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Total, Dietary, and Supplemental Vitamin C Intake and Risk of Incident Kidney Stones

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Abstract

Background—Previous studies of vitamin C and kidney stones were conducted mostly in men and either reported disparate results for supplemental and dietary vitamin C or did not examine dietary vitamin C.

Study Design—Prospective cohort analysis.

Setting & Participants—156,735 women in the Nurses' Health Study (NHS) I and II and 40,536 men in the Health Professionals Follow-up Study (HPFS).

Predictor—Total, dietary and supplemental vitamin C intake, adjusted for age, BMI, thiazide use, and dietary factors.

Outcomes—Incident kidney stones

Results—During median follow-up of 11.3–11.7 years, 6,245 incident kidney stones were identified. After multivariable adjustment, total vitamin C intake (<90 [reference], 90–249, 250–499, 500–999 and ≥1,000 mg/d) was not significantly associated with the risk of kidney stones among women, but was among men (HRs of 1.00 [reference], 1.19 [95% CI, 0.99–1.46], 1.15 [95% CI, 0.93–1.42], 1.29 [95% CI, 1.04–1.60] and 1.43 [95% CI, 1.15–1.79], respectively; p for

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Contributions: Research idea and study design: PMF, ENT, GG, GCC; data acquisition: ENT, GCC; data analysis/interpretation: PMF, ENT, GCC; statistical analysis: PMF; supervision or mentorship: ENT, GCC, GG. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. PMF takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

trend = 0.005). Median total vitamin C intake for the 500–999 mg/d category was about 700 mg/d. Supplemental vitamin C intake (no use [reference], <500, 500–999, and ≥1,000 mg/d) was not significantly associated with the risk of kidney stones among women, but was among men (HR, 1.19 [95% CI, 1.01–1.40] for ≥1,000 mg/d; p for trend = 0.001). Dietary vitamin C intake was not associated with stones among men or women, although few participants had dietary intakes >700 mg/d.

Limitations—Nutrient intakes derived from food-frequency questionnaires, lack of data on stone composition for all the cases.

Conclusions—Total and supplemental intake of vitamin C was significantly associated with a higher risk of incident kidney stones in men, but not among women.

Keywords

kidney disease; nutrition; diet; supplements; urolithiasis; vitamin C; ascorbic acid; kidney stone formation; incident kidney stone; calcium oxalate; urinary oxalate excretion; food-frequency questionnaire (FFQ); gender difference; risk factor

Kidney stones are common, with a lifetime prevalence of about 10% in the US population. Diet is thought to play an important role in the development of kidney stones, particularly intakes of calcium,[1–3] sodium,[1,3] fructose,[4] water and other beverages[5–8]. Ascorbic acid, or vitamin C, is an essential nutrient acting as a cofactor in several enzymatic pathways, the main dietary sources of which are fresh fruits and vegetables. Ingested vitamin C is partly converted to oxalate and excreted in the urine, thus potentially increasing the risk of calcium oxalate stone formation.[9,10] In a metabolic study in 24 individuals, 2 grams daily of ascorbic acid increased urinary oxalate excretion by about 22%.[11]

Two previous epidemiologic studies have addressed kidney stone risk associated with vitamin C intake in men. In a prospective cohort study of men in the Health Professionals Follow-Up Study (HPFS), 1,000 mg/d or more of total vitamin C intake was associated with a 41% higher risk of stones compared with 90 mg/d or less after adjusting for age, body mass index (BMI), use of thiazide diuretics, and dietary factors.[12] Recently, another study also reported a positive association between supplemental vitamin C intake and kidney stones in a cohort of 23,355 Swedish men; the multivariable adjusted relative risk associated with supplemental use of vitamin C was almost double compared with no use.[13] To date, the only study in women was performed in the Nurses' Health Study (NHS) I cohort and found no association between intake of vitamin C and risk of stones.[14]

However, the relationship between vitamin C intake and kidney stone formation remains unclear. First, the different results for men and women warrant further investigation. Dietary risk factors for kidney stones may vary by sex.[3,12,15] Second, the risk associated with a higher intake (≥1,000 mg/d) of supplemental vitamin C in the previous study in HPFS was of borderline statistical significance (hazard ratio [HR], 1.16; 95% confidence interval [CI], 0.97–1.39; p for trend = 0.01).[12] Finally, interpretation of urinary oxalate excretion rates after vitamin C loading in metabolic studies may be complicated by ex vivo non-enzymatic conversion of urinary vitamin C into oxalate.[16]

To examine the independent associations of total, supplemental and dietary vitamin C and risk of kidney stones in women, we analyzed data from a large prospective cohort, the NHS II. We also updated our previous analyses of the NHS I and the HPFS cohorts to include 12 years of additional follow-up for each cohort, which provided greater statistical power.

Methods

Study Population

The NHS I enrolled 121,700 female nurses aged 30–55 years in 1976; NHS II enrolled 116,430 female nurses aged 25–42 years in 1989; HPFS enrolled 51,529 male health professionals aged 40–75 years in 1986. Participants were asked to complete biennial questionnaires with information on medical history, lifestyle and medications; information from the questionnaires was updated every 2 years, or every 4 years for the food frequency questionnaires (FFQs). For the current analysis, participants who reported a history of kidney stones prior to the start of time at risk were excluded from the analysis. Similarly, those with a history of cancer (except for non-melanoma skin cancer) prior to baseline were excluded from the analysis, and those who developed cancer during follow-up were censored, as this condition might have affected their dietary or other behaviors. These studies were approved by the Partners HealthCare institutional review board. Return of completed baseline and biennial questionnaires was accepted by the institutional review board as implied informed consent.

Assessment of Vitamin C Intake and Other Nutrients

In 1986 (NHS I and HPFS) and 1991 (NHS II), participants were asked to complete a FFQ that asked about the average use of more than 130 foods and 22 beverages in the previous year; dietary information was updated every four years. Validation studies have demonstrated the reliability of the FFQ.[17,18] The intake of dietary factors was calculated from the reported frequency of consumption of each specified unit of food and, except for oxalate, from US Department of Agriculture data on the content of the relevant nutrient in specified portions. The oxalate content of most foods on the FFQ, as well as of frequently consumed foods written in, was measured by capillary electrophoresis as previously described.[19] The FFQ also inquires about vitamin and mineral supplements. Users of multivitamins and vitamin C supplements are asked to name the specific brand and to provide the amount and frequency of use. Our database contains the composition of over 1000 brands of multivitamins and calculates the amount of vitamin C (and other vitamins and minerals) as the frequency of intake multiplied by composition. The same method is used for individual vitamin C supplements. For the current analysis, we used data from the FFQ for total vitamin C (dietary plus supplement sources); intake of alcohol; dietary intake of calcium, sodium, potassium, magnesium, fructose, oxalate, phytate, animal protein, and total fluids; and calcium supplements. All nutrients were energy-adjusted.

Assessment of Kidney Stones

Participants who reported an incident kidney stone were asked to complete a supplementary questionnaire about the date of occurrence and associated signs and symptoms such as pain or hematuria. A kidney stone associated with pain or hematuria was the study outcome.

Medical record validation studies confirmed the kidney stone diagnosis in more than 95% of cases among participants who submitted the supplementary questionnaire.[20] Stone composition was available in a subsample of the cases and found to be ≥50% calcium oxalate in 77% of NHS I, 79% of NHS II and 86% of HPFS participants.[20]

Assessment of Other Covariates

Updated information from the questionnaires was used for the following variables: age, BMI, and use of thiazide diuretics. Self-reported weight, from which BMI was calculated, was validated in the NHS I and HPFS cohorts.[21]

Statistical Analysis

The study design was prospective; information on diet was collected before the diagnosis of the kidney stone. We analyzed the association between total vitamin C and risk of stones using categories of vitamin C of <90, 90–249, 250–499, 500–999 and ≥1,000 mg/day. We selected these cutpoints based on our previous study in men.[12] We updated exposure and covariates every four years. We allocated person-time contributed by each participant during follow-up to the respective category of vitamin C intake and calculated incidence rates of kidney stones for each category. Age- and multivariable adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for stones in each category of vitamin C intake were computed separately in each cohort with Cox proportional hazards regression models. We adjusted for age, BMI (13 categories), use of thiazides (yes/no), supplemental calcium intake (no use, <100, 100–499, ≥500 mg/d), intake of alcohol (7 categories), and dietary intakes of calcium, sodium, potassium, magnesium, fructose, oxalate, phytate, animal protein and fluid (all quintiles). We further analyzed the association using quintiles of total vitamin C intake and repeated the analyses in the NHS I and NHS II cohorts with a referent category of total vitamin C intake of <75 mg/d, which is the recommended daily allowance (RDA) for women. Linear trends were evaluated using mid-points for categories of vitamin C intake and median values of vitamin C intake for quintiles; non-linear relations were explored with models that included total vitamin C intake using restricted cubic splines with knots at quintiles. Finally, we constructed models of dietary and supplemental vitamin C intake separately with the following categories: <90, 90–249 and ≥250 mg/d for dietary intake and no use, <500 mg/d, 500–999 mg/d, and ≥1,000 mg/d for supplemental intake. Also in these analyses, midpoints for each category were used to test for linear trends across categories. Time at risk was 1986–2006 for NHS I, 1991–2011 for NHS II and 1986–2010 for HPFS.

Estimates obtained from the NHS I and NHS II cohorts were pooled with random-effects meta-analysis after evaluation of heterogeneity. Pooled results are presented for the two cohorts. For descriptive tables, variables were age-standardized using direct standardization to the overall age distribution (in 5-year age categories) in the study population.

Results

The analysis included 197,271 participants, with 2,494,789 person-years of follow-up. During a median follow-up of 11.7 years for NHS I, 11.5 years for NHS II, and 11.3 years for HPFS, 6,245 incident kidney stone events occurred. Baseline characteristics of the study

cohorts are reported in Tables 1 to 3. In all the cohorts, the use of calcium supplements as well as intakes of potassium, magnesium, oxalate and phytate tended to be higher across vitamin C categories. Among NHS I participants, age and intake of dietary calcium tended to be higher across total vitamin C categories. Among NHS II participants, BMI tended to be lower across total vitamin C categories.

Results of age-adjusted and multivariable adjusted analyses for total vitamin C intake are shown in Table 4. For the NHS cohorts, the age-adjusted HR for total vitamin C intake of ≥1,000 compared with <90 mg/d was 0.76 (95% CI, 0.69–0.82; p for trend = 0.001). After multivariable adjustment, the HR for the same comparison was 0.99 (95% CI, 0.90–1.09; p for trend = 0.1). The analysis of quintiles of total vitamin C intake yielded similar results: the adjusted HR for the highest quintile compared with the lowest was 1.05 (95% CI, 0.92–1.20; p for trend = 0.6). The multivariable adjusted HR for total vitamin C intake of ≥1,000 mg/d compared with taking less than the RDA of 75 mg/d was 1.04 (95% CI, 0.93–1.17).

For HPFS, the age-adjusted HR for total vitamin C intake of ≥1,000 compared with <90 mg/d was 0.98 (95% CI, 0.80–1.20; p for trend = 0.6). After multivariable adjustment, the HR was 1.43 (95% CI, 1.15–1.79; p for trend = 0.005). The association between total vitamin C and higher risk was statistically significant only for the highest two categories of intake, and the median total vitamin C for the 500–999 mg/d intake category averaged approximately 700 mg/d over the course of the study. The analysis of quintiles of total vitamin C intake yielded similar results: the multivariable adjusted HR for the highest quintile compared with the lowest was 1.22 (95% CI, 1.04–1.43; p for trend = 0.01).

Among NHS I participants, the change in point estimates from the age-adjusted to the multivariable-adjusted model for total vitamin C was due predominantly to inclusion of BMI and calcium and potassium intakes into the regression models. Among NHS II participants, the change in point estimates from the age-adjusted to the multivariable-adjusted model was due predominantly to inclusion of BMI and intakes of alcohol, total fluid, calcium and potassium. Among HPFS participants, the change in point estimates from the age-adjusted to the multivariableadjusted model was due predominantly to inclusion of potassium intake into the regression models, and to a lesser extent to BMI and intake of calcium.

Results of age-adjusted and multivariable-adjusted analyses for supplemental vitamin C intake are shown in Table 5. The multivariable-adjusted HR for those taking the highest amount of supplemental vitamin C (≥1,000 mg) compared with those not taking any supplemental vitamin C was 0.90 (95% CI, 0.79–1.04; p for trend = 0.5) in the NHS cohorts and 1.19 (95% CI, 1.01–1.40; p for trend = 0.001) in the HPFS cohort.

Restricted cubic splines analysis confirmed no significant association between intake of total vitamin C and risk of stones in the NHS cohorts (Figure 1). In HPFS, the p-value for non-linearity for the cubic spline was 0.4 (Figure 2). By inspection, the risk became statistically significant at total vitamin C intakes of 700–800 mg/d. The HPFS participants with total vitamin C intake >700 mg/d in general consumed vitamin C supplements: few men had dietary vitamin C intakes of 700 mg/d or more. Splines for dietary and supplemental intakes are reported in Figures S1–S4 (provided as online supplementary material).

There was no association between intake of dietary vitamin C and incident kidney stones in any cohort (Table S1): the multivariableadjusted HR for dietary vitamin C intake of ≥250 compared with <90 mg/d was 0.92 (95% CI, 0.68–1.24; p for trend = 0.3) in the NHS cohorts and 0.95 (95% CI, 0.75–1.19; p for trend = 0.7) in the HPFS cohort.

Discussion

We found no association between intake of total, dietary or supplemental vitamin C and risk of incident kidney stones in 2 large cohorts of women. We also confirmed the previously reported positive association in a cohort of men, with increased statistical power and precision.

Vitamin C intake has been proposed as a risk factor for kidney stone formation because vitamin C may increase urinary oxalate excretion.[10,11] However, it is possible that this finding might be due to non-enzymatic *ex vivo* conversion of vitamin C into oxalate in the collection vessel.[16] When urine specimens were treated with immediate acidification at a pH of 2 and frozen at −30°C, intravenous administration of large amounts of vitamin C up to 1.5 g per kilogram of body weight resulted in oxalate conversion of less than 0.5% of the vitamin C load.[22] In contrast, urine sample handling, storage and analysis without acidification and immediate freezing resulted in up to 25-fold increase in urine oxalate after intravenous administration of vitamin C.[22]

Two previous population-based studies have assessed the association between intake of vitamin C and incidence of kidney stones in men. In the prior study of HPFS, intake of 1,000 mg/d or more of total vitamin C was associated with a 41% (95% CI, 11%–80%) increased risk of developing a first stone, after multivariable adjustment for other risk factors.[12] In that study, the higher risk associated with supplemental intake of vitamin C was not statistically significant; the significant association between higher risk and supplemental vitamin C intake in the current, updated study is likely due to higher statistical power resulting from 12 years of additional follow-up and >25% more cases. A recent analysis of over 23,000 Swedish men showed an increased risk associated with use of supplemental vitamin C (multivariable-adjusted HR, 1.92; 95% CI, 1.33–2.77) compared with no use.[13] Although data on supplemental vitamin C dose was not available, a dose-response relation was suggested, with HRs of 1.66 (95% CI, 0.99–2.79) for intakes of less than 7 vitamin C capsules per day and of 2.23 (95% CI, 1.28–3.88) for intakes of 7 vitamin C capsules or more per day when compared with no use.[13] In that study, no data were presented for dietary or total vitamin C intake.

The reason for the disparate results between men and women is unclear. However, we previously reported differential associations by sex for several dietary risk factors for stones, including animal protein, sucrose, potassium, sodium and phytate.[3,12,15] It is possible that the effect of vitamin C on kidney stone risk is different in men and women, and some data suggest the potential for sex differences in vitamin C metabolism.[23,24]

We did not find any association between dietary vitamin C intake and risk of stones in the HPFS cohort. However, this finding might be due to the relative low number of participants

with very high intakes of dietary vitamin C: the median intake for the highest quintile of dietary vitamin C was 266 mg/d. Visual inspection of spline curves suggests that the risk would significantly increase at values of of 700–800 mg/d (Figure 2); in the HPFS cohort there were few participants with that level of dietary intake.

Our study has limitations. First, the possibility of unmeasured or residual confounding factors cannot be excluded. It is possible that the disparate results between dietary and supplemental vitamin C in men indicate unknown differences between supplement and non-supplement users that affected our results. Second, nutrient intakes were derived from FFQs, although they were validated. Third, we did not have stone composition reports or 24-hour urine data for most of the participants in our study. Although the majority of kidney stones in these cohorts were likely the calcium oxalate type, we would not expect to see associations between vitamin C intake and other types of kidney stones. Fourth, it is possible that much higher levels of vitamin C intake than we observed in our study might increase risk of kidney stones in women. Finally, our cohorts were predominantly white, and the results of our study might not be generalizable to different races.

In conclusion, higher total and supplemental vitamin C intakes were not associated with risk of incident kidney stones in two large cohorts of women, whereas they were associated with higher risk in a large cohort of men. Dietary vitamin C was not associated with risk in any cohort. We advise that male calcium oxalate stone formers abstain from supplemental but not dietary vitamin C. Future studies are needed to examine associations between vitamin C, oxalate metabolism, and kidney stone formation and to explore the possible effects of sex on the relationship between vitamin C intake and kidney stone risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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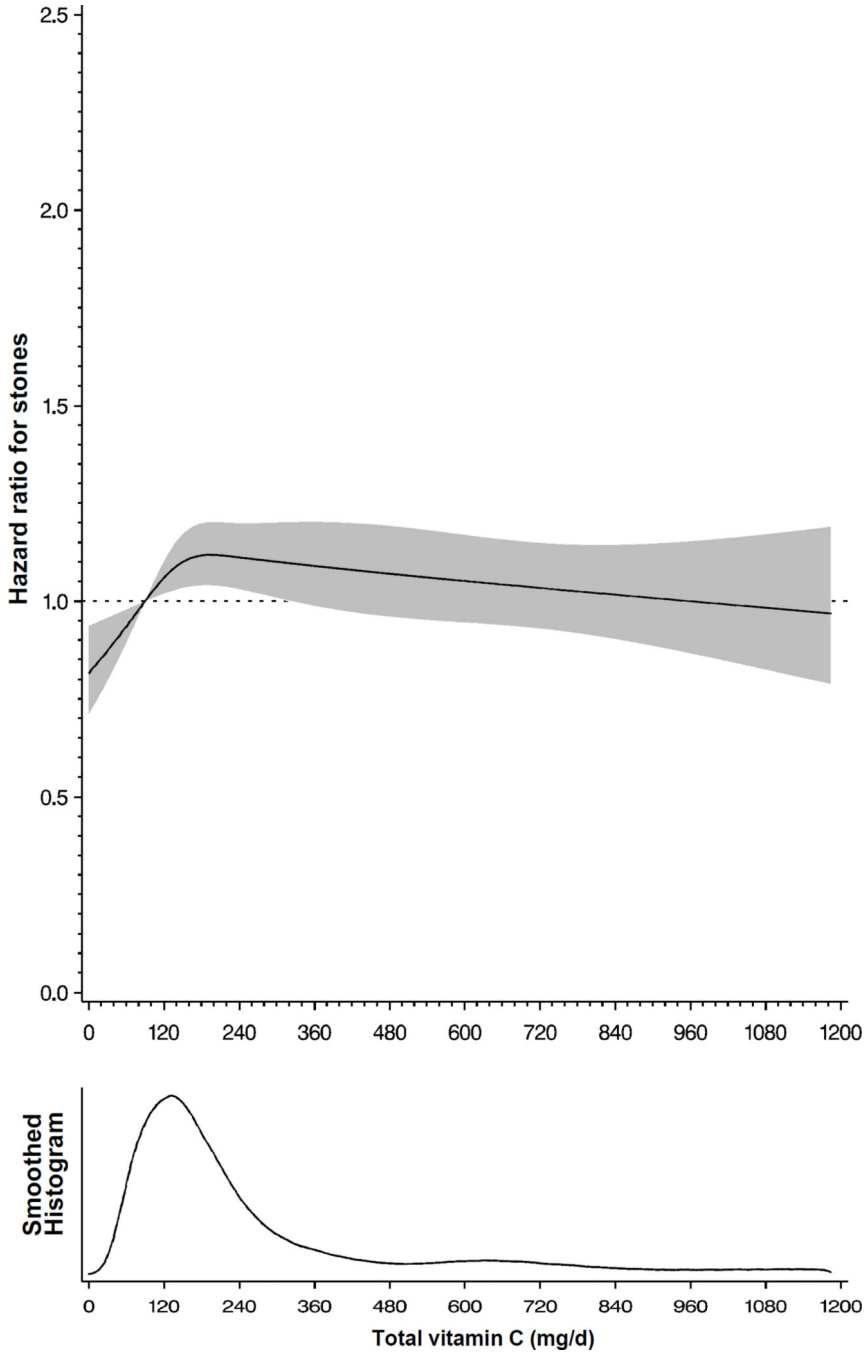

Figure 1. Restricted cubic spline of total vitamin C intake and risk of incident kidney stones: Nurses' Health Studies I and II

Model adjusted for age, BMI, thiazide use, use of calcium supplements, intake of calcium, sodium, potassium, magnesium, fructose, oxalate, phytate, animal protein, total fluid and alcohol.

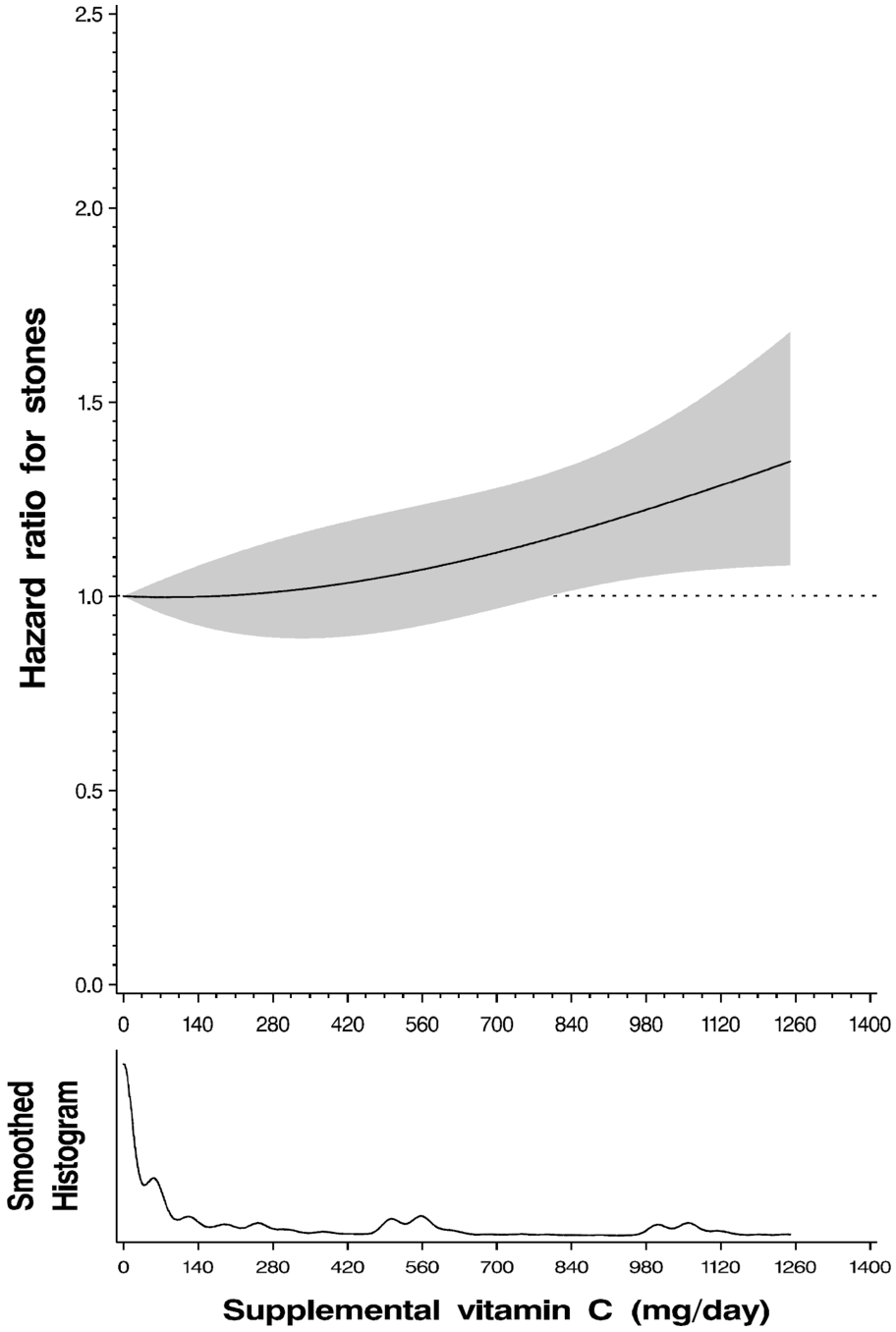

Figure 2. Restricted cubic spline of total vitamin C intake and risk of incident kidney stones: Health Professionals Follow-up Study

Model adjusted for age, BMI, thiazide use, use of calcium supplements, intake of calcium, sodium, potassium, magnesium, fructose, oxalate, phytate, animal protein, total fluid and alcohol.

Table 1

Age-standardized baseline characteristics by intake of total vitamin C: NHS I

	Total Vitamin C				
	<90 mg/d	**90–249 mg/d**	**250–499 mg/d**	**500–999 mg/d**	**≥1,000 mg/d**
Vitamin C, mg/d	67.8(15.8)	162(43)	337(67)	700(129)	1,405(343)
Age, y*	51.1(7.1)	52.7(7.2)	53.6(7.1)	53.9(7.1)	54.1(6.9)
BMI, kg/m^2	25.6(5.1)	25.4(4.8)	25.2(4.7)	24.8(4.5)	24.9(4.7)
Thiazide use	11	13	15	13	13
Calcium supplement use	32	48	66	79	86
Dietary calcium, mg/d	662(273)	718 (250)	733(249)	739 (251)	743(273)
Potassium, mg/d	2,547(508)	3,015(531)	3,272(662)	3,179(665)	3,284(724)
Magnesium, mg/d	252(53)	290(58)	321(72)	322(74)	339(84)
Total fructose, g/d	15.1(9.4)	20.8(7.6)	25.4(9.5)	23.2(9.6)	23.7(10.3)
Oxalate, mg/d	88.4(64.1)	113(80)	135(116)	130(104)	141(117)
Phytate, mg/d	621(235)	692(245)	727(278)	751(300)	793(335)
Animal protein, g/d	53.5(14.8)	54.9(13.4)	54.5(14.2)	54.8(14.0)	55.3(15.4)
Alcohol intake, g/d*	1.1 [0–7.5]	1.8[0–7.6]	1.8[0–7.4]	1.8[0–7.8])	1.8[0–7.8]
Fluid volume, L/d	1.84(0.73)	1.98(0.69)	2.13(0.74)	2.10(0.75)	2.06(0.73)

Note: Values for categorical variables are given as percentage and those for continuous variables, as mean ± standard deviation or median [interquartile range], and are standardized to age distribution of study population, except where otherwise specified. Nutrient intakes are energy-adjusted.
BMI, body mass index; NHS, Nurses' Health Study

*Value is not age adjusted;

Table 2

Age-standardized baseline characteristics by intake of total vitamin C: NHS II

	Total Vitamin C				
	<90 mg/d	**90–249 mg/d**	**250–499 mg/d**	**500–999 mg/d**	**≥1000 mg/d**
Vitamin C, mg/d	68.5(15.1)	154(43)	333(67)	699(136)	1,492(460)
Age, y *	36.4(4.6)	36.5(4.7)	36.4(4.7)	37.3(4.6)	37.8(4.5)
BMI, kg/m^2	25.1(5.8)	24.6(5.2)	24.3(5.1)	23.9(4.8)	23.9(5.1)
Thiazide use	2	2	2	2	2
Calcium supplements use	11	30	54	59	67
Dietary calcium, mg/d	815(313)	895(300)	911(303)	910(312)	909(311)
Potassium, mg/d	2,538(456)	2,963(477)	3,162(583)	3,091(591)	3,137(620)
Magnesium, mg/d	268(54)	314(65)	344(80)	352(89)	377(110)
Total fructose, g/d	19.1(13.5)	22.6(9.6)	26.7(11.1)	24.9(10.9)	25.4(11.6)
Oxalate, mg/d	98.1(72.0)	134(108)	158(139)	158(136)	180(184)
Phytate, mg/d	725(217)	782(232)	813(252)	825(268)	870(293)
Animal protein, g/d	64.1(16.7)	64.8(16.0)	62.2(17.3)	63.0(17.6)	61.7(19.4)
Alcohol intake, g/d*	0.9 [0–3.1]	0.9 [0–3.5]	0.9 [0–3.3]	1.0 [0–4.0]	1.0 [0–3.9]
Fluid volume, L/d	1.97(0.80)	2.13(0.81)	2.21(0.86)	2.19(0.88)	2.11(0.85)

Note: Values for categorical variables are given as percentage and those for continuous variables, as mean ± standard deviation or median [interquartile range], and are standardized to age distribution of study populati except where otherwise specified. Nutrient intakes are energy-adjusted.
BMI, body mass index; NHS, Nurses' Health Study

*Value is not age adjusted;

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Table 3

Age-standardized baseline characteristics by intake of total vitamin C: HPFS

	Total vitamin C				
	<90 mg/d	**90–249 mg/d**	**250–499 mg/d**	**500–999 mg/d**	**≥1,000 mg/d**
Vitamin C, mg/d	67.0(15.9)	164(43)	343(69)	716(126)	1,530(389)
Age, y *	51.5(9.1)	53.7(9.8)	54.4(9.9)	55.0(9.8)	54.3(9.5)
BMI, kg/m^2	25.8(3.4)	25.6(3.4)	25.4(3.4)	25.2(3.1)	25.1(3.3)
Thiazide use	8	9	9	9	9
Calcium supplement use	5	11	25	44	57
Dietary calcium, mg/d	746(325)	798(301)	815(292)	813(303)	814(314)
Potassium, mg/d	2,850(550)	3,338(588)	3,645(718)	3,619(787)	3,744(834)
Magnesium, mg/d	302(64)	337(67)	370(81)	381(89)	404(103)
Total fructose, g/d	17.8(10.9)	23.8(9.5)	28.9(11.4)	27.9(12.7)	27.9(12.7)
Oxalate, mg/d	103(75)	138(144)	157(139)	152(129)	168(160)
Phytate, mg/d	812(335)	905(358)	973(399)	1,009(417)	1,068(451)
Animal protein, g/d	67.6(18.0)	68.1(17.2)	66.7(17.7)	67.1(18.4)	67.9(18.8)
Alcohol intake, g/d*	6.0[0–17.1]	6.0[1.0–15.4]	5.3[0.9–13.9]	6.0[0.9–15.0]	5.8[0.9–15.0]
Fluid volume, L/d	1.93(0.81)	1.92(0.77)	1.99(0.80)	1.99(0.81)	1.91(0.78)

Note: Values for categorical variables are given as percentage and those for continuous variables, as mean ± standard deviation or median [interquartile range], and are standardized to age distribution of study population except where otherwise specified. Nutrient intakes are energy-adjusted.

BMI, body mass index; HPFS, Health Professionals Follow-up Study

* Value is not age adjusted

Table 4

HRs of incident kidney stones by categories of total vitamin C intake in NHS I and II and HPFS cohorts

	Total Vitamin C					P for trend
	<90 mg/d	90–249 mg/d	250–499 mg/d	500–999 mg/d	≥1,000 mg/d	
NHS I and II						
Median total vitamin C intake (mg/d)						
NHS I	71	158	321	683	1,310	
NHS II	71	148	315	678	1,377	
Cases	661	2,420	635	419	257	
Person-time (y)	318,326	1,327,698	397,669	272,045	179,051	
Age-adjusted HR (95% CI)	1.00 (reference)	0.93 (0.85–1.01)	0.84 (0.75–0.94)	0.82 (0.76–0.90)	0.76 (0.69–0.82)	0.001
Multivariable HR (95% CI)	1.00 (reference)	1.12 (1.02–1.23)	1.09 (0.97–1.24)	1.08 (0.98–1.19)	0.99 (0.90–1.09)	0.1
HPFS						
Median total vitamin C intake (mg/d)	69	160	329	709	1,440	
Cases	157	870	303	263	260	
Person-time (ys)	45,363	275,454	120,988	91,906	81,316	
Age-adjusted HR (95% CI)	1.00 (reference)	0.98 (0.82–1.16)	0.81 (0.67–0.98)	0.90 (0.74–1.10)	0.98 (0.80–1.20)	0.6
Multivariable HR (95% CI)	1.00 (reference)	1.19 (0.99–1.46)	1.15 (0.93–1.42)	1.29 (1.04–1.60)	1.43 (1.15–1.79)	0.005

Note: Multivariable analysis adjusted for age; body mass index; thiazide use; supplemental calcium intake; intake of dietary calcium, sodium, potassium, magnesium, fructose, oxalate, phytate, animal protein, and total fluid; and alcohol intake. For illustrative purposes, medians for total vitamin C were derived from responses to the 1986 (NHS I, HPFS) and 1991 (NHS II) dietary questionnaires. However, total vitamin C intake was updated throughout the study. CI, confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; NHS, Nurses' Health Study

Table 5

HRs of incident kidney stones by categories of supplemental intake of vitamin C in NHS I and II and HPFS cohorts

	Supplemental Vitamin C Intake				P for trend
	No use	<500 mg/d	500–999 mg/d	≥1,000 mg/d	
NHS I and II					
Median supp. vitamin C intake (mg/d)					
NHS I	0	90	560	1,060	
NHS II	0	60	545	1,060	
Cases	1,856	1,891	363	282	
Person-time (y)	988,407	1,086,075	228,542	191,764	
Age-adjusted HR (95% CI)	1.00 (reference)	0.90 (0.84–0.96)	0.88 (0.79–0.99)	0.79 (0.70–0.89)	0.002
Multivariable HR (95% CI)	1.00 (reference)	0.98 (0.90–1.06)	1.01 (0.90–1.15)	0.90 (0.79–1.04)	0.5
HPFS					
Median supp. vitamin C intake (mg/d)	0	125	560	1,120	
Cases	645	737	203	268	
Person-time (years)	189,156	271,029	74,713	80,129	
Age-adjusted HR (95% CI)	1.00 (reference)	0.83 (0.74–0.93)	0.82 (0.70–0.99)	0.98 (0.84–1.13)	0.3
Multivariable HR (95% CI)	1.00 (reference)	0.90 (0.80–1.02)	0.98 (0.82–1.16)	1.19 (1.01–1.40)	0.001

Note: Multivariable analysis adjusted for age; body mass index; thiazide use; supplemental calcium intake; intake of dietary vitamin C, calcium, sodium, potassium, magnesium, fructose, oxalate, phytate, animal protein, and total fluid; and alcohol intake. For illustrative purposes, medians for supplemental vitamin C were derived from responses to the 1986 (NHS I, HPFS) and 1991 (NHS II) dietary questionnaires. However, supplemental vitamin C intake was updated throughout the study. CI, confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; NHS, Nurses' Health Study; supp, supplemental