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Fructose consumption and the risk of kidney stones

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Fructose consumption has markedly increased over the past decades. This intake may increase the urinary excretion of calcium, oxalate, uric acid, and other factors associated with kidney stone risk. We prospectively examined the relationship between fructose intake and incident kidney stones in the Nurses' Health Study I (NHS I) (93 730 older women), the Nurses' Health Study II (NHS II) (101 824 younger women), and the Health Professionals Follow-up Study (45 984 men). Food frequency questionnaires were used to assess free fructose and sucrose intake every 4 years. Total-fructose intake was calculated as free fructose plus half the intake of sucrose, and expressed as percentage of total energy. Cox proportional hazard regressions were adjusted for age, body mass index (BMI), thiazide use, caloric intake, and other dietary factors. We documented 4902 incident kidney stones during a combined 48 years of follow-up. The multivariate relative risks of kidney stones significantly increased for participants in the highest compared to the lowest quintile of total-fructose intake for all three study groups. Free-fructose intake was also associated with increased risk. Non-fructose carbohydrates were not associated with increased risk in any cohort. Our study suggests that fructose intake is independently associated with an increased risk of incident kidney stones.

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Kidney stones are common, costly, and painful. The lifetime prevalence of symptomatic nephrolithiasis is approximately 10% in men and 5% in women,[1–3] and more than $2 billion is spent on treatment each year.[4] Diet plays an important role in the pathogenesis of stone disease, and changes in dietary habits likely contributed to the substantial increase in nephrolithiasis observed over the past several decades.[5]

Fructose intake increased approximately 2000% over 30 years after the widespread introduction of high-fructose corn syrup in 1967,[6] and fructose may increase the urinary excretion of calcium and oxalate, both of which are important risk factors for calcium nephrolithiasis. Rats fed high-fructose diets have higher urinary calcium excretion and an eightfold increase in nephrocalcinosis compared to rats fed high-starch diets.[7,8] A study of calcium and phosphorus balance in healthy men consuming controlled diets demonstrated higher urinary losses of calcium as a percentage of calcium intake on a high-fructose versus high-starch diet.[9] In another study on human, intravenous infusion of fructose increased urinary oxalate excretion by 60% compared to glucose infusion.[10] Of note, the effect of fructose intake on calcium balance and urinary oxalate excretion may vary depending on the intake of magnesium and vitamin B_6, respectively.[7–9,11]

Fructose intake may also increase insulin resistance, which is associated with low urinary pH,[12] a major risk factor for uric acid kidney stones. In addition, fructose is the only carbohydrate known to increase the production of uric acid.[13–16] Fructose infusion increases urinary uric acid,[14] which may be a risk factor for kidney stone formation.[17,18]

To examine the relationship between fructose intake and the incidence of kidney stones, we conducted a prospective study of three large cohorts: the Nurses' Health Study I (NHS I), the Nurses' Health Study II (NHS II), and the Health Professionals Follow-up Study (HPFS).

RESULTS

Over a combined 48 years of follow-up, we documented 4902 new symptomatic kidney stones in the three cohorts. In NHS I (older women), NHS II (younger women), and HPFS (men), there were 1711, 1564, and 1627 incident kidney stones, respectively.

Baseline characteristics by quintile of total-fructose intake are displayed in Table 1. There was a wide range of total-fructose intake in the study population: median intake in the

Table 1 | Age-standardized baseline characteristics according to quintile of total-fructose intake in older women (NHS I), younger women (NHS II), and men (HPFS)

	NHS I					NHS II					HPFS				
Quintile of total-fructose intake	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
Median total fructose (% of energy)	5.7	8.1	9.7	11.5	15.2	5.7	7.5	9.1	10.9	14.4	5.6	7.8	9.3	11.0	13.8
Age (years)	46.3	46.3	46.4	46.4	46.0	36.4	36.4	36.2	36.0	35.6	54.1	54.5	54.5	54.7	54.7
BMI (kg m^{-2})	24.4	24.3	24.2	24.2	24.4	25.4	25.0	24.5	24.1	24.0	25.2	25.1	24.8	24.7	24.7
Hypertension (%)	15	15	15	16	17	7	6	6	5	7	24	22	21	20	22
Diabetes (%)	3	2	2	2	1	1	1	<1	<1	<1	6	4	2	2	2
Thiazide use (%)	10	10	9	10	11	2	2	2	2	2	10	9	9	9	9

BMI, body mass index; HPFS, the Health Professionals Follow-up Study; NHS I, the Nurses' Health Study I; NHS II, the Nurses' Health Study II.
Values are expressed as means unless otherwise noted.

highest quintile was approximately 2.5 times that in the lowest. Age, prevalence of hypertension, and frequency of thiazide use were similar across quintiles of total-fructose intake. NHS II and HPFS participants in the highest quintile of total-fructose intake had lower body mass indices (BMIs) than those in the lowest quintile. In all three cohorts, participants in the highest quintile of total-fructose intake were less likely to have diabetes than participants in the lowest quintile.

Because the association between free-fructose intake and kidney stone risk persisted even after adjusting for sucrose, we report separate results for both free and total fructose. Free-fructose intake was associated with an increased risk of incident kidney stones (Table 2) in both age-adjusted and multivariate regression models. After adjustment for age, BMI, total energy intake, use of thiazide diuretics, fluid intake, caffeine, alcohol use, calcium supplement use, percentage of energy from non-fructose carbohydrate, percentage of energy from total protein, and intake of calcium, oxalate, potassium, and sodium, the relative risk for older women in the highest as compared to lowest quintile of free-fructose intake was 1.29 (95% confidence interval 1.08–1.53; P for trend <0.001), the relative risk for younger women was 1.22 (95% confidence interval 1.01–1.47; P for trend 0.01), and the relative risk for men was 1.28 (95% confidence interval 1.06–1.55; P for trend 0.002).

Total-fructose intake was also associated with an increased risk of incident kidney stones (Table 3). The multivariate relative risk for older women in the highest as compared to lowest quintile of total-fructose intake was 1.37 (95% confidence interval 1.13–1.65; P for trend <0.001), the multivariate relative risk for younger women was 1.35 (95% confidence interval 1.10–1.66; P for trend 0.004), and the multivariate relative risk for men was 1.27 (95% confidence interval 1.04–1.54; P for trend 0.006).

The intake of non-fructose carbohydrates was not associated with an increased risk of incident kidney stones in any cohort. Exclusion of participants with diabetes at baseline or during follow-up did not change the results, nor did adjustment for hypertension. When fructose was analyzed in absolute amounts, rather than as percentage of total energy, the results were similar. Finally, we performed analyses stratified by median magnesium intake, median vitamin B6 intake, and dichotomized BMI (BMI <25 versus BMI $\geqslant 25$). The relation between fructose intake (free or total) and risk did not vary by magnesium, vitamin B6, or BMI.

DISCUSSION

In this large prospective study of three distinct cohorts, fructose intake was positively associated with the risk of incident kidney stones. This relation was independent of other dietary factors, age, body size, and the use of thiazide diuretics. The intake of non-fructose carbohydrates was not associated with increased risk.

The mechanisms underlying the relation between fructose and stone risk are unknown, but may be related to the effect of fructose intake on urine composition. Fructose intake may alter calcium metabolism, particularly in the setting of low magnesium intake. Rats fed a magnesium-deficient, fructose-rich diet for 4 weeks had eightfold greater levels of nephrocalcinosis than rats with magnesium-deficient diets with energy derived from glucose or starch.[8] The nephrocalcinosis in the magnesium-deficient fructose diet was accompanied by hypercalciuria and consisted of calcium phosphate, rather than calcium oxalate, deposition.[7] The latter is an intriguing finding given that the initial phase of calcium oxalate stones may be interstitial deposits of calcium phosphate.[19] More recently, 11 healthy men consumed controlled diets with low or high magnesium content (170 versus 370 mg per 2500 kcal per day) and with starch versus fructose at 20% of energy intake.[9] The high-fructose diet, especially in conjunction with lower dietary magnesium, resulted in higher urinary losses of calcium as a percentage of calcium intake (22.7 versus 19.9%; $P<0.01$). The excretion of urinary calcium was similar on high- compared to low-fructose diets, but the high-fructose diet contained 12% less dietary calcium. Of note, in our study, we did not observe that the stone risk associated with fructose was greater in those with lower intake of magnesium.

Fructose intake may also increase urinary excretion of oxalate, an important risk factor for calcium oxalate nephrolithiasis. Carbohydrates, along with amino acids, provide the majority of the carbon for glyoxylate and oxalate synthesis, and fructose may be an important dietary sugar influencing the production of oxalate.[20] Data supporting this

Table 2 | Quintiles of free-fructose intake and the RR of incident kidney stones in older women (NHS I), younger women (NHS II), and men (HPFS)

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend
NHS I						
Free fructose (% of energy)	<3.5	3.5–4.5	4.6–5.5	5.6–6.9	>6.9	
Cases of new stones	347	311	331	333	389	
Person-years	317 700	317 859	317 653	317 762	317 587	
Age-adjusted RR (95% CI)	1.0 (ref)	0.91 (0.78–1.06)	0.98 (0.84–1.14)	0.99 (0.85–1.15)	1.16 (1.01–1.35)	0.003
Multivariate RR[a] (95% CI)	1.0 (ref)	0.98 (0.83–1.14)	1.10 (0.93–1.29)	1.13 (0.96–1.33)	1.29 (1.08–1.53)	<0.001
NHS II						
Free fructose (% of energy)	<3.1	3.1–4.0	4.1–5.0	5.1–6.5	>6.5	
Cases of new stones	303	288	265	301	407	
Person-years	169 569	169 486	169 762	169 425	169 343	
Age-adjusted RR (95% CI)	1.0 (ref)	0.96 (0.82–1.13)	0.88 (0.74–1.03)	0.99 (0.85–1.16)	1.33 (1.15–1.55)	<0.001
Multivariate RR[a] (95% CI)	1.0 (ref)	1.00 (0.85–1.18)	0.93 (0.78–1.10)	1.03 (0.86–1.23)	1.22 (1.01–1.47)	0.01
HPFS						
Free fructose (% of energy)	<3.4	3.4–4.3	4.4–5.3	5.4–6.8	>6.8	
Cases of new stones	324	301	321	338	343	
Person-years	107 033	107 069	107 130	107 226	107 010	
Age-adjusted RR (95% CI)	1.0 (ref)	0.95 (0.81–1.11)	1.02 (0.88–1.19)	1.09 (0.93–1.27)	1.10 (0.95–1.29)	0.06
Multivariate RR[a] (95% CI)	1.0 (ref)	1.00 (0.85–1.17)	1.10 (0.94–1.30)	1.21 (1.02–1.44)	1.28 (1.06–1.55)	0.002

CI, confidence interval; HPFS, the Health Professionals Follow-up Study; NHS I, the Nurses' Health Study I; NHS II, the Nurses' Health Study II; RR, relative risk.
For illustrative purposes, quintile cut points for free fructose were derived from responses to the 1994 (NHS I and HPFS) and 1995 (NHS II) dietary questionnaires.
[a]The multivariate model includes age, body mass index, total energy intake, use of thiazide diuretics (yes or no), fluid intake (in quintiles), caffeine (in quintiles), alcohol use (seven categories), calcium supplement use (four categories), percentage of energy from non-fructose carbohydrate (quintiles), percentage of energy from total protein (quintiles), and intake of calcium, oxalate, potassium, and sodium (all in quintiles).

Table 3 | Quintiles of total-fructose intake and the RR of incident kidney stones in older women (NHS I), younger women (NHS II), and men (HPFS)

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend
NHS I						
Total fructose (% of energy)	<7.2	7.2–8.9	9.0–10.5	10.6–12.6	>12.6	
Cases of new stones	310	292	355	361	393	
Person-years	317 729	317 863	317 674	317 661	317 634	
Age-adjusted RR (95% CI)	1.0 (ref)	0.96 (0.82–1.12)	1.17 (1.01–1.36)	1.21 (1.04–1.40)	1.32 (1.14–1.53)	<0.001
Multivariate RR[a] (95% CI)	1.0 (ref)	0.99 (0.84–1.17)	1.23 (1.05–1.46)	1.28 (1.08–1.52)	1.37 (1.13–1.65)	<0.001
NHS II						
Total fructose (% of energy)	<6.7	6.7–8.2	8.3–9.8	9.9–12.2	>12.2	
Cases of new stones	260	287	289	309	419	
Person-years	169 527	169 540	169 528	169 506	169 486	
Age-adjusted RR (95% CI)	1.0 (ref)	1.10 (0.93–1.30)	1.11 (0.94–1.31)	1.18 (1.00–1.39)	1.58 (1.36–1.85)	<0.001
Multivariate RR[a] (95% CI)	1.0 (ref)	1.10 (0.93–1.31)	1.11 (0.92–1.33)	1.15 (0.95–1.38)	1.35 (1.10–1.66)	0.004
HPFS						
Total fructose (% of energy)	<6.9	6.9–8.5	8.6–10.0	10.1–12.1	>12.1	
Cases of new stones	310	299	324	328	366	
Person-years	107 167	107 146	107 186	107 230	106 740	
Age-adjusted RR (95% CI)	1.0 (ref)	0.99 (0.84–1.16)	1.09 (0.93–1.28)	1.12 (0.96–1.31)	1.25 (1.08–1.46)	<0.001
Multivariate RR[a] (95% CI)	1.0 (ref)	0.98 (0.83–1.15)	1.07 (0.90–1.27)	1.11 (0.93–1.33)	1.27 (1.04–1.54)	0.006

CI, confidence interval; HPFS, the Health Professionals Follow-up Study; NHS I, the Nurses' Health Study I; NHS II, the Nurses' Health Study II; RR, relative risk.
For illustrative purposes, quintile cut points for total fructose were derived from responses to the 1994 (NHS I and HPFS) and 1995 (NHS II) dietary questionnaires.
[a]The multivariate model includes age, body mass index, total energy intake, use of thiazide diuretics (yes or no), fluid intake (in quintiles), caffeine (in quintiles), alcohol use (seven categories), calcium supplement use (four categories), percentage of energy from non-fructose carbohydrate (quintiles), percentage of energy from total protein (quintiles), and intake of calcium, oxalate, potassium, and sodium (all in quintiles).

contention are sparse but provocative. Experiments using isolated rat hepatocytes demonstrate that the addition of fructose stimulates oxalate production.[21,22] In a study of seven healthy individuals, intravenous infusion of approximately 35 g of fructose increased urinary oxalate excretion by 60% compared to glucose infusion.[10] Other experiments have not shown higher urinary oxalate levels after fructose administration.[23] Of interest, some animal data suggest that

the effect of fructose intake on urinary oxalate is more pronounced on diets deficient in vitamin B6.[11] However, in this study, we did not observe that the stone risk associated with fructose was greater in those with lower intake of vitamin B6.

Insulin resistance is likely an important risk factor for uric acid kidney stones and may mediate the relation between fructose intake and kidney stone risk. Data on animals demonstrate that high levels of fructose intake decrease insulin sensitivity.[24] For example, rats fed a diet containing 35% of energy as fructose for 4 weeks developed reduced insulin sensitivity and whole-body glucose disposal compared to rats fed a comparable amount of starch.[25] Insulin resistance may manifest in the kidney as a defect in ammonium production,[26] and experiments on humans utilizing hyperinsulinemic euglycemic clamp confirm that insulin resistance is associated with low urinary pH,[12] a major risk factor for uric acid nephrolithiasis.[17] Although the majority of incident kidney stones in this study likely were calcium oxalate, it is possible that fructose intake was associated with a very high risk of uric acid stone formation in a relatively small proportion of participants. It should be noted, however, that baseline characteristics in our study associated with insulin resistance and the development of kidney stones (i.e., higher BMI and higher prevalence of type II diabetes[27,28]) were not positively associated with fructose intake. In addition, data on humans linking fructose intake to impaired insulin sensitivity are inconsistent.[24]

A final possibility is that fructose increases stone risk by influencing uric acid metabolism. Higher urinary uric acid levels are a putative risk factor for kidney stone formation,[17,18] and fructose, unlike other carbohydrates, increases the production of uric acid.[29] Hepatic fructose phosphorylation depletes phosphate stores, inhibits the regeneration of ATP, and results in high levels of AMP that are subsequently metabolized to uric acid.[30] Fructose infusion increases both plasma and urinary concentrations of uric acid.[14] An important caveat to any proposed connection between fructose, uric acid, and kidney stones is that 24-h urinary uric acid levels in a subset of NHS I, NHS II, and HPFS participants were not associated with stone risk.[31]

Our data highlight a particular complexity of formulating specific dietary advice to reduce the risk of kidney stone recurrence. In general, diets are isocaloric: if an individual reduces the intake of certain foods, he or she will increase the intake of others to maintain constant energy intake. As a result, advising patients with recurrent stone disease to consume less of one dietary factor may lead to the consumption of another factor that increases the risk of stone formation. For example, a stone former with hypercalciuria and a high protein catabolic rate may be advised to reduce their intake of animal protein. If this individual reduces their consumption of animal protein but increases their consumption of free fructose or sucrose as a result, stone risk may remain constant (or even increase). Therefore, it is crucial for the clinician to gauge the impact of any dietary recommendation with follow-up 24-h urine collections.

An important limitation to this study is that we do not have stone composition reports or 24-h urine collections from all the stone formers in our cohorts. Thus, we were unable to determine if fructose intake increases the risk of certain stone types, such as uric acid, but not others. The generalizability of our study is also limited. Only a small proportion of our study population is non-white, and we do not have data on stone formation in men aged less than 40 years. Finally, we had limited statistical power to evaluate the relationship between fructose intake and stone risk in individuals consuming diets very low in magnesium or vitamin B6.

In conclusion, our prospective data indicate that the consumption of fructose is independently associated with an increased risk of incident kidney stones. Further research is needed to delineate the effect of fructose intake on the urinary excretion of calcium and to determine the role of dietary fructose in the endogenous generation of oxalate. Clinicians caring for patients with stone disease should ensure that individuals who decrease their intake of protein or fat do not subsequently increase their consumption of fructose-rich foods.

MATERIALS AND METHODS

Study population

Nurses' Health Study I. In 1976, 121 700 female registered nurses between the age of 30 and 55 years enrolled in NHS I by completing and returning an initial questionnaire that provided detailed information on diet, medical history, and medications. This cohort, similar to NHS II and HPFS, was followed by biennial mailed questionnaires, which included inquiries about newly diagnosed diseases such as kidney stones. Since we first asked NHS I participants about their lifetime history of kidney stones in 1992, this analysis was limited to women who answered questionnaires in 1992 or later. For this study, we started follow-up in 1980, since before that date we lacked information on diet. After excluding women with kidney stones before 1980, our study population included 93 730 women.

Nurses' Health Study II. In 1989, 116 671 female registered nurses between the age of 25 and 42 years enrolled in NHS II by completing and returning an initial questionnaire. Dietary information was first collected from this cohort in 1991. We limited the analysis to women who completed at least one dietary questionnaire and excluded participants with a history of kidney stones before 1991. A total of 101 824 women remained in the study group.

Health Professionals Follow-up Study. In 1986, 51 529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians between the age of 40 and 75 years enrolled in HPFS by completing and returning an initial questionnaire. We limited the analysis to men who completed at least one dietary questionnaire and excluded participants with a history of kidney stones before 1986. A total of 45 984 men remained in the study group.

Assessment of dietary intake

To assess dietary intake, we used a semiquantitative food-frequency questionnaire (FFQ) that asked about the average use of more than

130 foods and beverages during the previous year. The baseline dietary questionnaires were completed in 1986 (HPFS), 1980 (NHS I), and 1991 (NHS II), and were updated every 4 years.

Intake of fructose and other dietary factors was computed from the reported frequency of consumption of each specified unit of food and, with the exception of oxalate, from United States Department of Agriculture data on the content of the relevant nutrient in specified portions. The oxalate content of the majority of foods on the FFQ, as well as frequently consumed write-in foods, was measured by capillary electrophoresis in the laboratory of Dr Ross Holmes.[32] The intake of supplements (such as calcium and vitamin C) in multivitamin or isolated form was determined by the brand, type, and frequency of reported use.

Fructose is consumed as a monosaccharide or as part of sucrose, a disaccharide that is hydrolyzed to glucose and fructose in the small intestine. Therefore, total-fructose intake is equal to the intake of free fructose (i.e., fructose consumed as a monosaccharide) plus half the intake of sucrose. The main sources of free fructose in each cohort were sugar-sweetened soft drinks, fruit juice, and fruit. For example, at baseline in HPFS, consumption of the following foods accounted for 57.2% of free-fructose intake: sugar-sweetened soft drinks (15.5%), apples (11.6%), orange juice (9.3%), bananas (6.9%), apple juice (4.8%), raisins (4.7%), and fruit punch (4.4%). The main sources of sucrose varied by cohort and FFQ year, but generally included table sugar, sugar-sweetened soft drinks, fruit juices, fruit punch, cake, ice cream, cold cereal, milk chocolate, canned peaches, and fruit. For example, at baseline in HPFS, consumption of the following foods accounted for 50.6% of sucrose intake: table sugar (7.7%), sugar-sweetened soft drinks (7.5%), orange juice (7.5%), cake (of various types, totaling 7.4%), ice cream (5.7%), cold cereal (4.1%), milk chocolate (3.7%), canned peaches (3.7%), and oranges (3.3%).

The reproducibility and validity of the FFQs in NHS I and HPFS have been documented.[33,34] Correlations between intake of foods high in free fructose as measured by the FFQ and as assessed by dietary records were 0.84 for sugar-sweetened cola, 0.55 for other sugar-sweetened soft drinks, 0.78 for orange juice, 0.77 for apple juice, 0.89 for other fruit juices, 0.70 for apples, 0.76 for oranges, 0.95 for bananas, and 0.59 for raisins.[35]

Assessment of non-dietary covariates

For each cohort, information on age, weight, and height was obtained on the baseline questionnaire, and age and weight were updated every 2 years. BMI was calculated as weight (kg) divided by height (m^2). In NHS I, thiazide use was determined in 1980, 1982, and then every 6 years until 1994, when biennial updates started. Information on thiazide diuretics was updated every 2 years in HPFS and NHS II.

Assessment of incident kidney stones

The primary outcome was an incident kidney stone accompanied by pain or hematuria. The participants reported on the interval diagnosis of kidney stones every 2 years. Any study participant who reported a new kidney stone on the biennial questionnaire was sent an additional questionnaire to determine the date of occurrence and the symptoms from the stone. In NHS I, we obtained medical records from 194 women who reported a kidney stone, and 96% of the records confirmed the diagnosis. There were 78 records that contained a stone composition report, and 60 women (77%) had a stone that contained $\geqslant$50% calcium oxalate. In NHS II, we obtained medical records from 858 women who reported a kidney stone, and 98% of the records confirmed the diagnosis. There were 243 records that contained a stone composition report, and 191 women (79%) had a stone that contained $\geqslant$50% calcium oxalate. In HPFS, we obtained medical records from 582 men who reported a kidney stone, and the diagnosis was confirmed in 95%. There were 148 records that contained a stone composition report, and 127 men (86%) had a stone that contained $\geqslant$50% calcium oxalate.

Statistical analysis

The study design was prospective; information on diet was collected before the diagnosis of the kidney stone. The relative risk was used as the measure of association between fructose intake and incident kidney stones. Fructose intake was expressed as a percentage of total caloric intake (i.e., as nutrient density[36]) and was divided into quintiles, with the lowest quintile serving as the referent group. The Mantel extension test was used to evaluate linear trends across categories of intake.

Dietary exposures were updated every 4 years. We allocated person-months of follow-up according to exposure status at the start of each follow-up period. If complete information on diet was missing at the start of a time period, the subject was excluded for that time period. For NHS I, person-months of follow-up were counted from the date of the return of the 1980 questionnaire to the date of a kidney stone or death or to 31 May 2002, whichever came first. For NHS II, person-months of follow-up were counted from the date of the return of the 1991 questionnaire to the date of a kidney stone or death or to 31 May 2001. For HPFS, person-months of follow-up were counted from the date of the return of the 1986 questionnaire to the date of a kidney stone or death or to 31 January 2002.

We used Cox proportional hazards regression to estimate the relative risk for incident kidney stones in all multivariate analyses. The multivariate models simultaneously included total energy intake, the percentage of energy derived from protein, and the percentage of energy derived from non-fructose carbohydrates. Therefore, the coefficients from the multivariate nutrient density models can be interpreted as the estimated effect of substituting a specific percentage of energy from fructose for the same percentage of energy from fat.[36] Potentially confounding variables considered for inclusion in the multivariate models were age (continuous), BMI (six categories), alcohol intake (seven categories), the use of thiazide diuretics (yes or no), supplemental calcium use (four categories), and the intake of fluid, potassium, sodium, phosphorus, magnesium, vitamin C, vitamin B6, phytate, vitamin D, oxalate, and dietary calcium (quintile groups).

We calculated 95% confidence intervals for all relative risks. All *P*-values are two-tailed. Data were analyzed by using SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). The research protocol for this study was reviewed and approved by the Institutional Review Board of Brigham and Women's Hospital.

DISCLOSURES

The authors state no conflict of interest.

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REFERENCES

1. Hiatt RA, Dales LG, Friedman GD *et al.* Frequency of urolithiasis in a prepaid medical care program. *Am J Epidemiol* 1982; **115**: 255–265.
2. Johnson CM, Wilson DM, O'Fallon WM *et al.* Renal stone epidemiology: a 25-year study in Rochester, Minnesota. *Kidney Int* 1979; **16**: 624–631.
3. Stamatelou KK, Francis ME, Jones CA *et al.* Time trends in reported prevalence of kidney stones in the United States: 1976–1994. *Kidney Int* 2003; **63**: 1817–1823.
4. Pearle M, Calhoun E, Curhan GC. Urolithiasis. In: Litwin MS, Saigal CS (eds). *Urologic Diseases in America*. US Dept of Health and Human Services: Washington, DC, 2004: 34.
5. Taylor EN, Curhan GC. Diet and fluid prescription in stone disease. *Kidney Int* 2006; **70**: 835–839.
6. Gross LS, Li L, Ford ES *et al.* Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am J Clin Nutr* 2004; **79**: 774–779.
7. Koh ET, Min KW. Fructose precipitates calcium phosphate in the kidneys of female rats fed magnesium-deficient diets. *Magnes Res* 1991; **4**: 171–176.
8. Koh ET, Reiser S, Fields M. Dietary fructose as compared to glucose and starch increases the calcium content of kidney of magnesium-deficient rats. *J Nutr* 1989; **119**: 1173–1178.
9. Milne DB, Nielsen FH. The interaction between dietary fructose and magnesium adversely affects macromineral homeostasis in men. *J Am Coll Nutr* 2000; **19**: 31–37.
10. Nguyen NU, Dumoulin G, Henriet MT *et al.* Increase in urinary calcium and oxalate after fructose infusion. *Horm Metab Res* 1995; **27**: 155–158.
11. Kaul P, Sidhu H, Sharma SK *et al.* Calculogenic potential of galactose and fructose in relation to urinary excretion of lithogenic substances in vitamin B6 deficient and control rats. *J Am Coll Nutr* 1996; **15**: 295–302.
12. Abate N, Chandalia M, Cabo-Chan Jr AV *et al.* The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. *Kidney Int* 2004; **65**: 386–392.
13. Emmerson BT. Effect of oral fructose on urate production. *Ann Rheum Dis* 1974; **33**: 276–280.
14. Fox IH, Kelley WN. Studies on the mechanism of fructose-induced hyperuricemia in man. *Metabolism* 1972; **21**: 713–721.
15. Perheentupa J, Raivio K. Fructose-induced hyperuricaemia. *Lancet* 1967; **2**: 528–531.
16. Stirpe F, Della Corte E, Bonetti E *et al.* Fructose-induced hyperuricaemia. *Lancet* 1970; **2**: 1310–1311.
17. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. *N Engl J Med* 1992; **327**: 1141–1152.
18. Ettinger B, Tang A, Citro J *et al.* Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med* 1986; **315**: 1386–1389.
19. Evan A, Lingeman J, Coe FL *et al.* Randall's plaque: pathogenesis and role in calcium oxalate nephrolithiasis. *Kidney Int* 2006; **69**: 1313–1318.
20. Holmes RP, Assimos DG. Glyoxylate synthesis, and its modulation and influence on oxalate synthesis. *J Urol* 1998; **160**: 1617–1624.
21. Rofe AM, James HM, Bais R *et al.* Hepatic oxalate production: the role of hydroxypyruvate. *Biochem Med Metab Biol* 1986; **36**: 141–150.
22. Rofe AM, James HM, Bais R *et al.* The production of (^{14}C) oxalate during the metabolism of (^{14}C) carbohydrates in isolated rat hepatocytes. *Aust J Exp Biol Med Sci* 1980; **58**: 103–116.
23. Nguyen NU, Dumoulin G, Wolf JP *et al.* Urinary calcium and oxalate excretion during oral fructose or glucose load in man. *Horm Metab Res* 1989; **21**: 96–99.
24. Daly M. Sugars, insulin sensitivity, and the postprandial state. *Am J Clin Nutr* 2003; **78**: 865S–872S.
25. Thorburn AW, Storlien LH, Jenkins AB *et al.* Fructose-induced *in vivo* insulin resistance and elevated plasma triglyceride levels in rats. *Am J Clin Nutr* 1989; **49**: 1155–1163.
26. Krivosikova Z, Spustova V, Dzurik R. Participation of P-dependent and P-independent glutaminases in rat kidney ammoniagenesis and their modulation by metabolic acidosis, hippurate and insulin. *Physiol Res* 1998; **47**: 177–183.
27. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. *JAMA* 2005; **293**: 455–462.
28. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int* 2005; **68**: 1230–1235.
29. Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. *Ann Intern Med* 2005; **143**: 499–516.
30. Fox IH, Palella TD, Kelley WN. Hyperuricemia: a marker for cell energy crisis. *N Engl J Med* 1987; **317**: 111–112.
31. Curhan GC, Willett WC, Speizer FE *et al.* Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. *Kidney Int* 2001; **59**: 2290–2298.
32. Holmes R, Kennedy M. Estimation of the oxalate content of foods and daily oxalate intake. *Kidney Int* 2000; **57**: 1662–1667.
33. Rimm EB, Giovannucci EL, Stampfer MJ *et al.* Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 1992; **135**: 1114–1126; discussion 1127–1136.
34. Willett WC, Sampson L, Stampfer MJ *et al.* Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985; **122**: 51–65.
35. Feskanich D, Rimm E, Giovannucci E *et al.* Reproducibility and validity of food intake measurements from a semi-quantitative food frequency questionnaire. *J Am Diet Assoc* 1993; **93**: 790–796.
36. Willett WC. *Nutritional Epidemiology*, 2nd edn. Oxford University Press: New York, 1998.