

The Dietary Fructose:Vitamin C Intake Ratio Is Associated with Hyperuricemia in African-American Adults

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Abstract

Background: A high fructose intake has been shown to be associated with increased serum urate concentration, whereas ascorbate (vitamin C) may lower serum urate by competing with urate for renal reabsorption.

Objective: We assessed the combined association, as the fructose:vitamin C intake ratio, and the separate associations of dietary fructose and vitamin C intakes on prevalent hyperuricemia.

Methods: We conducted cross-sectional analyses of dietary intakes of fructose and vitamin C and serum urate concentrations among Jackson Heart Study participants, a cohort of African Americans in Jackson, Mississippi, aged 21–91 y. In the analytic sample ($n = 4576$), multivariable logistic regression was used to examine the separate associations of dietary intakes of fructose and vitamin C and the fructose:vitamin C intake ratio with prevalent hyperuricemia (serum urate ≥ 7 mg/dL), after adjusting for age, sex, smoking, waist circumference, systolic blood pressure, estimated glomerular filtration rate, diuretic medication use, vitamin C supplement use, total energy intake, alcohol consumption, and dietary intake of animal protein. Analyses for individual dietary factors (vitamin C, fructose) were adjusted for the other dietary factor.

Results: In the fully adjusted model, there were 17% greater odds of hyperuricemia associated with a doubling of the fructose:vitamin C intake ratio (OR: 1.17; 95% CI: 1.08, 1.28), 20% greater odds associated with a doubling of fructose intake (OR: 1.20; 95% CI: 1.08, 1.34), and 13% lower odds associated with a doubling of vitamin C intake (OR: 0.87; 95% CI: 0.78, 0.97). Dietary fructose and the fructose:vitamin C intake ratio were more strongly associated with hyperuricemia among men than women (P -interaction ≤ 0.04).

Conclusion: Dietary intakes of fructose and vitamin C are associated with prevalent hyperuricemia in a community-based population of African Americans. *J Nutr* 2018;148:419–426.

Keywords: urate, fructose, vitamin C, dietary intake, hyperuricemia

Introduction

Elevated serum uric acid or urate has been found to be associated with an increased risk of developing multiple chronic diseases, including hypertension (1–5), cardiovascular

disease (6–9), and chronic kidney disease (10–13), all of which are particularly prevalent among African Americans. Hyperuricemia is a direct cause of gout through urate crystallization in joint fluid (14, 15). Excessive serum urate appears to increase renin production and cause microvascular and glomerular

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Abbreviations used: eGFR, estimated glomerular filtration rate; JHS, Jackson Heart Study; NIRI, Nutrition Intervention Research Initiative.

lesions, which contributes to the development of glomerular hypertension and kidney injury (10). A randomized clinical trial also reported that reducing serum urate concentrations slowed chronic kidney disease progression (16). A recent study that used data from the NHANES found that the population average serum urate concentration increased by 0.15 mg/dL and the prevalence of hyperuricemia increased by 3.2% from 1988–1994 to 2007–2008 (17). Gout incidence was higher among African Americans than among whites and the magnitude of the prevalence increase over time was higher among African Americans (17, 18).

Dietary factors may influence serum urate concentrations (19). Fructose and vitamin C, which are common in the diet, have been found to have opposing actions on serum concentrations of urate. Both observational and experimental studies have shown that a higher dietary intake of fructose is associated with higher serum urate concentrations (20, 21). The metabolism of fructose produces xanthine and hypoxanthine, which are then used to synthesize uric acid, resulting in elevated serum urate (22). In contrast, vitamin C (ascorbic acid) competes with serum urate for renal reabsorption, thereby reducing serum urate concentrations, especially among people with hyperuricemia (23). Evidence has shown that a coregulation process exists between urate and ascorbate in antioxidant and oxidant activities (24).

The dietary intake of fructose has steadily increased in the United States (25). In a study incorporating data from NHANES and the National Food Consumption Survey, the estimated average dietary intake of fructose increased from 37 g/d to 49 g/d from 1977 to 2005 (26), approaching fructose intake amounts that are associated with adverse health outcomes (27–29). The predominant sources of fructose in the diet are nonalcoholic beverages, contributing 46% of total fructose intake (26). Vitamin C intakes have improved in the United States, especially among African Americans. The prevalence of vitamin C deficiency (defined as a serum concentration $<11.4 \mu\text{mol/L}$) in non-Hispanic blacks decreased from 21.9% in 1988–1994 to 6.7% in 2003–2004 (30). In 1999–2000, ~12% of US adults were taking vitamin C supplements; however, the usage was significantly lower among African Americans (5.1%) than among whites (14.7%) (31). Given the increasing trend of both fructose and vitamin C intakes and their opposite direction of association with serum urate concentrations, we examined the association of dietary fructose and vitamin C, as a ratio and separately, with serum urate concentration and prevalent hyperuricemia in a community-based African-American population.

Methods

Study design. The Jackson Heart Study (JHS) is a prospective cohort of African-American men and women that was designed to investigate risk factors for cardiovascular disease and related cardiometabolic disorders. The details on the design of this study have been previously published (32). Briefly, between 2000 and 2004, 5306 participants were recruited and enrolled from 3 counties in the Jackson, Mississippi metropolitan statistical area (Hinds, Madison, and Rankin). The JHS consists of 22% participants randomly selected from the Jackson, Mississippi study site of the Atherosclerosis Risk in Communities Study (ARIC; 1989) Jackson site, 17% from a randomly selected community sample, 30% from a structured volunteer sample, and the remaining 31% enrolled as family members of JHS participants (33). The original cohort had an eligible age range of 35–84 y of age. Allowance for flexibility in age of family members resulted in a broader age range of enrolled JHS participants (21–91 y).

In the present study, we conducted cross-sectional analyses of baseline dietary and serum urate data. Home interviews and clinical medical examinations were conducted, and blood and urine specimens were collected during the baseline visit. The study protocol was approved by the institutional review boards at the University of Mississippi Medical Center and Johns Hopkins University, and the research was conducted in compliance with the Helsinki Declaration.

Study population. This analysis targeted the entire JHS cohort. We excluded those who had missing data for dietary intake of fructose, dietary intake of vitamin C, or serum urate ($n = 252$); those who were taking medication for gout ($n = 61$); and those who had missing information on covariates ($n = 417$). After applying these exclusion criteria, the analytic sample size was 4576 participants.

Assessment of dietary intake. Dietary intake was assessed with the use of an FFQ modified from the Delta Nutrition Intervention Research Initiative (NIRI) FFQ (34). This FFQ was administered by trained interviewers to JHS participants during the baseline study visit. Participants reported their usual frequency of consumption and portion sizes for 158 food items over the past 6 mo. The Delta NIRI FFQ was developed by the Lower Mississippi NIRI Food Frequency Working Group to assess intakes of regional foods (35). Dietary intakes of fructose and vitamin C were estimated on the basis of the frequency of consumption and portion size of each food item and its nutritional content.

The main exposures were fructose (grams per day), vitamin C (milligrams per day), and the fructose:vitamin C intake ratio (fructose:vitamin C intake ratio = fructose/vitamin C). Fructose, vitamin C, and the fructose:vitamin C intake ratio were \log_2 -transformed to allow for the interpretation of each unit increase on the \log_2 scale as a doubling. Given that the \log_2 -transformed ratio is equivalent to the difference in the individual \log_2 -transformed dietary factors [$\log_2(\text{fructose:vitamin C intake ratio}) = \log_2(\text{fructose/vitamin C}) = \log_2(\text{fructose}) - \log_2(\text{vitamin C})$], this quantity can be interpreted as the relative intake difference between fructose and vitamin C. These dietary exposures were then divided into quartiles for the analysis. We compared levels of dietary intake of fructose and vitamin C in our study population with established levels. Fructose intake was dichotomized as normal (≤ 50 g/d) or high (> 50 g/d) (29). Vitamin C intake was dichotomized as meeting the Institute of Medicine recommendation (> 90 mg/d for men and > 75 mg/d for women) or not meeting the Institute of Medicine recommendation (≤ 90 mg/d for men and ≤ 75 mg/d for women) (36). Other dietary variables included in the analysis were total energy intake (kilocalories per day), alcohol intake (grams per day), and animal protein intake (grams per day).

Outcome ascertainment. The primary outcome of interest was serum urate concentration. In addition to analyzing serum urate concentration as a continuous variable, we defined prevalent hyperuricemia as serum urate ≥ 7 mg/dL, which has been used in previous studies (17, 37). Fasting blood samples were collected from study participants during the baseline study visit. Serum specimens were prepared and stored at -80°C within 2 h after collection. Serum urate concentrations were measured in the University of Mississippi Medical Center laboratory with the use of the uricase method (CV: 1–2%) (38).

Measurement of other covariates. During the baseline study visit, information was obtained on demographic characteristics (date of birth, sex) and health behaviors (smoking status) with the use of a structured questionnaire. We categorized smoking status as current smoker, former smoker, or never smoker.

During the study visit, blood pressure and waist circumference were measured. Sitting blood pressure was obtained with the use of a Hawksley random zero sphygmomanometer (Hawksley and Sons Ltd.) with the proper cuff size. The average of 2 blood pressure measurements was used in the analysis. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or taking antihypertensive medication. Waist circumference was measured to the nearest centimeter. Serum creatinine was measured with the use of the enzymatic method with the Vitros Ortho-Clinical Diagnostics Analyzer and

standardized with the use of the isotope dilution MS traceable method (39). We calculated estimated glomerular filtration rate (eGFR) with the use of the 2009 Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine (40). Participants were asked to bring their current medications (used within the past 2 wk) to the study visit, including prescription and over-the-counter medications, vitamin and mineral supplements, and herbal or home remedies.

Statistical analysis. Baseline characteristics of the study population and dietary factors were reported with the use of descriptive statistics (means, SDs, proportions) for the overall analytic population, according to quartiles of fructose:vitamin C intake ratio and by sex. We used linear regression models to examine the association between each of the 3 dietary exposures separately (fructose, vitamin C, and fructose:vitamin C intake ratio) and serum urate concentration. We used logistic regression models to calculate ORs for the association between the 3 dietary exposures and prevalent hyperuricemia. We tested for trend with the use of the median within each quartile to evaluate the ordered relation across quartiles of the 3 dietary exposures for both the continuous (serum urate concentration) and binary (hyperuricemia) outcomes. We graphically displayed the association between fructose:vitamin C intake ratio and serum urate concentration with the use of a restricted cubic spline with knots at the 25th, 50th, and 75th percentiles. In addition, we graphically displayed the association between eGFR and serum urate concentration with the use of a scatterplot and a locally weighted scatterplot smoothing curve.

We constructed multivariable regression models adjusted for different sets of covariates: model 1 was adjusted for age, sex, smoking status, waist circumference, systolic blood pressure, eGFR, and medication use (diuretic medication, vitamin C supplement); model 2 was adjusted for age, sex, smoking status, waist circumference, systolic blood pressure, eGFR, and dietary factors (total energy, alcohol, animal protein); and model 3 was adjusted for the covariates in models 1 and 2 (age, sex, smoking status, waist circumference, systolic blood pressure, eGFR, medication use, dietary factors). In model 4, vitamin C and fructose were mutually adjusted for each other (i.e., when fructose was the main

exposure, we adjusted for vitamin C; when vitamin C was the main exposure, we adjusted for fructose).

To examine whether an extremely high intake of vitamin C would influence our results, we conducted 2 sensitivity analyses: 1) we excluded individuals taking vitamin C supplements and 2) we excluded individuals with high dietary intakes of vitamin C (>500 mg/d). To assess a priori-hypothesized sex differences in the association between the dietary exposures and serum urate concentration and prevalent hyperuricemia, we conducted stratified analyses by sex and tested for interaction with the use of a likelihood ratio test.

We performed statistical analyses with Stata statistical software, version 13.0 (StataCorp). Tests were 2-sided and significance was assessed at an α level of 0.05.

Results

Baseline characteristics. Among the 4576 JHS participants in the analytic sample, the mean age at baseline was 56 y and 35% were men (Table 1). Approximately one-third of participants were taking diuretic medications and 9% were taking vitamin C supplements. Those participants in the lowest quartile (quartile 1) of fructose:vitamin C intake ratio were older, had a lower baseline eGFR, were more likely to have hypertension and diabetes, and were more likely to report taking diuretic medications and vitamin C supplements at baseline than the higher quartiles (quartiles 2–4). We did not observe substantial variations in BMI, waist circumference, or systolic blood pressure across quartiles. At lower quartiles of fructose:vitamin C intake ratios, total energy intake as well as the consumption of alcohol, animal protein, and sugar-sweetened beverages were lower relative to higher quartiles of fructose:vitamin C intake ratio.

TABLE 1 Baseline demographic and health characteristics and dietary factors by quartile of the dietary fructose:vitamin C intake ratio in African-American adults¹

	Quartile of fructose:vitamin C intake ratio				
	Overall study population (n = 4576)	Quartile 1: 0.0–0.1 (n = 1144)	Quartile 2: 0.1–0.2 (n = 1144)	Quartile 3: 0.2–0.3 (n = 1144)	Quartile 4: 0.3–4.6 (n = 1144)
Age, y	55.5 ± 12.6	58.3 ± 12.0	55.3 ± 12.7	54.3 ± 13.0	54.2 ± 12.5
Male sex, %	35.4	31.8	35.7	38.5	35.7
BMI, kg/m ²	31.8 ± 7.2	31.6 ± 7.1	31.8 ± 6.8	31.6 ± 7.3	32.1 ± 7.7
Waist circumference, cm	100.6 ± 16.1	100.6 ± 16.3	100.5 ± 15.3	100.2 ± 16.6	101.0 ± 16.0
Systolic blood pressure, mm Hg	126.9 ± 18.2	127.1 ± 17.6	126.0 ± 17.5	127.5 ± 18.9	127.1 ± 18.9
eGFR, mL/(min × 1.73 m ²)	94.0 ± 21.7	91.8 ± 21.3	93.9 ± 21.6	94.9 ± 22.4	95.6 ± 21.2
Smoking status, %					
Current smoker	12.3	10.1	10.5	11.5	17.1
Former smoker	18.7	21.7	17.0	16.3	19.8
Never smoker	69.0	68.3	72.6	72.2	63.1
Hypertension (yes), %	60.1	64.5	60.8	58.7	56.6
Diabetes (yes), %	21.7	28.5	25.1	18.0	15.2
Diuretic medication use, %	32.6	38.4	33.7	28.8	29.7
Vitamin C supplement use, %	9.0	30.2	3.0	1.9	1.0
Fructose:vitamin C intake ratio, g/mg	0.20 (0.13–0.30)	0.08 (0.04–0.11)	0.16 (0.14–0.18)	0.24 (0.22–0.27)	0.44 (0.36–0.62)
Intakes of					
Fructose, g/d	24.2 (14.9–39.2)	15.3 (10.0–24.4)	20.0 (12.7–28.6)	28.2 (19.0–39.7)	43.0 (28.2–65.5)
Vitamin C, mg/d	120 (78–191)	216 (116–606)	123 (82–176)	116 (80–163)	84 (58–123)
Energy, kcal/d	2235 ± 911	2056 ± 891	2152 ± 875	2339 ± 913	2393 ± 923
Alcohol, g/d	3.8 ± 11.9	3.5 ± 10.9	3.4 ± 9.5	4.3 ± 12.6	4.1 ± 14.0
Animal protein, g/d	49.7 ± 28.9	47.1 ± 29.7	48.7 ± 28.2	51.7 ± 28.2	51.2 ± 29.2
SSBs, mL/d	561 ± 792	232 ± 395	307 ± 450	572 ± 677	1130 ± 1096

¹Values are means ± SDs, medians (IQRs), or percentages. eGFR, estimated glomerular filtration rate; SSB, sugar-sweetened beverage.

TABLE 2 Associations between dietary intakes of fructose and vitamin C or the fructose:vitamin C intake ratio and serum urate concentrations in African-American adults¹

	Continuous exposures ²	Quartile of 3 dietary exposures ³				P-trend
		Quartile 1 (n = 1114)	Quartile 2 (n = 1114)	Quartile 3 (n = 1114)	Quartile 4 (n = 1114)	
Fructose, g/d		1.0–15.2	15.2–25.0	25.0–41.5	41.5–339.5	
Model 1	0.06 (0.02, 0.09)	Reference	0.05 (–0.06, 0.15)	0.10 (0.00, 0.20)	0.18 (0.07, 0.28)	0.001
Model 2	0.08 (0.04, 0.13)	Reference	0.07 (–0.04, 0.18)	0.15 (0.03, 0.26)	0.26 (0.13, 0.38)	<0.001
Model 3	0.09 (0.05, 0.13)	Reference	0.07 (–0.03, 0.18)	0.16 (0.05, 0.27)	0.26 (0.14, 0.38)	<0.001
Model 4	0.11 (0.06, 0.15)	Reference	0.09 (–0.02, 0.19)	0.18 (0.07, 0.29)	0.30 (0.17, 0.42)	0.53
Vitamin C, mg/d		16.8–78.8	78.9–123.6	123.6–199.3	199.8–1037.6	
Model 1	–0.02 (–0.06, 0.02)	Reference	–0.03 (–0.13, 0.07)	0.00 (–0.10, 0.11)	–0.06 (–0.17, 0.06)	0.43
Model 2	–0.06 (–0.09, –0.02)	Reference	–0.02 (–0.12, 0.09)	0.00 (–0.11, 0.11)	–0.13 (–0.25, –0.02)	0.02
Model 3	–0.02 (–0.06, 0.02)	Reference	–0.02 (–0.13, 0.08)	0.01 (–0.10, 0.11)	–0.05 (–0.17, 0.08)	0.58
Model 4	–0.05 (–0.09, –0.01)	Reference	–0.06 (–0.16, 0.05)	–0.05 (–0.16, 0.06)	–0.13 (–0.26, 0.00)	0.30
Fructose:vitamin C intake ratio, g/mg		0.0–0.1	0.1–0.2	0.2–0.3	0.3–4.6	
Model 1	0.07 (0.04, 0.11)	Reference	0.02 (–0.09, 0.13)	0.05 (–0.06, 0.16)	0.15 (0.04, 0.26)	0.008
Model 2	0.08 (0.05, 0.12)	Reference	0.09 (–0.02, 0.19)	0.09 (–0.01, 0.2)	0.20 (0.09, 0.31)	<0.001
Model 3	0.08 (0.04, 0.11)	Reference	0.03 (–0.08, 0.14)	0.06 (–0.06, 0.17)	0.17 (0.05, 0.28)	0.004

¹Values are β -coefficients (95% CIs); n = 4576. Model 1 adjusted for age, sex, smoking status, waist circumference, systolic blood pressure, estimated glomerular filtration rate, and medication use (diuretic medication, vitamin C supplement); model 2 adjusted for age, sex, smoking status, waist circumference, systolic blood pressure, estimated glomerular filtration rate, and dietary factors (total energy intake, alcohol, animal protein); model 3 adjusted as for model 1 plus dietary factors; and model 4 adjusted as for model 3 plus vitamin C (for the models with fructose as the main exposure) or fructose (for the models with vitamin C as the main exposure).

²The results (β -coefficients) from the continuous analysis can be interpreted as the increase (if positive) or decrease (if negative) in serum urate concentration per doubling of the dietary factor.

³The results (β -coefficients) from the quartile analysis can be interpreted as the increase (if positive) or decrease (if negative) in serum urate concentration associated with a higher quartile (quartile 2, 3, or 4) of dietary intakes of fructose and vitamin C and the fructose:vitamin C intake ratio relative to the lowest quartile (quartile 1).

Levels of dietary intake of fructose and vitamin C. For the overall study population, the median intake of fructose was 24.2 g/d (IQR: 14.9–39.2 g/d), the median intake of vitamin C was 120 mg/d (IQR: 78–191 mg/d), and the median fructose:vitamin C intake ratio was 0.20 g · mg^{–1} · d^{–1} (IQR: 0.13–0.30 g · mg^{–1} · d^{–1}) (Table 1). A total of 709 (15.5%) participants consumed a high amount of fructose (>50 g/d) and 1209 (26.4%) participants consumed amounts of vitamin C below the recommended level of dietary intake (Supplemental Table 1).

Association between dietary factors and serum urate. After adjusting for age, sex, smoking, waist circumference, systolic blood pressure, eGFR, diuretic medication use, vitamin C supplement use, total energy intake, alcohol consumption, and dietary intake of animal protein and vitamin C (model 4), a doubling of fructose intake was associated with an increase in serum urate concentration of 0.11 mg/dL (95% CI: 0.06, 0.15 mg/dL; Table 2). Relative to the lowest quartile, participants in the highest quartile of fructose intake had a 0.30-mg/dL higher serum urate concentration (95% CI: 0.17, 0.42 mg/dL; model 4).

A doubling of vitamin C intake was associated with a decrease in serum urate (–0.05 mg/dL; 95% CI: –0.09, –0.01 mg/dL) in the fully adjusted model (model 4). Participants in the highest quartile of vitamin C intake had a 0.13-mg/dL lower serum urate concentration (95% CI: –0.26, 0.00 mg/dL) relative to those in the lowest quartile of vitamin C intake (model 4).

When these 2 dietary factors were expressed together as a ratio, there was a 0.08-mg/dL (95% CI: 0.04, 0.11 mg/dL) increase in serum urate per doubling of the fructose:vitamin C intake ratio in the fully adjusted model (model 4; Table 2). Participants in the highest quartile of fructose:vitamin C intake ratio had 0.17-mg/dL (95% CI: 0.05-, 0.28-mg/dL) higher serum

urate concentrations than did participants in the lowest quartile of the fructose: vitamin C intake ratio (P-trend = 0.004). Results for the association between fructose:vitamin C intake ratio and serum urate were similar across the 3 models, with a slight attenuation after adjusting for use of diuretic medications and use of vitamin C supplements (model 1 and model 3 compared with model 2). There was a significant inverse association between eGFR and the serum urate concentration (Pearson's $r = -0.41$, $P < 0.001$; Figure 1).

Association between dietary factors and hyperuricemia. Similar patterns were observed for the dichotomized outcome of hyperuricemia defined as serum urate ≥ 7 mg/dL (Table 3) as

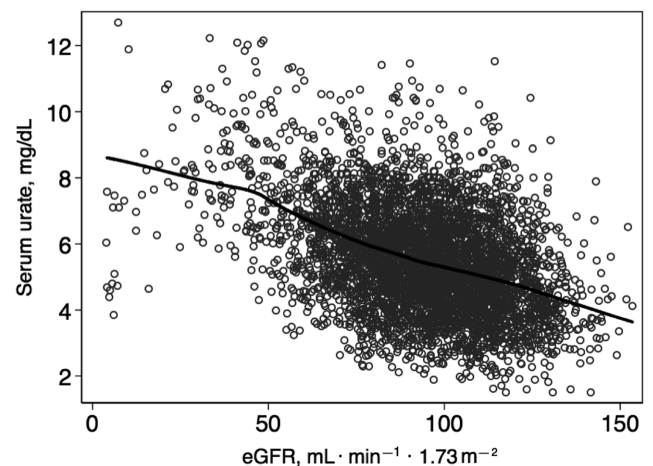


FIGURE 1 Scatterplot of kidney function (eGFR) and serum urate concentrations in African-American adults (n = 4576). The solid line represents the lowess curve for eGFR and serum urate concentration. eGFR, estimated glomerular filtration rate; lowess, locally weighted scatterplot smoothing.

TABLE 3 Association between dietary intakes of fructose and vitamin C and fructose:vitamin C intake ratio and odds of hyperuricemia (≥ 7 mg/dL) in African-American adults¹

	Continuous exposures ²	Quartile of 3 dietary exposures ³				P-trend
		Quartile 1 (n = 1114)	Quartile 2 (n = 1114)	Quartile 3 (n = 1114)	Quartile 4 (n = 1114)	
Fructose, g/d		1.0–15.2	15.2–25.0	25.0–41.5	41.5–339.5	
Model 1	1.08 (0.99, 1.18)	Reference	0.99 (0.77, 1.27)	1.07 (0.83, 1.38)	1.25 (0.97, 1.62)	0.11
Model 2	1.13 (1.02, 1.25)	Reference	1.02 (0.80, 1.31)	1.16 (0.90, 1.51)	1.43 (1.07, 1.90)	0.02
Model 3	1.15 (1.04, 1.28)	Reference	1.05 (0.81, 1.36)	1.19 (0.91, 1.56)	1.48 (1.10, 1.99)	0.01
Model 4	1.20 (1.08, 1.34)	Reference	1.10 (0.85, 1.43)	1.28 (0.98, 1.69)	1.63 (1.20, 2.21)	0.64
Vitamin C, mg/d		16.8–78.8	78.9–123.6	123.6–199.3	199.8–1037.6	
Model 1	0.91 (0.83, 1.00)	Reference	0.89 (0.70, 1.14)	0.87 (0.68, 1.11)	0.76 (0.57, 1.00)	0.08
Model 2	0.89 (0.81, 0.97)	Reference	0.90 (0.71, 1.14)	0.88 (0.69, 1.14)	0.70 (0.54, 0.92)	0.02
Model 3	0.92 (0.83, 1.02)	Reference	0.90 (0.70, 1.15)	0.88 (0.68, 1.14)	0.77 (0.57, 1.04)	0.16
Model 4	0.87 (0.78, 0.97)	Reference	0.85 (0.66, 1.09)	0.80 (0.61, 1.04)	0.66 (0.48, 0.91)	0.90
Fructose:vitamin C intake ratio, g/mg		0.0–0.1	0.1–0.2	0.2–0.3	0.3–4.6	
Model 1	1.16 (1.07, 1.26)	Reference	0.96 (0.74, 1.26)	1.01 (0.77, 1.33)	1.48 (1.14, 1.92)	0.003
Model 2	1.17 (1.08, 1.26)	Reference	1.06 (0.82, 1.36)	1.07 (0.83, 1.37)	1.56 (1.22, 1.99)	<0.001
Model 3	1.17 (1.08, 1.28)	Reference	0.98 (0.75, 1.28)	1.03 (0.79, 1.35)	1.54 (1.18, 2.01)	0.001

¹Values are ORs (95% CIs); n = 4576. Model 1 adjusted for age, sex, smoking status, waist circumference, systolic blood pressure, estimated glomerular filtration rate, and medication use (diuretic medication, vitamin C supplement); model 2 adjusted for age, sex, smoking status, waist circumference, systolic blood pressure, estimated glomerular filtration rate, and dietary factors (total energy intake, alcohol, animal protein); model 3 adjusted as for model 1 plus dietary factors; and model 4 adjusted as for model 3 plus vitamin C (for the models with fructose as the main exposure) or fructose (for the models with vitamin C as the main exposure).

²ORs for hyperuricemia per doubling of the dietary factor.

³The results (ORs) from the quartile analysis can be interpreted as greater (if >1) or lower (if <1) odds of hyperuricemia associated with a higher quartile (quartile 2, 3, or 4) of dietary intakes of fructose and vitamin C or the fructose:vitamin C intake ratio relative to the lowest quartile (quartile 1).

for the continuous outcome of serum urate. A doubling of fructose intake was associated with 20% (OR: 1.20; 95% CI: 1.08, 1.34) greater odds of hyperuricemia in the fully adjusted model (model 4). Participants in the highest quartile of fructose intake had 1.63 times (OR: 1.63; 95% CI: 1.20, 2.21) greater odds of hyperuricemia compared with participants in the lowest quartile of fructose intake. Higher dietary intakes of vitamin C were significantly associated with lower odds of hyperuricemia in the fully adjusted model (model 4).

When these 2 dietary factors were combined as the fructose:vitamin C intake ratio, the odds of hyperuricemia were 1.54 times greater for participants in the highest compared with the lowest quartile of fructose:vitamin C intake ratio (model 3 OR: 1.54; 95% CI: 1.18, 2.01; P-trend = 0.001). The odds of hyperuricemia were 17% greater per doubling of fructose:vitamin C intake ratio in the fully adjusted model (model 3 OR: 1.17; 95% CI: 1.08, 1.28).

Sensitivity analyses of vitamin C intakes. After excluding participants who were using vitamin C supplements (n = 413), the results for the remaining 4163 participants who were not using vitamin C supplements were similar to the main findings for serum urate (Supplemental Table 2) and hyperuricemia (Supplemental Table 3). Likewise, among the 4047 participants with vitamin C intakes ≤ 500 mg/d, results were similar to those from the main analysis for the outcome of serum urate concentration (Supplemental Table 4) as well as for the outcome of hyperuricemia (Supplemental Table 5).

Evaluation of sex differences. Dietary intakes of fructose and vitamin C and serum urate concentrations were higher among men than among women (Supplemental Table 6). In sex-stratified analyses, the magnitude of the results was stronger for men than for women for the association between the 3 dietary exposures and serum urate concentration

(Supplemental Table 7) as well as for the association between the 3 dietary exposures and hyperuricemia (Supplemental Table 8). For example, per doubling of the fructose:vitamin C intake ratio, serum urate concentration was higher by 0.05 mg/dL among women (95% CI: 0.01, 0.09 mg/dL; model 3) and by 0.13 mg/dL among men (95% CI: 0.06, 0.19 mg/dL; model 3) (Supplemental Table 7). The increase in serum urate concentrations as the fructose:vitamin C intake ratio increased was more pronounced among men (Figure 2A) than among women (Figure 2B). There was a significant interaction by sex on the association between fructose (both P ≤ 0.04) and the fructose:vitamin C intake ratio (both P-interaction = 0.01) and both outcomes (i.e., serum urate and hyperuricemia) but not for vitamin C as a separate exposure (both P-interaction > 0.40).

Discussion

In this study in 4576 community-based African Americans, we found that a dietary intake of fructose that is relatively higher than the intake of vitamin C (i.e., the fructose:vitamin C intake ratio) was significantly associated with higher serum urate concentration and greater odds of hyperuricemia. The magnitude of the association between the fructose:vitamin C intake ratio and both serum urate and hyperuricemia were stronger among men than women.

Several previous studies have shown that certain dietary factors influence serum urate concentration. Alcohol, animal sources of protein (e.g., red meat and seafood), and fructose-enriched food items (e.g., high-fructose corn syrup and sugar-sweetened beverages) have been identified as modifiable risk factors for elevated serum urate and gout, whereas vegetable sources of protein (e.g., soy), low-fat dairy products, coffee, and vitamin C have been associated with lower serum urate concentrations (23, 41–44). A clinical trial found that there

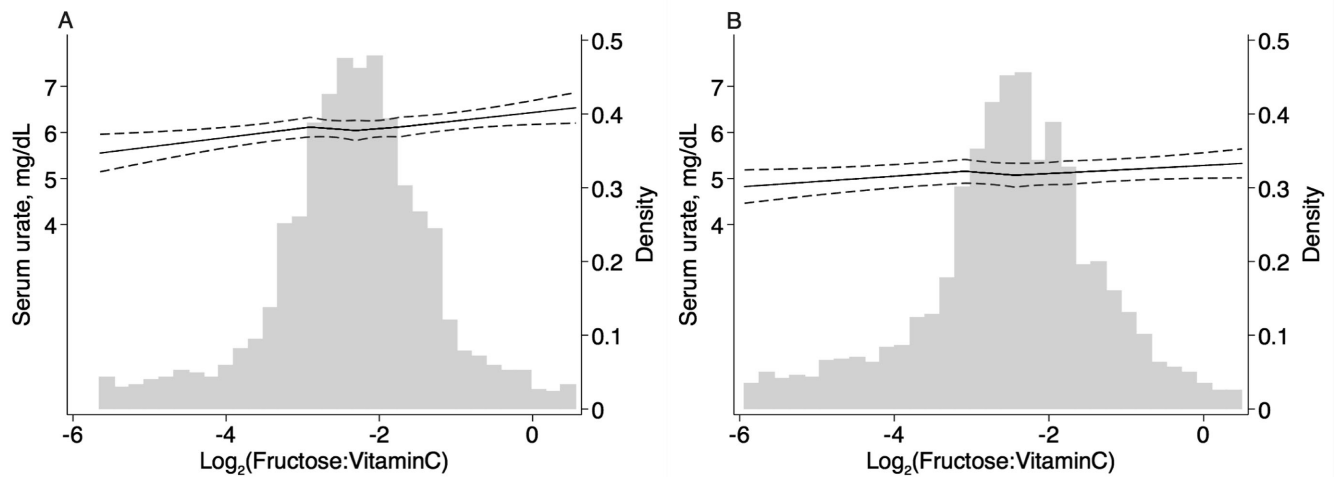


FIGURE 2 Restricted cubic spline of serum urate concentration by fructose:vitamin C intake ratio among men (A) ($n = 1620$) and women (B) ($n = 2956$). The solid lines represent the restricted cubic spline of serum urate concentration by fructose:vitamin C intake ratio, with knots at the 25th, 50th, and 75th percentiles. Fructose:vitamin C intake ratios were truncated at the 1st and 99th percentiles. Dashed lines represent 95% CIs. The gray-shaded histogram represents the distribution of the fructose:vitamin C intake ratio. Regression models were adjusted for age, smoking status, waist circumference, systolic blood pressure, estimated glomerular filtration rate, medication use (diuretic medication, vitamin C supplement), and dietary factors (total energy, alcohol, and animal protein intakes).

was a significant dose-response effect of different consumption amounts of high-fructose corn syrup-sweetened beverages (providing 0%, 10%, 17.5%, and 25% of energy requirements) on 24-h mean serum urate concentration (45). In another randomized clinical trial, Huang et al. (46) found that the use of a vitamin C supplement (500 mg/d) for 2 mo compared with placebo significantly reduced the serum urate concentration among non-smokers.

To the best of our knowledge, the present study is the first to examine the combined influence of dietary intakes of fructose and vitamin C on serum urate concentration with the use of the fructose:vitamin C intake ratio as a measure of relative difference in these 2 dietary factors. In an analysis of 3 prospective cohorts (Nurses' Health Study I, Nurses' Health Study II, and Health Professionals Follow-Up Study), dietary intakes of fructose and vitamin C were not independently associated with incident hypertension after adjusting for the other dietary factor (analyses of fructose intake were adjusted for vitamin C and vice versa) (47). These investigators suggested a mediating role of serum urate on the association between fructose, vitamin C, and incident hypertension, but the results for serum urate as a mediator were not reported.

In our analyses, we found that the dietary intake of fructose as a separate exposure, and when combined as a ratio with vitamin C, had significant independent associations with serum urate concentrations and hyperuricemia after controlling for other covariates. If reducing the intake of fructose is difficult to achieve, then increasing the intake of foods that are rich in vitamin C and low in fructose (e.g., fruit and vegetables) is a potentially easier approach to maintaining or reducing serum urate.

Our a priori-specified sex-stratified analyses showed that the association between the dietary intake of fructose and the fructose:vitamin C intake ratio and serum urate concentration was stronger among men than in women. This observation is supported by findings from previous research. For example, in NHANES 2001–2002, it was reported that men with a high dietary intake of added sugars and sugar-sweetened beverages had higher plasma uric acid concentrations, and there was no significant association among women (P -interaction < 0.01) (48). In

a mouse study, there were differences in the types and locations of transport proteins expressed in female compared with male mice in response to a high-fructose diet, which suggests that sex is a determinant of metabolic adaptation to fructose intake (49). Furthermore, there are differences by sex on the association between genetic variants of the putative fructose transporter solute carrier family 2, facilitated glucose transporter member 9 (SLC2A9) and serum uric acid concentrations (50).

The underlying mechanism of the opposing actions of fructose and vitamin C on serum urate has been documented in previous studies. The phosphorylation of fructose increases the degradation from ATP to AMP, which, as a result, turns on the purine degradation pathway and generates serum urate (51). In contrast, vitamin C lowers serum urate concentration through a uricosuric effect by competing with serum urate on the urate transporter 1 (also known as solute carrier family 22, member 12, or SLC22A12) for re-absorption in the kidney proximal tubule (52, 53). Thus, a higher dietary intake of vitamin C could stimulate renal excretion of urate synthesized during the fructose metabolic process, thereby balancing the serum urate concentration.

Our study has several limitations to acknowledge. First, dietary intakes of fructose and vitamin C were estimated with the use of self-report of food consumption assessed via FFQ, which may be influenced by measurement error and recall bias. Second, the cross-sectional study design limited our ability to establish temporality between dietary intake and serum urate concentration. However, because the FFQ estimated the average dietary intake during the past 6 mo, we can be confident that these estimates of dietary intakes of fructose and vitamin C preceded the measurement of serum urate concentration. Measurements of serum urate were not available at follow-up study visits. Reverse causality was less likely to be a concern in our study, especially after we excluded individuals who were taking gout medication at baseline. Third, there may be residual confounding due to incomplete adjustment for dietary factors. In conclusion, the dietary fructose:vitamin C intake ratio was significantly associated with the serum urate concentration and prevalent hyperuricemia among African Americans.

Acknowledgments

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