Original Article

Association between vitamin C intake and risk of hyperuricemia in US adults

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Background and Objectives: The relationship between vitamin C intake and hyperuricemia among the general US adult population has seldom been reported; thus, the present study examined the associations of total vitamin C (dietary vitamin C plus supplementary vitamin C) and dietary vitamin C intake with the risk of hyperuricemia. **Methods and Study Design:** Pooled data from three 2-year cycles (2007–2012) of the cross-sectional National Health and Nutrition Examination Survey were used in the present study. Dietary intake data were extracted from two 24-hour dietary recall interviews. Logistic regression models were used to determine the associations between vitamin C intake and hyperuricemia risk. **Results:** A total of 14885 adults aged 20 years or older (7269 men and 7616 women) were registered in the present study. The prevalence of hyperuricemia was 19.1%. Based on the lowest quartile of dietary vitamin C intake, multivariate adjusted odds ratios with 95% confidence intervals of hyperuricemia for quartiles 2–4 were 0.84 (0.74–0.95), 0.83 (0.73–0.94), and 0.72 (0.63–0.82), and those for total vitamin C intake were 0.87 (0.77–0.99), 0.85 (0.75–0.96), and 0.66 (0.58–0.76). Inverse associations between vitamin C intake and hyperuricemia were discovered in both men and women, even with or without covariate adjustments. **Conclusions:** Total vitamin C and dietary vitamin C intake are inversely associated with hyperuricemia in the general US adult population.

Key Words: vitamin C, hyperuricemia, uric acid, cross-sectional study, dietary intake

INTRODUCTION

Uric acid is an organic compound produced through the hepatic metabolism of purine from endogenous and exogenous sources.[1] As the body's principal endogenous antioxidant, uric acid plays bioprotective roles.[2,3] Hyperuricemia occurs because of urate overproduction or impaired urate excretion through the kidney and gastrointestinal tract. The global prevalence of hyperuricemia has been increasing.[4] The prevalence of hyperuricemia ranges from 8.9% to 24.4% in various populations.[5,6] A prospective cohort study demonstrated that 21% of 5819 older adults had hyperuricemia.[7] Hyperuricemia is a precursor to gout and is strongly associated with type 2 diabetes,[8] metabolic syndrome, and cardiovascular disease.[9,10] However, the pathophysiology of hyperuricemia has not been fully understood.[11]

The complex phenotypes of hyperuricemia result from the interplay between inherited genetic risk variants and environmental exposures.[12] A genome-wide association study identified 28 major genome-wide loci associated with serum urate concentrations.[13] Moreover, epidemiological investigations have discovered that behavioral factors, including dietary factors, affect uric acid metabolism.[14,15] Vitamin C is a potential dietary factor that alleviates hyperuricemia, itself with antioxidative and prooxidant properties and immunological relevance.[16] In the 1970s, the uricosuric effects of vitamin C in humans were assessed,[17,18] but the mechanisms were poorly defined. Increased renal fractional clearance of uric acid and reduced microvascular ischemia in glomeruli by vitamin C antioxidation were the possible mechanisms[17,19] for the effect of oral vitamin C supplementation on serum uric acid concentration.[19-21] In a double-blind placebo-controlled randomized trial, vitamin C supplementation at 500 mg/d for 2 months decreased serum uric acid in nonsmokers.[19] Vitamin C has also been demonstrated to lower uric acid concentrations during intense training or in hemodialysis patients.[20,21] A meta-analysis of randomized controlled trials found that vitamin C supplementation lowered serum uric acid.[22] However, Stamp et al. did not find support for vitamin C supplementation as a urate-lowering therapy in gout patients.[23] Several human observational studies have reported an inverse association be-

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tween plasma ascorbic acid or vitamin C intake and serum uric acid concentrations.[1,24-26] The Health Professional Follow-Up Study indicated that vitamin C intake is negatively associated with serum uric acid concentrations in men.[25] To date, the relationship between vitamin C intake and serum uric acid concentrations among the general US adult population stratified by sex has not been reported. We used data from the 2007–2012 National Health and Nutrition Examination Survey (NHANES) to evaluate the associations of total and dietary vitamin C intakes with the risk of hyperuricemia in the general US adult population.

METHODS

Study population

The present analyses were conducted using data from three 2-year cycles (2007–2012) of the NHANES.[27] With a complex, multistage probability design, the NHANES examines a nationally representative sample of the US civilian non-institutionalized population of all ages. After an interview at home, participants were invited to complete additional questionnaires, undergo tests, and provide blood and other biological specimens at a mobile examination center. The National Center for Health Statistics Research Ethics Review Board granted approval for the NHANES, and all participants provided informed consent for both at-home interviews and examinations at the mobile examination center. The response rates of the interviewed sample were 78.4%, 79.4%, and 72.6% for 2007–2008, 2009–2010, and 2011–2012, respectively. The response rates of the examined sample were 75.4%, 77.3%, and 69.5% for 2007–2008, 2009-2010, and 2011–2012, respectively.[28] The 2007–2012 NHANES included 30442 participants. We limited our analysis to participants aged 20 years or older who underwent medical examination, and we excluded individuals who did not provide vitamin C intake information and those who did not provide blood specimens (n=15403). Furthermore, individuals whose total daily energy intake >mean+3 standard deviations (4630 kcal) or <mean–3 standard deviations (0 kcal) were also excluded (n=154). Thus, 14885 individuals aged 20 or older (7269 men and 7616 women) were included in our analysis.

Dietary and supplemental vitamin C intake measures

The dietary intake of vitamin C was assessed using 24-hour dietary recall interviews. The dietary intake data were used to estimate the types and amounts of foods and beverages (including all types of water) consumed during the 24-hour period prior to the interview (midnight to midnight). Daily aggregates of energy, nutrients, and other food components from foods and beverages were calculated using the US Department of Agriculture Food and Nutrient Database for Dietary Studies (FNDDS 2007-2008, 2009-2010 and 2011-2012, respectively). All NHANES examinees underwent two 24-hour dietary recall interviews. The first dietary recall interview was conducted in-person at the mobile examination center, and the second interview was conducted by telephone 3 to 10 days later. If an individual completed both 24-hour recalls, we used the average dietary vitamin C intake from the two 24-hour recalls. Otherwise, we used the single dietary recall. Among all participants, 88.5% completed both 24-hour recalls.

We also assessed supplemental vitamin C intake. Beginning in 2007, data were collected regarding the use of all vitamins, minerals, herbal and other dietary supplements, and nonprescription antacids as part of the 24-hour recall dietary interviews. The average daily amount of supplemental vitamin C consumed was calculated by summing all supplemental nutrients and dividing the sum by 30.

Total daily vitamin C intake was calculated by summing each participant's vitamin C intake from dietary sources and supplements.

Serum uric acid measurement

Serum uric acid levels were measured through oxidization with the specific enzyme uricase to form allantoin and H_2O_2. Analyses were performed using a Beckman Synchron LX20 and Beckman UniCel® DxC800 Synchron. Details on quality-control procedures are available elsewhere.[29] Values were reported in milligrams per deciliter (to convert to micromoles per liter, multiply by 59.48). Hyperuricemia was defined as serum uric acid levels >7.0 mg/dL in men and >6.0 mg/dL in women.[30]

Covariates

Demographic characteristics included age, sex, ethnicity (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, and other race), and educational level. Educational level was divided into <high school graduate, high school graduate, and >high school graduate. Other covariates included body mass index (BMI), smoking status (smoking at least 100 cigarettes in life or not), and alcohol consumption (having at least 12 alcoholic drinks/year or not). A history of hypertension or diabetes was defined as a self-reported physician's diagnosis of hypertension or diabetes. Blood specimens were processed, stored, and shipped to respective laboratories for analysis. Total cholesterol (TC) and triglycerides were analyzed using the enzymatic method. High-density lipoprotein cholesterol (HDL) was analyzed using the direct HDL immunoassay method on the Roche Modular P chemistry analyzer (Roche Diagnostics, 9115 Hague Road, Indianapolis, IN 46250).

Statistical analysis

Student's t test was used to compare the mean levels of continuous variables between participants with and without hyperuricemia. Chi-squared tests were employed to compare differences in categorical variables between groups. Total vitamin C and dietary vitamin C intake were categorized based on quartiles (quartile 1: <25th percentile, quartile 2: ≥25–50th percentile, quartile 3: ≥50–75th percentile, quartile 4: ≥75th percentile). Logistic regression models were used to examine the association between total vitamin C and dietary vitamin C intake and hyperuricemia, separately, and the lowest quartile was used as the reference category. Crude odds ratios (ORs), age- and sex-adjusted ORs, and multivariate-adjusted ORs with 95% confidence intervals (CIs) were calculated from logistic regression analyses. The final multivariable models were adjusted for age, sex, race,

BMI, educational level, smoking status, alcohol consumption, daily total energy intake, hypertension, diabetes, physical activity, TC, and HDL levels. Subsequently, the aforementioned logistic regression analyses stratified by sex were conducted separately to determine the associations between total vitamin C and dietary vitamin C intake and hyperuricemia. Statistical analyses were performed using SPSS version 18.0. All analyses were two-sided, and $p \leq 0.05$ indicated statistical significance.

RESULTS

Among 14 885 participants, the overall prevalence of hyperuricemia was 19.1% (21.5% in men; 16.8% in women). Baseline characteristics of individuals according to hyperuricemia status are presented in Table 1. Compared with controls, both men and women with hyperuricemia tended to be older, Non-Hispanic Black, have hypertension and diabetes, have higher levels of BMI and TC, and have lower HDL levels, dietary vitamin C intake, total vitamin C intake, daily total energy intake, and vigorous recreational activity (all p values <0.05).

Dietary vitamin C intake and risk of hyperuricemia

As presented in Table 2, compared with participants in quartile 1, those in quartiles 2–4 of dietary vitamin C intake had a significantly lower risk of hyperuricemia in the unadjusted model. Similar results were observed after adjustment for age and sex (model 1). The results remained unchanged after further adjustment for race, BMI, educational level, smoking status, alcohol consumption, daily total energy intake, hypertension, diabetes, physical activity, TC, and HDL (model 2). The ORs (95% CIs) of hyperuricemia were 0.84 (0.74–0.95) in quartile 2, 0.83 (0.73–0.94) in quartile 3, and 0.72 (0.63–0.82) in quartile 4. For men, the ORs (95% CIs) of hyperuricemia were 0.79 (0.67–0.93) in quartile 2, 0.87 (0.74–1.02) in quartile 3, and 0.76 (0.63–0.90) in quartile 4 (model 2), and for women, the corresponding quartile results were 0.88 (0.73–1.07), 0.83 (0.69–1.09), and 0.64 (0.52–0.78) in model 2.

Total vitamin C intake and risk of hyperuricemia

As presented in Table 2, compared with participants in quartile 1, those in quartiles 2–4 of total vitamin C intake had a significantly lower risk of hyperuricemia in the unadjusted model, and similar results were obtained after adjustment for age and sex (model 1). The ORs (95% CIs) were 0.87 (0.77–0.99) in quartile 2, 0.85 (0.75–0.96) in quartile 3 and 0.66 (0.58–0.76) in quartile 4 (model 2). Analysis stratified by sex indicated that the association was more pronounced in women. For men, the ORs (95% CIs) of hyperuricemia were 0.95 (0.81–1.12) in quartile 2, 0.95 (0.80–1.12) in quartile 3, and 0.75 (0.63–0.89) in quartile 4 (model 2), and for women, the corresponding results were 0.80 (0.67–0.97), 0.75 (0.62–0.91), and 0.59 (0.49–0.73) in model 2.

DISCUSSION

The current study explored the association between vitamin C intake and the risk of hyperuricemia in the US general adult population, and 14885 participants were assessed. Among the study participants, the overall prevalence of hyperuricemia was 19.1%. After adjustment for cofactors (BMI, smoking status, alcohol consumption, diabetes, physical activity, etc.), total vitamin C and dietary vitamin C intake were inversely associated with the risk of hyperuricemia. In analysis stratified by sex, the inverse correlation between vitamin C intake and hyperuricemia risk was also apparent in both men and women.

Several studies have also demonstrated that vitamin C intake is inversely associated with hyperuricemia. A Korean Multi-Rural Communities Cohort study showed that higher levels of dietary vitamin C intake, but not total vitamin C intake, are associated with a lower risk of hyperuricemia in both men and women.[1] Another population-based cohort study reported that men who consumed higher levels of vitamin C had lower serum uric acid concentration.[25] In addition, a number of clinical randomized controlled trials have demonstrated that vitamin C supplementation decreases serum uric acid.[17,31] A meta-analysis also suggested that oral vitamin C supplementation results in modest serum uric acid reduction.[22] Consistent with these findings, our study found that hyperuricemia was negatively related to dietary vitamin C intake and total vitamin C intake in both men and women.

The clinical benefits of vitamin C on serum uric acid concentrations may be achieved through multiple mechanisms. Notably, vitamin C is already considered as a modulator of serum uric acid via its uricosuric effect, which includes increasing the glomerular filtration rate and competing for renal reabsorption with uric acid; vitamin C and uric acid are both reabsorbed through anion-exchange transport at proximal tubules.[17,18,32] Vitamin C may also act specifically at uric acid reabsorption sites in the apical brush border of the proximal tubule; for example, urate transporter 1 (URAT1), and a Na^+-dependent anion cotransporter (e.g., SLC5A8/A12).[33] The antioxidant effect of vitamin C can reduce oxidative stress and inflammation, which can lower uric acid synthesis and thus provide another potential mechanism.[34]

For achieving validated outcomes and eliminating variants in this study, a major strength was the large sample (14885 participants included), which increased the statistical power for investigating the association between dietary and total vitamin C intakes and hyperuricemia risk. We also conducted an analysis stratified by sex to assess the outcomes in men and women. In addition, the negative association of dietary vitamin C intake and total vitamin C intake with hyperuricemia risk was still statistically significant after adjustment for confounders, which authenticated the associations. However, the cross-sectional design of the study makes it difficult to determine the causality. Additional prospective longitudinal studies and trials should be undertaken to establish a causal association between vitamin C intake and hyperuricemia risk in the general US population. In addition, it was suggested that 24-hour recall tended to underestimate food intake by approximately 10% relative to observed intake.[35]

In conclusion, in this population-based study, we determined that dietary vitamin C and total vitamin C intakes were negatively associated with the risk of hyperuricemia.

Table 1. Modifications of biochemical parameters[†]

Characteristics	Hyperuricemia (total)			Hyperuricemia (men)			Hyperuricemia (women)		
	No	Yes	*p* value	No	Yes	*p* value	No	Yes	*p* value
Number of subjects (%)	12049 (80.9)	2836 (19.1)		5709 (78.5)	1560 (21.5)		6340 (83.2)	1276 (16.8)	
Age (year)	48.4±17.5	54.8±18.0	<0.01	49.6±17.6	51.3±18.4	<0.01	47.3±17.3	59.1±16.6	<0.01
Age group (%)			<0.01			<0.01			<0.01
20-44	44.8	30.2		41.7	39.1		47.5	19.4	
45-59	24.7	23.3		24.9	22.7		24.6	23.9	
60-74	21.2	29.1		22.8	24.2		19.7	35.1	
≥75	9.3	17.4		10.6	14.0		8.2	21.6	
Race (%)			<0.01			<0.01			<0.01
Mexican American	16.7	11.5		16.6	12.2		16.8	10.7	
Other Hispanic	11.2	7.2		10.3	7.4		12.0	7.0	
Non- Hispanic White	45.3	47.7		46.1	48.3		44.5	47.0	
Non- Hispanic Black	18.9	26.0		18.9	23.5		19.0	29.0	
Other Race	7.9	7.6		8.1	8.6		7.7	6.3	
Educational level (%)			0.03			0.35			<0.01
<high school	27.3	27.9		28.4	26.4		26.3	29.7	
High school	22.3	24.3		23.8	23.5		21.0	25.2	
>high school	50.4	47.8		47.8	50.1		52.7	45.1	
Smoke at least 100 cigarettes in life (%)	44.6	50.1	<0.01	55.0	55.1	0.27	29.4	44.0	<0.01
Have at least 12 alcohol drinks/year (%)	67.8	68.7	<0.01	79.3	82.6	<0.01	57.4	51.8	<0.01
BMI (kg/m^2)	28.3±6.3	32.3±7.4	<0.01	28.0±5.6	31.2±6.4	<0.01	28.6±6.9	33.6±8.3	<0.01
Vigorous recreational activity (%)	21.2	14.9	<0.01	26.2	21.9	<0.01	16.8	6.3	<0.01
Hypertension (%)	30. 7	56.2	<0.01	32.2	46.9	<0.01	29.3	67.6	<0.01
Diabetes (%)	10.6	18.7	<0.01	12.4	13.6	<0.01	9.0	25.0	<0.01
TC (mg/dL)	195±41.3	198±42.9	<0.01	191±41.8	196±42.5	<0.01	198±40.6	202±43.3	<0.01
HDL (mg/dL)	53.3±15.8	48.5±15.2	<0.01	48.5±14.2	45.0±13.9	<0.01	57.6±15.9	52.8±15.6	<0.01
Uric acid (mg/dL)	5.0±1.0	7.6±1.0	<0.01	5.6±0.9	8.0±0.9	<0.01	4.5±0.9	7.1±1.0	<0.01
Dietary intake (/day)									
Daily total energy intake (kcal)	2025±773	1922±770	<0.01	2322±813	2178±792	<0.01	1758±624	1610±611	<0.01
Dietary vitamin C intake (mg)	87.9±82.2	76.7±75.0	<0.01	93.0±91.7	82.1±84.9	<0.01	83.2±72.3	70.0±60.1	<0.01
Total vitamin C intake (mg)	163±266	140±228	<0.01	170±302	139±227	<0.01	160±227	142±230	0.03

BMI: body mass index; TC: total cholesterol; HDL: high density lipoprotein cholesterol.
[†]Data are presented as mean ± SD for continuous variables and number (percentage) for categorical variables.

Table 2. Associations between hyperuricemia and vitamin C concentrations among US adults aged ≥20 years, NHANES 2007–2012

	Quartile of vitamin C intake (mg/day)				*p*-trend
	Q1	Q2	Q3	Q4	
Total					
Dietary vitamin C intake (mg/day)	≤30.0	30.0-65.0	65.0-117	117-1837	-
Cases/participants	821/3716	726/3727	695/3721	594/3721	-
Crude OR (95% CI)	1.00 (ref.)	0.85 (0.76-0.95)	0.81 (0.72-0.91)	0.67 (0.60-0.75)	<0.01
Model 1†	1.00 (ref.)	0.81 (0.72-0.91)	0.76 (0.68-0.86)	0.64 (0.57-0.72)	<0.01
Model 2‡	1.00 (ref.)	0.84 (0.74-0.95)	0.83 (0.73-0.94)	0.72 (0.63-0.82)	<0.01
Total vitamin C intake (mg/day)	≤39.4	39.4-91.4	91.4-171	171-6096	-
Cases/participants	822/3722	720/3719	704/3721	590/3723	-
Crude OR (95% CI)	1.00 (ref.)	0.85 (0.76-0.95)	0.82 (0.74-0.92)	0.66 (0.59-0.75)	<0.01
Model 1†	1.00 (ref.)	0.81 (0.73-0.91)	0.77 (0.69-0.86)	0.59 (0.52-0.67)	<0.01
Model 2‡	1.00 (ref.)	0.87 (0.77-0.99)	0.85 (0.75-0.96)	0.66 (0.58-0.76)	<0.01
Men					
Dietary vitamin C intake (mg/day)	≤29.9	29.9-65.7	65.7-123	123-1837	-
Cases/participants	455/1820	375/1818	395/1814	335/1817	-
Crude OR (95% CI)	1.00 (ref.)	0.78 (0.67-0.91)	0.84 (0.72-0.97)	0.68 (0.58-0.80)	<0.01
Model 1†	1.00 (ref.)	0.77 (0.66-0.90)	0.82 (0.70-0.95)	0.68 (0.58-0.79)	<0.01
Model 2‡	1.00 (ref.)	0.79 (0.67-0.93)	0.87 (0.74-1.02)	0.76 (0.63-0.90)	<0.01
Total vitamin C intake (mg/day)	≤38.6	38.6-92.1	92.1-176	176-6096	-
Cases/participants	433/1817	399/1818	400/1819	328/1815	-
Crude OR (95% CI)	1.00 (ref.)	0.90 (0.77-1.05)	0.90 (0.77-1.05)	0.71 (0.60-0.83)	<0.01
Model 1†	1.00 (ref.)	0.89 (0.76-1.04)	0.88 (0.76-1.03)	0.69 (0.58-0.81)	<0.01
Model 2‡	1.00 (ref.)	0.95 (0.81-1.12)	0.95 (0.80-1.12)	0.75 (0.63-0.89)	<0.01
Women					
Dietary vitamin C intake (mg/day)	≤30.0	30.0-64.1	64.1-110	110-1071	-
Cases/participants	369/1904	346/1904	320/1907	241/1901	-
Crude OR (95% CI)	1.00 (ref.)	0.92 (0.79-1.09)	0.84 (0.71-0.99)	0.60 (0.51-0.72)	<0.01
Model 1†	1.00 (ref.)	0.82 (0.69-0.97)	0.71 (0.60-0.85)	0.53 (0.44-0.64)	<0.01
Model 2‡	1.00 (ref.)	0.88 (0.73-1.07)	0.83 (0.69-1.09)	0.64 (0.52-0.78)	<0.01
Total vitamin C intake (mg/day)	≤39.8	39.8-91.0	91.0-167	167-3821	-
Cases/participants	388/1906	323/1902	304/1906	261/1902	-
Crude OR (95% CI)	1.00 (ref.)	0.80 (0.68-0.94)	0.74 (0.63-0.88)	0.62 (0.52-0.74)	<0.01
Model 1†	1.00 (ref.)	0.73 (0.61-0.86)	0.63 (0.53-0.75)	0.48 (0.40-0.57)	<0.01
Model 2‡	1.00 (ref.)	0.80 (0.67-0.97)	0.75 (0.62-0.91)	0.59 (0.49-0.73)	<0.01

OR: odds ratio; CI: confidence interval.
†Model 1 adjusted for age and sex.
‡Model 2 adjusted for age, sex, race, BMI, educational level, smoking status, alcohol consumption, daily total energy intake, hypertension, diabetes, physical activity, TC, and HDL.

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AUTHOR DISCLOSURES

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