycopene (0.75 [0.65–0.87]), cis-lycopene (0.83 [0.65–1.06]), total-lycopene (0.75 [0.64–0.87]), and lutein + zeaxanthin (0.66 [0.57–0.77]). Subgroup analyses indicated stronger associations among younger individuals, women, and those without any history of diabetes or cardiovascular disease.

Conclusions Higher serum carotenoid levels are associated with reduced odds of hyperuricemia. These results underscore the potential role of carotenoids in managing hyperuricemia and its related health complications.

Keywords Hyperuricemia, Serum carotenoids, NHANES

†Hong He and Ping Li contributed equally to this work.

*Correspondence:
Hui Ge
geh@mail.sysy.edu.cn
Full list of author information is available at the end of the article

Introduction

Hyperuricemia (HUA) was defined as the overproduction or impaired excretion of uric acid (UA) in the blood [1], being defined by a UA > 7 mg/dL (> 420 μM) in men and > 6 mg/dL (> 360 μM) in women [2]. According to the previous National Health and Nutrition Examination Survey (NHANES) report, the prevalence of HUA in the U.S. more than doubled between 1960 and 1990 and continued to increase afterward, reaching 20.1% (95% confidence interval [CI]17.8%−22.4%) and affecting 47.13 millions of U.S. adults during 2015–2016 [3]. Epidemiological evidence has indicated that HUA is not only the most important risk factor for the development of gout [4], but also associated with various diseases, including cardiovascular diseases (CVDs) [5, 6], chronic kidney disease [7], metabolic syndrome or hypertension [8], as well as worsen prognosis in patients with myocardial infarction [9], non-alcoholic fatty liver disease [10]. This highlights the need for strategies controlling HUA and alleviating its relevant disease burden.

The process, by which UA is formed, is caused by the breakdown of purine nucleotides, which come from both internal sources and diet [6]. In particular, nutritional epidemiological evidence has indicated that diet could be one of the cost-effective factors that could be used to control HUA [11]. On the one hand, nutrient patterns that are characterized by high purine levels obtained from purine-rich foods, high fat, and low vitamin levels were positively associated with the risk of HUA [12, 13]. On the other hand, the serum UA was found to be negatively associated with plant-based diet patterns, which are rich in carbohydrates, calcium, and vitamin B2 [14], as well as total and cereal fiber [15–17].

Carotenoids are oil-soluble natural plant pigments, and the dietary intakes of certain fruits and vegetables are good predictors of blood concentrations of carotenoids [18]. However, serum carotenoids had stronger and more linear inverse associations with diseases, compared to dietary intakes of carotenoids [19]. Six carotenoids are commonly found in human serum, including lutein, zeaxanthin, β-carotene, α-carotene, β-cryptoxanthin, and lycopene [20]. There is epidemiological evidence supporting the beneficial health effects of various serum carotenoids. A study in Italy revealed inverse associations between serum UA and serum carotenoids, including α-carotene (regression coefficient β = −0.04), lutein (β = −0.04), zeaxanthin (β = −0.06), and lycopene (β = −0.03) [21]. In addition, higher serum carotenoids were associated with lower metabolic syndrome (MetS) risk [22], which is closely related to the development of HUA [23]. Some studies consistently yielded evidence supporting that circulating UA level or HUA risk may be negatively associated with specific serum levels of β-carotene [24, 25] or retinol [26]. Carotenoids have the antioxidative properties and capacity to scavenge reactive oxygen species [19]. In detail, as one of the natural carotenoids, lycopene can lower the blood urea nitrogen level and UA in mice with Di (2-ethylhexyl) phthalate-induced renal tubular cell and glomerular damage by mediating the aromatic hydrocarbon receptor (AhR) and AhR nuclear transporter signalling system [27]. However, limited research unveiled the potential health effects of other commonly measured carotenoids on serum UA or HUA risk.

Using the data from the National Health and Nutrition Examination Survey (NHANES), the primary objective of our study is to investigate whether various serum carotenoids are associated with HUA in U.S. adults. Our findings might provide large-scale epidemiological evidence to emphasize the roles of carotenoids in HUA prevention and management.

Materials and methods

Study population

This population-based cross-sectional study used data from the NHANES, a nationally representative survey conducted by the Centers for Disease Control and Prevention (CDC) to assess the health and nutritional status of the non-institutionalized U.S. population. NHANES employs a complex, multistage, stratified probability sampling design to ensure national representation and that the data are released in biennial cycles. For this study, we extracted data from three independent NHANES waves (2003–2004, 2005–2006, 2017–2018), which included the most complete data on serum carotenoids of interest, detailed demographic information, physical examination, and other laboratory results.

The NHANES protocol was approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and written informed consent was obtained from all participants before they were included in the survey. The study followed the guiding principles of the Declaration of Helsinki. Full details of the NHANES research protocol and data collection methodology are available on the NCHS website (https://www.cdc.gov/nchs/nhanes/index.htm).

The initial dataset included 29,732 participants. For this study, we excluded participants under 20 years of age (n = 14,134), those with missing data on serum carotenoids (n = 1,577), and those with missing HUA status (n = 1,759). The final analytical sample size was 12,253 (Fig. 1).

Serum carotenoids measurement

Serum levels of different carotenoids, including α-carotene, β-carotene, lutein/zeaxanthin, trans-lycopene, cis-lycopene,

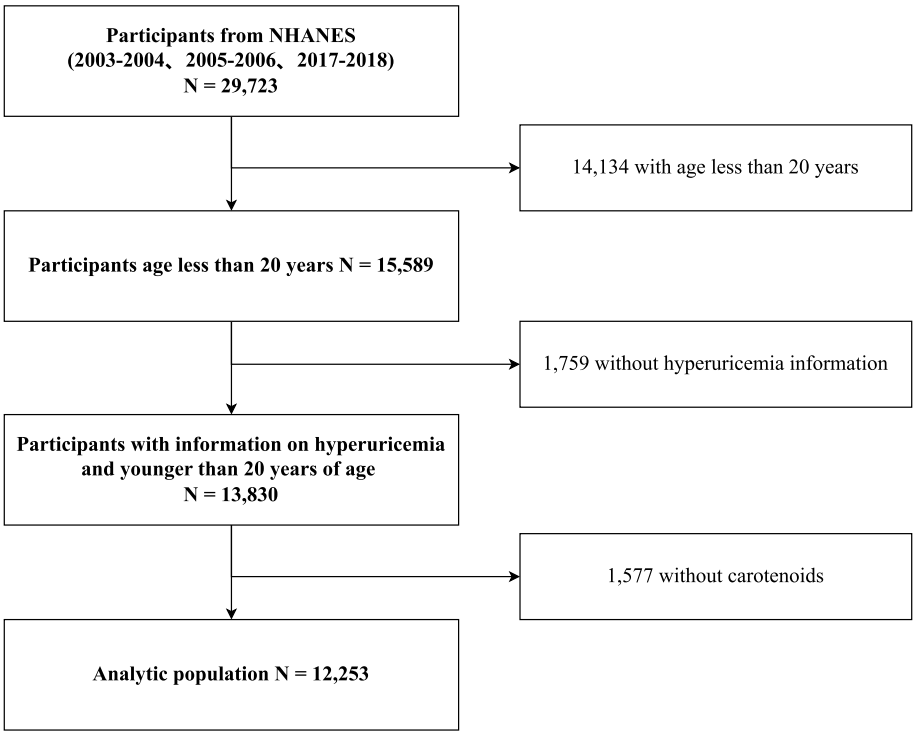

Fig. 1 Study profile

and β-cryptoxanthin, were quantified using high-performance liquid chromatography (HPLC) with multi-wavelength photodiode-array absorbance detection. The laboratory procedures and quality control methods for serum carotenoid measurements have been described previously [28]. The total β-carotene level was calculated as the sum of the cis-β-carotene and trans-β-carotene levels. Total carotenoids were derived by summing the serum concentrations of α-carotene, β-carotene, lutein, zeaxanthin, trans-lycopene, cis-lycopene, and β-cryptoxanthin.

Definition and measurement of HUA

HUA was defined based on serum UA levels, which were measured on a Beckman Synchron LX20 (Beckman Coulter, Inc., Brea, CA) using a colorimetric method. All measurements were conducted following NHANES quality assurance and control procedures. HUA was defined as serum UA levels ≥ 416 μmol/L (7.0 mg/dl) in men and ≥ 357 μmol/L (6.0 mg/dl) in women [29].

Covariates

Several covariates were selected and included in the analysis to account for potential confounding effects. During the NHANES interview portion, demographic information was collected, including age, gender, race/ethnicity (Hispanics, non-Hispanic Whites, non-Hispanic Blacks, and other races), education level (less than high school, high school graduate, and more than high school), marital status, smoking and alcohol drinking status, and poverty ratio to income (PIR), with a PIR of 1 or below indicating relative poverty. The study also used data on lifestyle factors (smoking status and alcohol consumption) and anthropometric measurements. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). We also used laboratory data including creatinine, triglycerides, and total cholesterol because HUA can significantly impair kidney function and lipids [30, 31]. The estimated glomerular filtration rate (eGFR) was calculated using the four-variable modification of diet in renal disease (MDRD) equation. Given that HUA is significantly associated with hypertension, diabetes, and CVDs [24–26], the comorbidities of these diseases were also included in the analysis.

Statistical analysis

All statistical analyses were conducted using R version 4.2.3. All *P* values were two-sided and statistical significance was determined at a $P < 0.05$ level. All analyses were conducted following NHANES analytical guidelines to enhance data accuracy and account for the complexities of the multi-stage sampling design employed in the NHANES (https://wwwn.cdc.gov/nchs/nhanes/tutorials/weighting.aspx). Sample weights, strata, and primary sampling units (PSUs) were incorporated into all analyses

to ensure nationally representative estimates of the U.S. population. In detail, the base weight was computed accounting for the unequal probabilities of selection given that some demographic groups were over-sampled; PSU-level adjustment factors were applied to participant base weights to equalize the contribution of each stratum to the overall survey sample; the weights for interviews and examinations were calculated using the adjusted base weights. The sample weights for combining three survey cycles (2003–2004, 2005–2006, 2017–2018) were calculated by a constant equal to (1 / number of survey cycles).

Participants were stratified into quartiles based on the total or individual serum carotenoids. Descriptive statistics for continuous variables were expressed as the unweighted means ± standard deviations (SDs) or medians and interquartile ranges (IQRs), while the categorical variables were denoted as unweighted counts and percentages. The one-way ANOVA (normally distributed) test, Kruskal–Wallis test (skewed distributed), and chi-square test were used in the comparative analysis of the baseline characteristics by quartiles. The multiple imputation was carried out using the MICE R package for covariables with minor missing data.

The multivariable logistic regression models with appropriate sample weight, cluster, and strata were used to evaluate the association between total or individual serum carotenoids and HUA odds. By treating the quartiles (Q1–Q4) as categorical variables in the model, we estimated the odds ratios (ORs) and 95% confidence intervals (CIs) for each quartile compared to the reference quartile using the lowest serum carotenoids (Q1) as a reference group. Moreover, we investigated whether HUA was associated with total or individual serum carotenoids per 1 unit increase. Regression models were constructed in three models: model 1 is the crude model without adjustment; model 2 adjusted for age, sex, race/ethnicity; model 3 additionally adjusted for education level, family monthly poverty levels, drinking, smoking, BMI, hypertension, CVDs, diabetes, eGFR, triglycerides, and total cholesterol.

To further explore the nonlinear relationship and avoid overfitting, the restricted cubic spline (RCS) model with 3 knots located at the 25th, 50th, and 75th percentiles was used to examine the dose–response relationship in Model 3 using the R package "rms." *P* values for nonlinearity were calculated using a Wald test. To assess the robustness of the findings, subgroup and interaction analyses were conducted by age (20–40, 40–59, ≥ 60 years), sex (men vs. women), race/ethnicity (Hispanic, non-Hispanic Whites, non-Hispanic Blacks, other races), educational levels (less than high school, high school graduate, more than high school), economic status (low, middle, high), BMI (< 25 kg/m^2, 25–30 kg/m^2, ≥ 30 kg/m^2), smoking (non-drinker, moderate drinker, heavy drinker), alcohol drinking (never, current, former), eGFR (< 60, 60–90, and > 90 mL/min/1.73 m^2), history of HBP (no vs. yes), history of DM (no vs. yes) and history of CVDs (no vs. yes).

Results

Baseline characteristics

The demographic and clinical characteristics of the study population are summarized in Table 1. The mean age of them was 50.1 ± 18.7 years, with 51.9% of them being women. Overall, 2,482 (20.5%) participants had a prevalent HUA. Compared to participants in the lowest serum carotenoids (Q1) group, those in the higher carotenoids quartiles had a relatively lower prevalence of HUA (Q1: 27.2%; Q2: 21.6%; Q3: 18.6%; Q4: 14.8%, $P < 0.001$). In addition, participants with higher carotenoid quartiles were more likely to be younger, female, Hispanic, higher levels of education, higher family PIR, no smoker, moderate or heavy drinker, higher TC and eGFR, were less likely to have any history of hypertension, diabetes, and CVDs, but lower BMI, than those in the lower carotenoid quartile (all $P < 0.05$).

The serum concentration of total carotenoids was 1.543 (1.121, 2.089) umol/L and the distributions of total and individual carotenoids are shown in Table 2.

The associations between serum carotenoids and HUA

Logistic regression results showed that total carotenoids and most of the individual serum carotenoids were negatively associated with the odds of HUA (Table 3). In the continuous model, aside from Cis-lycopene, strong negative associations of HUA with total and all individual serum carotenoids were observed in models 1 to 3. The maximally adjusted ORs and 95%CIs for per 1 unit increase were 0.77 (0.72, 0.82) for total carotenoids, 0.33 (0.19, 0.56) for α-carotene, 0.64 (0.55, 0.74) for β-carotene, 0.27 (0.18, 0.39) for β-cryptoxanthin, 0.60 (0.46, 0.78) for trans-lycopene, 0.75 (0.65, 0.87) for total-lycopene, 0.40 (0.29, 0.54) for lutein + zeaxanthin, respectively.

In particular, similar findings were observed in the categorical model, in which total and individual serum carotenoids were divided into quartiles, thus confirming a stable, statistically significant inverse association between total or individual serum carotenoids and HUA prevalence. Compared with those in the lowest quartile (Q1), the maximally adjusted ORs and 95%CIs for the odds of HUA in the highest quartiles (Q4) were 0.55 (0.47, 0.64) for total carotenoids, 0.60 (0.52, 0.71) for α-carotene, 0.56 (0.48, 0.65) for β-carotene, 0.58 (0.49, 0.67) for β-cryptoxanthin, 0.75 (0.65, 0.87) for trans-lycopene, 0.75 (0.64, 0.87) for total-lycopene, 0.66 (0.57,

Table 1 Baseline characteristics of included participants

	Serum total carotenoids (nmol/L)					*P*
	Overall (*N* = 12,253)	Q1 (*N* = 3,064)	Q2 (*N* = 3,065)	Q3 (*N* = 3,061)	Q4 (*N* = 3,063)	
Hyperuricemia, n (%)	2482 (20.5)	822 (27.2)	652 (21.6)	562 (18.6)	446 (14.8)	< 0.001
Age, years (mean [SD])	50.2 (18.7)	52.5 (19.1)	49.2 (18.9)	48.4 (18.8)	50.8 (17.9)	< 0.001
Sex, n (%)						< 0.001
Men	5892 (48.1)	1558 (50.8)	1527 (49.8)	1504 (49.1)	1303 (42.5)	
Women	6361 (51.9)	1506 (49.2)	1538 (50.2)	1557 (50.9)	1760 (57.5)	
Races, n (%)						< 0.001
Hispanic	2830 (23.1)	582 (19.0)	727 (23.7)	768 (25.1)	753 (24.6)	
Non-Hispanic White	5729 (46.8)	1583 (51.7)	1449 (47.3)	1391 (45.4)	1306 (42.6)	
Non-Hispanic Black	2625 (21.4)	679 (22.2)	670 (21.9)	671 (21.9)	605 (19.8)	
Other races	1069 (8.7)	220 (7.2)	219 (7.1)	231 (7.5)	399 (13.0)	
Education level, n (%)						< 0.001
Below high school	1889 (15.4)	544 (17.8)	458 (14.9)	439 (14.3)	448 (14.6)	
High school	4227 (34.5)	1274 (41.6)	1145 (37.4)	999 (32.6)	809 (26.4)	
Above high school	6137 (50.1)	1246 (40.7)	1462 (47.7)	1623 (53.0)	1806 (59.0)	
Family PIR, n (%)						< 0.001
< 1	2598 (21.2)	774 (25.3)	688 (22.4)	607 (19.8)	529 (17.3)	
1 ~ 3	5129 (41.9)	1444 (47.1)	1332 (43.5)	1242 (40.6)	1111 (36.3)	
> 3	4526 (36.9)	846 (27.6)	1045 (34.1)	1212 (39.6)	1423 (46.5)	
BMI, kg/m^2 (mean [SD])	29.0 (6.8)	30.5 (8.1)	29.8 (7.0)	28.6 (6.0)	27.0 (5.0)	< 0.001
Smoking, n (%)						< 0.001
Never	6526 (53.3)	1292 (42.2)	1516 (49.5)	1722 (56.3)	1996 (65.2)	
Current	2548 (20.8)	962 (31.4)	746 (24.3)	540 (17.6)	300 (9.8)	
Former	3179 (25.9)	810 (26.4)	803 (26.2)	799 (26.1)	767 (25.0)	
Alcohol drinking, n (%)						< 0.001
Nondrinker	8774 (71.6)	2296 (74.9)	2187 (71.4)	2131 (69.6)	2160 (70.5)	
Moderate drinker	1846 (15.1)	364 (11.9)	455 (14.8)	492 (16.1)	535 (17.5)	
Heavy drinker	1633 (13.3)	404 (13.2)	423 (13.8)	438 (14.3)	368 (12.0)	
TG, mg/dL (mean [SD])	147.1 (124.8)	146.2 (118.4)	148.6 (115.6)	148.1 (144.0)	145.4 (119.2)	0.713
TC, mg/dL (mean [SD])	197.0 (43.4)	177.2 (40.1)	191.0 (37.5)	202.2 (40.7)	217.7 (44.4)	< 0.001
eGFR, mL/min per 1.73 m^2 (mean [SD])	75.8 (37.5)	72.6 (36.2)	75.1 (24.1)	77.8 (20.7)	79.8 (30.4)	< 0.001
History of HBP, n (%)	6619 (54.0)	1893 (61.8)	1691 (55.2)	1527 (49.9)	1508 (49.2)	< 0.001
History of DM, n (%)	1792 (14.6)	640 (20.9)	483 (15.8)	335 (10.9)	334 (10.9)	< 0.001
History of CVDs, n (%)	1046 (8.5)	345 (11.3)	258 (8.4)	221 (7.2)	222 (7.2)	< 0.001

Mean ± SD for normally distributed continuous variables and n (%) for categorical variables

Abbreviations: *NHANES* National Health and Nutrition Examination Survey, *Q* quartile, *SD* standard deviation, *PIR* ratio of family income to poverty, *BMI* body mass index, *DM* diabetes mellitus, *CVDs* cardiovascular disease, *TG* triglycerides, *TC* total cholesterol, *HBP* hypertension

0.77) for lutein + zeaxanthin, respectively. By comparing the analysis results of the three circles, we found that the associations among the circles were generally consistent with the overall results, and no significant differences were observed (Table S1).

Furthermore, as depicted in Fig. 2, the RCS model demonstrated significant linear and nonlinear trends were observed for α-carotene and β-carotene (both $P < 0.001$), β-cryptoxanthin (P linear < 0.001, P nonlinear = 0.008). Only linear trends were observed for trans-lycopene, total-lycopene, lutein + zeaxanthin, and total carotenoids (all P linear < 0.001 and P nonlinear > 0.05).

Subgroup and interaction analyses

Participants were stratified according to different characteristics. As shown in Table 4, notable interactions were identified concerning age (P for interaction = 0.001), sex (P for interaction = 0.024), and history of DM and

Table 2 Distribution of different serum carotenoids

	Serum carotenoids (nmol/L)					*P*
	Overall (*N* = 12,253)	Q1 (*N* = 3,064)	Q2 (*N* = 3,065)	Q3 (*N* = 3,061)	Q4 (*N* = 3,063)	
Total carotenoids, umol/L (median [IQR])	1.543 (1.121, 2.089)	0.874 (0.701, 1.004)	1.334 (1.233, 1.441)	1.785 (1.657, 1.924)	2.611 (2.299, 3.175)	< 0.001
α-carotene, umol/L (median [IQR])	0.052 (0.026, 0.102)	0.023 (0.014, 0.038)	0.042 (0.025, 0.067)	0.065 (0.039, 0.102)	0.132 (0.078, 0.222)	< 0.001
β-carotene, umol/L (median [IQR])	0.246 (0.140, 0.452)	0.113 (0.076, 0.170)	0.195 (0.136, 0.287)	0.307 (0.208, 0.439)	0.654 (0.419, 0.994)	< 0.001
β-cryptoxanthin, umol/L (median [IQR])	0.136 (0.083, 0.227)	0.069 (0.047, 0.103)	0.114 (0.082, 0.168)	0.165 (0.116, 0.242)	0.261 (0.173, 0.414)	< 0.001
Trans-lycopene, umol/L (median [IQR])	0.371 (0.248, 0.514)	0.211 (0.143, 0.283)	0.357 (0.274, 0.443)	0.451 (0.343, 0.566)	0.540 (0.388, 0.710)	< 0.001
Cis-Lycopene, umol/L (median [IQR])	0.329 (0.220, 0.447)	0.187 (0.131, 0.247)	0.326 (0.252, 0.389)	0.407 (0.324, 0.496)	0.506 (0.364, 0.661)	< 0.001
Total-lycopene, umol/L (median [IQR])	0.697 (0.475, 0.957)	0.401 (0.278, 0.523)	0.673 (0.525, 0.810)	0.850 (0.663, 1.043)	1.039 (0.758, 1.349)	< 0.001
Lutein + zeaxanthin, umol/L (median [IQR])	0.272 (0.195, 0.385)	0.172 (0.133, 0.227)	0.243 (0.193, 0.306)	0.308 (0.244, 0.392)	0.434 (0.331, 0.572)	< 0.001

Abbreviations: *Q* quartile, *IQR* interquartile range

CVDs (both *P* for interaction < 0.001). Noteworthy, stronger protective effects against HUA were observed among younger individuals (Age 20–40 years: OR = 0.31; 40–59 years: OR = 0.45; 60 years and above: OR = 0.68) and women (OR = 0.46). Significant inverse associations were observed among those without any history of DM (OR = 0.43) or CVDs (OR = 0.48). No significant interactions were detected concerning other factors, such as race/ethnicity, education level, economic status, BMI, smoking, alcohol drinking, eGFR and history of HBP.

Discussion

In this nationwide cross-sectional study involving 12,253 U.S. adults, we observed the existence of significant associations between the serum concentrations of total carotenoids and their subtypes (α-carotene, β-carotene, β-cryptoxanthin, trans lycopene, total lycopene, and lutein + zeaxanthin) and the decreased odds of HUA. Besides, such associations appeared to be modified by age, sex, and pre-existing comorbidities, with the declined odds of HUA in response to increased total carotenoid levels being stronger among younger adults, women, and those without DM or CVDs.

Although the current studies directly explored the effect of serum carotenoids on HUA is limited, our findings of the inverse associations between serum carotenoids and UA align with previous studies. Of them, an early community-based cross-sectional study in Italy consistently reported that UA circulating levels were inversely associated with plasma antioxidants, including total carotenoids, α-carotene, lycopene, lutein, and zeaxanthin [21]. Similarly, an early NHANES study consistently found that the serum UA level and the frequency of HUA decreased with increasing serum β-carotene level [24]. In addition, a cross-sectional study involving 32,365 adults in China reported that high dietary consumption of seaweeds, which is rich in carotenoids, was associated with lower odds of HUA [32]. Despite not being included in our study, there is supporting evidence regarding the protective effect against kidney damage associated with other carotenoids, including bixin [33] and astaxanthin [34], with inconsistent evidence coming for serum retinol [24, 26, 35, 36]. A variety of NHANES-based literature has assessed the beneficial health effects of carotenoids. Such as the inverse associations between total carotenoids or serum β-carotene and MetS [22, 37], as well as the inverse relationships between serum total carotenoids and non-MetS outcomes (HOMA-IR and C-reactive protein [CRP]) [38]. Furthermore, inverse associations of serum CRP or fibrinogen level with different serum carotenoids, including α-carotene, trans-β-carotene, cis-β-carotene, β-cryptoxanthin, combined lutein/zeaxanthin, trans-lycopene, were noticed in NHANES U.S. adults between 2001 and 2002 [39], highlighting the antioxidant properties of carotenoids. A limited amount of evidence exists, however, to compare the effects of different types of carotenoids. In other words, we may be able to obtain more robust results with our study than with studies that only focus on overall carotenoids or specific types of carotenoids due to the fact that we have larger sample sizes and a larger number of serum carotenoids of interest.

Table 3 Associations of serum total and individual carotenoids with hyperuricemia in the participants

	Model 1		Model 2		Model 3	
	OR (95%CI)	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
Total carotenoids						
Q1	Ref		Ref		Ref	
Q2	0.74 (0.65, 0.83)	< 0.001	0.79 (0.70, 0.89)	< 0.001	0.78 (0.69, 0.89)	< 0.001
Q3	0.61 (0.54, 0.69)	< 0.001	0.67 (0.59, 0.75)	< 0.001	0.72 (0.62, 0.82)	< 0.001
Q4	0.46 (0.41, 0.53)	< 0.001	0.47 (0.41, 0.54)	< 0.001	0.55 (0.47, 0.64)	< 0.001
For 1-unit increase	0.71 (0.67, 0.75)	**< 0.001**	0.71 (0.67, 0.75)	**< 0.001**	0.77 (0.72, 0.82)	**< 0.001**
α-carotene						
Q1	Ref		Ref		Ref	
Q2	0.84 (0.74, 0.94)	0.003	0.80 (0.71, 0.91)	< 0.001	0.85 (0.75, 0.97)	0.018
Q3	0.77 (0.68, 0.87)	< 0.001	0.70 (0.61, 0.79)	< 0.001	0.80 (0.70, 0.92)	0.002
Q4	0.51 (0.45, 0.58)	< 0.001	0.46 (0.40, 0.52)	< 0.001	0.60 (0.52, 0.71)	**< 0.001**
For 1-unit increase	0.13 (0.07, 0.21)	**< 0.001**	0.10 (0.05, 0.17)	**< 0.001**	0.33 (0.19, 0.56)	**< 0.001**
β-carotene						
Q1	Ref		Ref		Ref	
Q2	0.69 (0.61, 0.78)	< 0.001	0.64 (0.57, 0.72)	< 0.001	0.70 (0.61, 0.80)	< 0.001
Q3	0.69 (0.61, 0.77)	< 0.001	0.57 (0.51, 0.65)	< 0.001	0.67 (0.58, 0.77)	< 0.001
Q4	0.54 (0.48, 0.61)	< 0.001	0.40 (0.35, 0.45)	< 0.001	0.56 (0.48, 0.65)	< 0.001
For 1-unit increase	0.59 (0.52, 0.67)	**< 0.001**	0.44 (0.38, 0.51)	**< 0.001**	0.64 (0.55, 0.74)	**< 0.001**
β-cryptoxanthin						
Q1	Ref		Ref		Ref	
Q2	0.82 (0.73, 0.92)	< 0.001	0.86 (0.77, 0.97)	0.017	0.90 (0.79, 1.02)	0.099
Q3	0.66 (0.58, 0.74)	< 0.001	0.70 (0.62, 0.79)	< 0.001	0.78 (0.68, 0.89)	< 0.001
Q4	0.43 (0.38, 0.49)	< 0.001	0.46 (0.40, 0.53)	< 0.001	0.58 (0.49, 0.67)	< 0.001
For 1-unit increase	0.12 (0.08, 0.17)	**< 0.001**	0.15 (0.10, 0.21)	**< 0.001**	0.27 (0.18, 0.39)	**< 0.001**
Trans-lycopene						
Q1	Ref		Ref		Ref	
Q2	0.80 (0.71, 0.90)	< 0.001	0.96 (0.85, 1.09)	0.535	0.91 (0.80, 1.04)	0.185
Q3	0.73 (0.65, 0.83)	< 0.001	0.93 (0.82, 1.06)	0.28	0.91 (0.79, 1.04)	0.169
Q4	0.63 (0.55, 0.71)	< 0.001	0.81 (0.71, 0.93)	0.002	0.75 (0.65, 0.87)	< 0.001
For 1-unit increase	0.43 (0.34, 0.54)	**< 0.001**	0.70 (0.55, 0.88)	**0.002**	0.60 (0.46, 0.78)	**< 0.001**
Cis-lycopene						
Q1	Ref		Ref		Ref	
Q2	0.72 (0.58, 0.88)	0.001	0.89 (0.72, 1.09)	0.256	0.88 (0.70, 1.10)	0.259
Q3	0.75 (0.61, 0.92)	0.006	0.98 (0.79, 1.21)	0.829	0.98 (0.77, 1.23)	0.839
Q4	0.64 (0.52, 0.79)	< 0.001	0.81 (0.65, 1.01)	0.067	0.83 (0.65, 1.06)	0.138
For 1-unit increase	0.42 (0.27, 0.64)	**< 0.001**	0.68 (0.44, 1.05)	0.085	0.68 (0.41, 1.11)	0.127
Total-lycopene						
Q1	Ref		Ref		Ref	
Q2	0.82 (0.73, 0.92)	0.001	0.98 (0.87, 1.11)	0.767	0.94 (0.82, 1.07)	0.356
Q3	0.69 (0.61, 0.78)	< 0.001	0.87 (0.77, 0.99)	0.035	0.86 (0.75, 0.99)	0.030
Q4	0.62 (0.54, 0.70)	< 0.001	0.78 (0.69, 0.89)	< 0.001	0.75 (0.64, 0.87)	< 0.001
For 1-unit increase	0.63 (0.56, 0.71)	**< 0.001**	0.79 (0.70, 0.90)	**< 0.001**	0.75 (0.65, 0.87)	**< 0.001**
Lutein + zeaxanthin						
Q1	Ref		Ref		Ref	
Q2	0.81 (0.72, 0.91)	< 0.001	0.79 (0.70, 0.90)	< 0.001	0.87 (0.76, 0.99)	0.040
Q3	0.74 (0.65, 0.83)	< 0.001	0.70 (0.61, 0.79)	< 0.001	0.80 (0.69, 0.91)	0.001
Q4	0.63 (0.56, 0.71)	< 0.001	0.54 (0.47, 0.62)	< 0.001	0.66 (0.57, 0.77)	< 0.001
For 1-unit increase	0.37 (0.29, 0.49)	**< 0.001**	0.26 (0.20, 0.34)	**< 0.001**	0.40 (0.29, 0.54)	**< 0.001**

Model 1 was the crude model without adjustment; Model 2 adjusted for age, sex, and race; Model 3 additionally adjusted for education level, family monthly poverty levels, drinking, smoking, BMI, hypertension, cardiovascular diseases, diabetes, eGFR, triglycerides, and total cholesterol.

Abbreviations: *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *Q* quartile

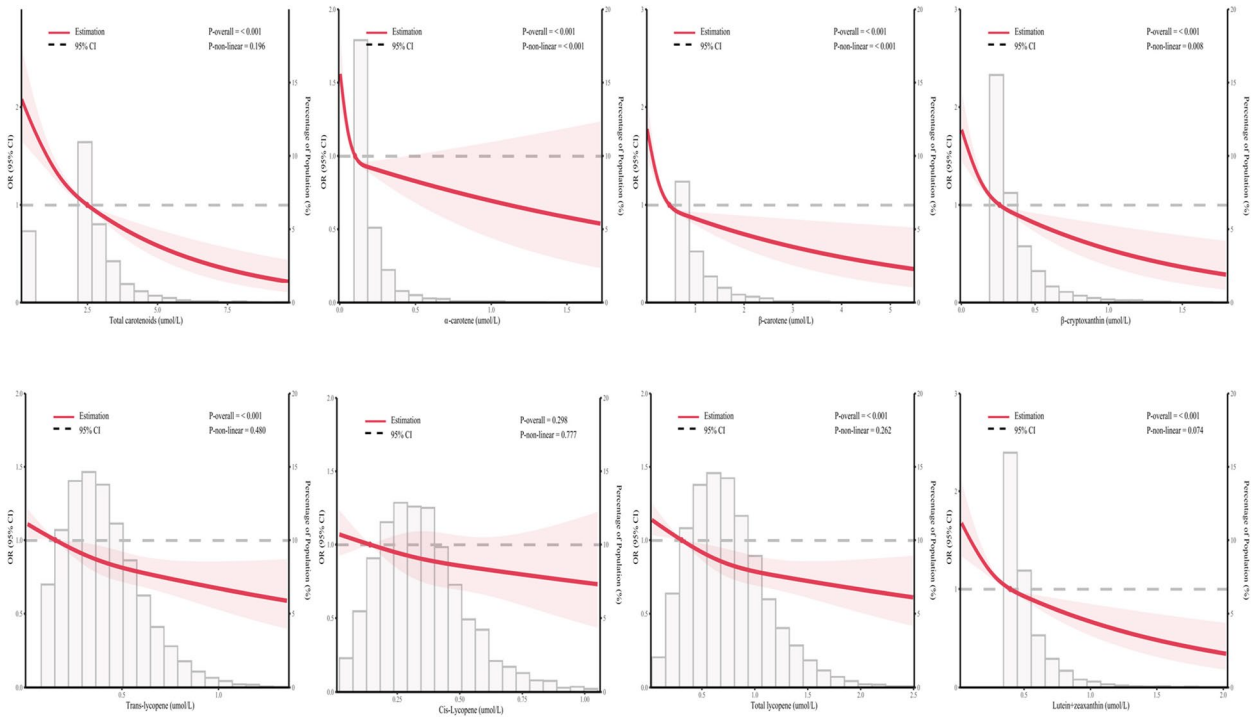

Fig. 2 The dose–response relationship between total or individual serum carotenoids and hyperuricemia

The specific biological mechanisms underlying the inverse association between serum carotenoids and the prevalence of HUA remain unclear. Several risk factors stimulate the development of HUA, including genetic and physiologic circumstances, renal disorders, lifestyle, and diet (consumption of purine-rich foods, soft drinks, fructose, and alcohol) [40]. As for lifestyle and diet, purines are derived from both endogenous and dietary sources in vivo, with dietary purine being primarily obtained from purine-fortified foods (e.g., meat, liver, anchovy, sardine, soybean, shiitake mushrooms) and alcoholic beverages [41]. Carotenoid concentrations in blood are biomarkers of fruit and vegetable intakes [42], suggesting that higher serum carotenoids are positively associated with the dietary intakes of carotenoids-enriched food. Thus, it is reasonable to assume that the dietary purine might decrease as the dietary consumption of fruit and vegetables increases, which might further limit the synthesis of UA and the development of HUA. For physiologic circumstances, the major cause of HUA is a dysfunction of the enzyme xanthine oxidoreductase (XOD), which causes increased purine content in the body and facilitates the accumulation of UA in the serum and the HUA [23]. Despite not being included in our study due to data limitations, previous studies have unveiled the beneficial effect of other carotenoids on health status. For instance, astaxanthin was proven to alleviate the ochratoxin A-induced renal oxidative stress in mice through the related nuclear factor erythroid 2 (NRF2)/Kelch-like ECH-associated protein (KEAP1) pathway [34]. According to a mice model, astaxanthin, a xanthophyll carotenoid, was demonstrated to help reduce UA synthesis by inhibiting the mRNA expressions and enzyme activities of XOD and adenosine deaminase (ADA), thereby contributing to the prevention of fructose-induced HUA [43]. In addition, bixin, a natural carotenoid extracted from the seeds of the Bixa Orellana, was also found to inhibit oxidative stress, inflammation, and fibrosis in the kidney by activating the NRF2 antioxidant system [33]. However, more studies are needed to clarify whether the antioxidant properties of carotenoids would potentially be responsible for their beneficial health effect on metabolites.

The stratified analyses indicated that the associations remained consistent in the majority of subgroups, except for the groups by age, sex, and pre-existing comorbidities. Their bioavailability primarily determines the serum levels of different carotenoids [44], which is primarily determined by carotenoids-related factors (carotenoid species) and host-related factors (sex, age, nutritional status, physiological/pathological condition, and genetic variations) [45, 46]. In particular, being in line with our findings regarding the sex difference, serum β-carotene

Table 4 Stratified analyses of the associations between serum levels of total carotenoids with hyperuricemia

	Total carotenoids concentrations				For 1-unit increase	P for interaction
	Q1	Q2	Q3	Q4		
Age, years						**0.001**
20–40	Ref	0.58 (0.45,0.75)	0.44 (0.33,0.58)	0.31 (0.22,0.43)	< 0.001	
40–59	Ref	0.69 (0.54,0.88)	0.69 (0.54,0.90)	0.45 (0.34,0.61)	< 0.001	
60 and above	Ref	0.91 (0.75,1.10)	0.77 (0.62,0.94)	0.68 (0.54,0.84)	< 0.001	
Sex						**0.024**
Men	Ref	0.79 (0.66,0.95)	0.62 (0.51,0.75)	0.58 (0.46,0.72)	< 0.001	
Women	Ref	0.71 (0.59,0.86)	0.69 (0.56,0.84)	0.46 (0.37,0.58)	< 0.001	
Races						0.699
Hispanic	Ref	0.66 (0.49,0.89)	0.56 (0.41,0.77)	0.35 (0.24,0.50)	< 0.001	
Non-Hispanic Whites	Ref	0.81 (0.67,0.98)	0.68 (0.56,0.84)	0.57 (0.45,0.71)	< 0.001	
Non-Hispanic Blacks	Ref	0.73 (0.56,0.95)	0.64 (0.49,0.85)	0.52 (0.37,0.71)	< 0.001	
Other races	Ref	0.73 (0.46,1.16)	0.67 (0.41,1.08)	0.59 (0.36,0.96)	0.029	
Education						0.102
Less than high school	Ref	0.81 (0.59,1.12)	0.64 (0.45,0.91)	0.41 (0.28,0.62)	< 0.001	
High school diploma	Ref	0.83 (0.67,1.02)	0.67 (0.53,0.84)	0.66 (0.51,0.86)	< 0.001	
More than high school	Ref	0.69 (0.57,0.84)	0.65 (0.53,0.79)	0.48 (0.39,0.60)	< 0.001	
Economic status						0.143
Low	Ref	0.78 (0.60,1.02)	0.61 (0.45,0.82)	0.46 (0.33,0.65)	< 0.001	
Middle	Ref	0.85 (0.70,1.03)	0.73 (0.59,0.90)	0.64 (0.50,0.82)	< 0.001	
High	Ref	0.64 (0.51,0.80)	0.59 (0.47,0.74)	0.42 (0.33,0.55)	< 0.001	
Drinking						0.929
Nondrinker	Ref	0.79 (0.68,0.92)	0.70 (0.60,0.83)	0.55 (0.46,0.66)	< 0.001	
Moderate drinker	Ref	0.73 (0.51,1.05)	0.63 (0.43,0.92)	0.44 (0.29,0.68)	< 0.001	
Heavy drinker	Ref	0.57 (0.40,0.81)	0.39 (0.27,0.57)	0.42 (0.28,0.65)	< 0.001	
BMI, kg/m^2						0.700
< 25	Ref	0.78 (0.56,1.09)	0.69 (0.49,0.97)	0.62 (0.44,0.89)	0.004	
25–30	Ref	0.72 (0.56,0.91)	0.62 (0.49,0.79)	0.48 (0.36,0.63)	< 0.001	
> 30	Ref	0.78 (0.65,0.92)	0.68 (0.56,0.82)	0.51 (0.41,0.65)	< 0.001	
Smoking						0.108
Never	Ref	0.77 (0.64,0.92)	0.61 (0.50,0.74)	0.44 (0.36,0.55)	< 0.001	
Current	Ref	0.82 (0.62,1.08)	0.72 (0.52,1.00)	0.66 (0.43,1.01)	0.010	
Former	Ref	0.69 (0.54,0.87)	0.67 (0.53,0.87)	0.60 (0.45,0.79)	< 0.001	
eGFR, mL/min per 1.73 m^2						0.289
< 60	Ref	0.83 (0.60,1.16)	0.72 (0.51,1.08)	0.67(0.36,1.00)	0.012	
60 ~ 90	Ref	0.80 (0.65,1.00)	0.71 (0.55,0.95)	0.60(0.40,0.85)	< 0.001	
> 90	Ref	0.77 (0.51,1.10)	0.73(0.50,1.01)	0.69 (0.48,0.99)	0.001	
HBP						0.400
No	Ref	0.68 (0.53,0.87)	0.67 (0.52,0.86)	0.42 (0.31,0.57)	< 0.001	
Yes	Ref	0.79 (0.68,0.92)	0.64 (0.54,0.75)	0.56 (0.46,0.67)	< 0.001	
DM						**< 0.001**
No	Ref	0.70 (0.60,0.80)	0.59 (0.50,0.68)	0.43 (0.37,0.52)	< 0.001	
Yes	Ref	0.95 (0.72,1.27)	1.02 (0.73,1.42)	1.09 (0.77,1.56)	0.422	
CVDs						**< 0.001**
No	Ref	0.73 (0.64,0.84)	0.61 (0.53,0.71)	0.48 (0.41,0.57)	< 0.001	
Yes	Ref	0.97 (0.65,1.45)	1.07 (0.70,1.64)	0.82 (0.52,1.29)	0.569	

Adjusted for age (categorical), sex, race, education level, family monthly poverty levels, drinking, smoking, BMI (categorical), hypertension, cardiovascular diseases, diabetes, eGFR, triglycerides (quintile), and total cholesterol (quintile). The strata variable was not included in the model when stratifying by itself

Abbreviations: *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *HBP* hypertension, *DM* diabetes mellitus, *CVDs* cardiovascular diseases

exhibited a similar pattern with an inverse association with MetS in both sexes, with β-cryptoxanthin in men and lutein + zeaxanthin in women being significantly and inversely related to MetS [22]. This may be partly explained by the fact that women tend to have higher bloody concentrations of carotenoids than men because of their higher intakes of carotenoids-enriched foods and relatively lower body weight and plasma volume, compared to their male counterparts [46]. Regarding the more pronounced relationships observed among younger participants and those without any comorbidities, it may be ascribed to their potential higher bioavailability of carotenoids [20, 47]. Consistently, a study noticed the lower circulating carotenoids in patients with CVDs [48], and this may be related to the fact that CVDs and type 2 diabetes are both associated with inflammation and oxidative stress, which may cause differences in carotenoid status compared with healthy counterparts [20]. However, more studies are warranted to clarify the causes of modification effect by age, sex, and comorbidities associations with circulating carotenoids.

Our analysis revealed that the α-carotene, β-carotene, and β-cryptoxanthin exhibited a dominant linear trend with additional non-linear features with the odds of HUA, indicating the complexity behind these serum carotenoids and HUA. This significant non-linearity may indicate subtle deviations that cannot be captured by a simple linear model, such as thresholds or plateaus. Moreover, using splines might provide more flexibility in modeling the data, and this suggested that slight fluctuations could also reveal non-linearity, even if the overall trend is largely linear. Further research is necessary to confirm these patterns and explore their biological underpinnings.

This study has several limitations. First, the cross-sectional study design limited us to exploring the causal association between circulating carotenoids and HUA. So, further well-designed studies with the prospective design are needed to make a causal inference. Second, since our research was conducted exclusively among adults in the U.S., this will undoubtedly impede us from generalizing our findings to other populations since we were unable to test the external validity of our findings for other populations with different racial/ethnic backgrounds or ages. More multi-central studies are needed to validate our findings across different populations. Third, due to limited availability in the database, we cannot eliminate the residual confounding even though we developed several adjustment models controlling many known confounders. The association between circulating carotenoids and HUA; however, was sufficiently stable across different adjustment models. Finally, using data from three independent NHANES surveys, the difference in laboratory measurement of the serum carotenoids and the selection of the study population may also cause measurement bias and volunteer bias, thus affecting the accuracy of the observed trends. In future studies, a comparison of different biomarkers across surveys will be critical to provide a better understanding of the relationship between serum carotenoids and health status.

Conclusions

In a national survey of the U.S. adults, we observed an inverse association between serum levels of total and individual carotenoids (α-carotene, β-carotene, β-cryptoxanthin, trans lycopene, total lycopene, and lutein + zeaxanthin) and the odds of HUA. Besides, such associations seem to be more evident in young people, women, and a healthier population without any comorbidities. Given the limitations of this study, the findings should be confirmed in future experiments and prospective design studies with larger sample sizes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22060-4.

Supplementary Material 1

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Authors' contributions
Hong He and Ping Li wrote the manuscript. Haokun Huang, Shiqi Huang, Yanlin Zeng and Min Zhang performed the data analysis. ZhibingChen and Fangfang Zeng reviewed the manuscript and provided critical suggestions. Hui Ge revised the manuscript and improve the writing quality.

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Data availability
Publicly available datasets were analyzed in this study. All the raw data used in this study are derived from the public NHANES data portal https://wwwn.cdc.gov/nchs/nhanes/search/default.aspx.

Declarations

Ethics approval and consent to participate
This study was conducted according to the guideline laid down in the Declaration of Helsinki, and all procedures involving study participants were approved by the Institutional Review Board of the National Center for Health Statistics (NCHS). Ethical review and approval were waived for this study as it solely used publicly available data for research and publication. Informed consent was obtained from all subjects involved in the NHANES.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Healthcare Outpatient Center, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China. [2]Department of Plastic Surgery, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou 510080, China. [3]Department of Public Health and Preventive Medicine, School of Medicine, Jinan University, Guangzhou 510632, China. [4]School of Public Health, Sun Yat-sen University, Guangzhou 510080, China.

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