Dietary Factors and the Risk of Incident Kidney Stones in Men: New Insights after 14 Years of Follow-up

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Abstract. Diet plays an important role in the pathogenesis of kidney stones. Because the metabolism of many dietary factors, such as calcium, may change with age, the relation between diet and kidney stones may be different in older adults. Uncertainty also remains about the association between many dietary factors, such as vitamin C, magnesium, and animal protein, and the risk of kidney stone formation. To examine the association between dietary factors and the risk of incident, symptomatic kidney stones in men and to determine whether these associations vary with age, a prospective cohort study was conducted of 45,619 men without a history of nephrolithiasis. Self-administered food frequency questionnaires were used to assess diet every 4 yr. A total of 1473 incident symptomatic kidney stones were documented during 477,700 person-years of follow-up. For men aged <60 yr, the multivariate relative risk (RR) for stone formation in the highest quintile of dietary calcium as compared with the lowest quintile was 0.69 (95% confidence interval [CI], 0.56 to 0.87; $P = 0.01$ for trend). By contrast, there was no association between dietary calcium and stone formation in men aged 60 yr or older. The multivariate RR for men who consumed 1000 mg or greater of vitamin C per day compared with those who consumed less than the recommended dietary allowance of 90 mg/d was 1.41 (95% CI, 1.11 to 1.80; $P = 0.01$ for trend). Other dietary factors showed the following multivariate RR among men in the highest quintile of intake compared with those in the lowest: magnesium, 0.71 (95% CI, 0.56 to 0.89; $P = 0.01$ for trend); potassium, 0.54 (95% CI, 0.42 to 0.68; $P < 0.001$ for trend); and fluid, 0.71 (95% CI, 0.59 to 0.85; $P < 0.001$ for trend). Animal protein was associated with risk only in men with a body mass index <25 kg/m^2 (RR, 1.38; 95% CI, 1.05 to 1.81; $P = 0.03$ for trend). Sodium, phosphorus, sucrose, phytate, vitamin B$_6$, vitamin D, and supplemental calcium were not independently associated with risk. In conclusion, the association between calcium intake and kidney stone formation varies with age. Magnesium intake decreases and total vitamin C intake seems to increase the risk of symptomatic nephrolithiasis. Because age and body size affect the relation between diet and kidney stones, dietary recommendations for stone prevention should be tailored to the individual patient.

Diet plays an important role in the pathogenesis of kidney stones (1), but little is known about the effect of aging on the association between specific dietary factors and nephrolithiasis. In the past, prospective studies that evaluated dietary influences on kidney stone formation included only small numbers of older participants. The first observational studies to demonstrate an inverse association between dietary calcium and incident kidney stones analyzed stone formers who as a group were predominately younger than 60 yr (2,3). The mean age of subjects in the controlled, randomized trial that supported the results of these studies was 45 yr (4).

The relation between diet and kidney stones may be different in older adults. The intestinal absorption of many nutrients that influence stone formation, such as calcium, may be reduced in the elderly (5,6). In men, the incidence of kidney stones declines markedly after 60 yr of age (2,7,8), suggesting that the pathophysiology of nephrolithiasis is different in the elderly. As a group, older stone formers excrete less urinary calcium than their younger counterparts (9) and may exhibit defects in urinary inhibitors of crystallization (10).

The role of vitamin C and magnesium intake in calcium stone formation also remains unclear. Early observational studies found no significant association between these nutrients and stones (2,3,11), but the effect of vitamin C and magnesium intake on urinary composition is compelling. A recent metabolic trial demonstrated that large doses of vitamin C supplementation resulted in an increased excretion of urinary oxalate (12), an important risk factor for calcium oxalate nephrolithiasis (13,14). Magnesium supplementation may reduce the intestinal absorption of oxalate and diminish urinary oxalate excretion (15,16). An observational study found that dietary magnesium was inversely associated with the risk of kidney stones (17).

Animal protein and potassium intake also may influence the risk of calcium kidney stone formation. Ingested animal protein generates an acid load that increases urinary calcium excretion and reduces the excretion of citrate (18–21), an

inhibitor of calcium stones. Some observational studies have shown a positive association between animal protein intake and stones (2), whereas others have not (3,22). Dietary potassium restriction increases and potassium supplementation may decrease urinary calcium excretion (23).

We first studied the relation between diet and kidney stones in the Health Professionals Follow-up Study after 4 yr of follow-up (2). We now report results obtained after 14 yr of follow-up. The aging of the study participants allowed us to examine the effect of age on dietary risk factors for nephrolithiasis. The increase in statistical power obtained from the near tripling of incident kidney stones and person-years of follow-up permitted us to reevaluate the previously null associations between the intake of vitamin C and magnesium and the risk of incident kidney stones.

Materials and Methods

Study Population

The Health Professionals Follow-up Study enrolled 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians who were 40 to 75 yr of age in 1986. At baseline, study participants filled out a detailed questionnaire about diet, medical history, and medications. Of the 49,976 men who provided full information on their diet, 4357 (8.7%) reported a history of kidney stones. Because these participants may have changed their diet after having a kidney stone, we excluded them from the analysis.

Assessment of Diet

The semiquantitative food-frequency questionnaire (FFQ) mailed in 1986 asked about the annual average use of 131 foods and beverages. In addition, respondents provided information on the use of supplemental vitamins, taken either alone or in multivitamin form. Subsequently, a version of this FFQ has been mailed to the Health Professionals Follow-up Study participants every 4 yr.

Nutrient intake was computed from the reported frequency of consumption of each specified unit of food and from USDA data on the content of the relevant nutrient in specified portions. Nutrient values were adjusted for total caloric intake to determine the nutrient composition of the diet independent of the total amount of food eaten. Adjustment was performed using a regression model, with total caloric intake as the independent variable and absolute nutrient intake as the dependent variable (24,25). Correcting self-reported intake for total energy intake improves accuracy in the determination of specific nutrient consumption.

For supplemental vitamin C, respondents chose from the following categories: 0, 1 to 399, 400 to 700, 750 to 1250, and 1300 mg or more daily. The amount of vitamin C in multivitamin preparations was determined by the brand, type, and frequency of reported use. The intake of supplemental calcium was determined in a similar manner. The reproducibility and validity of the FFQ in this cohort have been documented (26), and a similar questionnaire has been shown to be reproducible and valid in women (27).

Assessment of Nondietary Covariates

Information on age, weight, and height was obtained on the baseline questionnaire, and age and weight were updated every 2 yr. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Information on medication use (*e.g.*, thiazide diuretics) was updated every 2 yr.

Outcomes and Their Measurement

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 yr. Any study participant who reported a new kidney stone was sent an additional questionnaire to determine the date of occurrence and the symptoms from the stone. We confirmed the validity of the self-reported stones by obtaining medical records from a random sample of 60 men in the cohort; chart review confirmed 97% of the cases (2).

Statistical Analyses

The study design was prospective; information on diet was collected before the onset of the kidney stone. For each participant, 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 January 31, 2000 (whichever came first). Dietary exposures were updated every 4 yr. We allocated person-months of follow-up according to exposure status at the start of each follow-up period. When complete information on diet was missing at the start of a time period, the participant was excluded for that time period.

The relative risk (RR; the incidence rate among men in a particular category of intake divided by the corresponding rate in the referent group) was used as the measure of association between dietary factors and incident kidney stones. For each dietary factor, intake was divided into quintiles, and the lowest quintile served as the referent group. For vitamin C, intake was also examined in five categories, with the upper limit of the lowest category representing the current recommended dietary allowance of 90 mg/d. The intake of supplemental calcium was divided into the following four groups: none, 1 to 100 mg/d, 101 to 500 mg/d, and >500 mg/d. The Mantel extension test was used to evaluate linear trends across categories of intake.

We adjusted our analyses for potentially confounding variables using Cox proportional hazards regression. The confounding variables considered 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, animal protein, phosphorous, magnesium, sucrose, vitamin C, vitamin B_6, phytate, vitamin D, and dietary calcium (quintile groups). We calculated 95% confidence intervals (CI) for all RR. All *P* values are two tailed.

To evaluate whether the association between a specific dietary factor and the risk of stones varied with age, we stratified the analysis into two age categories: men aged 60 and above and men <60. We chose the cutoff of 60 yr because the incidence of kidney stones in men declines after this age, both in this cohort (2) and in others (7,8). To test for statistical significance between the two strata, we added interaction terms to the multivariable regression model and performed log likelihood ratio testing. To ensure that an observed interaction between age and a particular dietary component did not depend on a single age cutoff, we also tested interaction terms that included age as a continuous rather than a dichotomous variable.

All data were analyzed by using SAS software, version 8.2 (SAS Institute Inc., Cary, NC). The research protocol for this study was reviewed and approved by the institutional review board of Brigham and Women's Hospital.

Results

During 477,700 person-years of follow-up, we documented 1473 cases of new symptomatic kidney stones. The incidence was highest among men aged 40 to 59 yr, declined among men aged 60 to 69 yr, and was markedly lower among men older

than 70 yr (Table 1). The number of cases in men aged 60 or older was 483, compared with 130 in our previous analysis (2).

Dietary Calcium

After adjusting for age, a higher intake of dietary calcium was associated with a reduced risk of incident kidney stones. The RR for men in the highest as compared with the lowest quintile of dietary calcium intake was 0.64 (95% CI, 0.54 to 0.75; $P < 0.001$ for trend). After further adjusting for BMI; thiazide diuretic use; calcium supplement use; and the intake of animal protein, potassium, sodium, vitamin C, magnesium, alcohol, and fluid, the RR was attenuated (RR, 0.83; 95% CI, 0.69 to 1.00; $P = 0.08$ for trend).

The association between dietary calcium and kidney stones varied with age ($P = 0.04$ for interaction). For men aged <60 yr (Table 2), the multivariate RR for stone formation in the highest quintile of dietary calcium as compared with the lowest quintile was 0.69 (95% CI, 0.56 to 0.87; $P = 0.01$ for trend). By contrast, there was no association between dietary calcium and stone formation in men aged 60 yr or greater (Table 2). Further adjustment for the intake of vitamin D, phosphorus, sucrose, phytate, and vitamin B_6 did not materially change the results.

The incidence of kidney stones in men younger than 60 yr in the highest quintile of dietary calcium intake was 2.84 per 1000 person-years. The number of additional incident kidney stones associated with dietary calcium in the lowest four quintiles of intake was 0.44 per 1000 men annually.

Vitamin C

After adjusting for age, there was no association between vitamin C intake and the risk of incident stone formation. However, after multivariate adjustment, increased vitamin C intake was positively associated with the risk of stone formation ($P = 0.01$ for trend; Table 3). The RR for men who consumed 1000 mg or greater of vitamin C per day compared with those who consumed less than the recommended dietary allowance of 90 mg/d was 1.41 (95 CI, 1.11 to 1.80). An increased risk was observed even at relatively modest intakes of vitamin C; the RR for men who consumed 90 to 249 mg of vitamin C per day compared with those who consumed <90 mg/d was 1.22 (95% CI, 1.01 to 1.49). The relation between

vitamin C intake and stones emerged only after the inclusion of dietary potassium in the multivariate analysis; potassium intake was inversely associated with stone formation and was positively associated with dietary vitamin C (correlation coefficient, 0.52).

For men in the lowest category of vitamin C intake, the incidence of kidney stones was 3.47 per 1000 person-years. The number of additional incident kidney stones associated with total vitamin C intake in the highest four categories was 0.84 per 1000 men annually.

We also separated total vitamin C intake into dietary and supplemental sources and then included both variables in the multivariate analysis. The multivariate RR of kidney stone formation in men in the highest quintile of dietary vitamin C intake (>218 mg/d) compared with the lowest (<105 mg/d) was 1.31 (95% CI, 1.08 to 1.60; $P = 0.01$ for trend). The multivariate RR in men who consumed 1000 mg or greater of supplemental vitamin C per day compared with those who took no supplemental vitamin C was 1.16 (95% CI, 0.97 to 1.39; $P = 0.01$ for trend; Table 4). Further adjusting for the intake of vitamin D, phosphorus, sucrose, phytate, and vitamin B_6 did not change the results. The association between vitamin C intake and stone formation did not vary by age.

Magnesium

Magnesium intake was inversely associated with the risk of incident kidney stones (Table 5). The multivariate RR for the men in the highest as compared with the lowest quintile of magnesium intake was 0.71 (95% CI, 0.56 to 0.89; $P = 0.01$ for trend). Further adjustment for the intake of vitamin D, phosphorus, sucrose, phytate, and vitamin B_6 did not change the results, and the risk did not vary with age.

The incidence of kidney stones in men in the highest quintile of magnesium intake was 2.11 per 1000 person-years. The number of additional incident kidney stones associated with magnesium intake in the lowest four quintiles was 0.37 per 1000 men annually.

Other Dietary Factors

Overall, animal protein intake was not associated with kidney stone formation (Table 5). However, among men with a

Table 1. Incidence of kidney stones among men according to five-year age groups, 1986–2000

Age Group (Years)	No. of Cases	Person-Years	Incidence (Cases per 100,000 Person-Years)
40–44	194	50,784	382
45–49	293	65,970	444
50–54	275	76,622	359
55–59	228	73,396	311
60–64	199	71,663	278
65–69	163	64,343	253
≥70	121	74,922	162
Total	1473	477,700	308

Table 2. Dietary calcium intake and the RR of incident kidney stones in men, 1986–2000, stratified by age[a]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for Trend[b]
<60 years of age						
quintile median of dietary calcium (mg/d)	503	633	748	893	1194	
cases	266	211	178	188	147	
person-years	53,142	55,081	54,007	52,858	51,685	
age-adjusted RR (95% CI)	1.0	0.76 (0.64–0.92)	0.66 (0.54–0.80)	0.71 (0.59–0.86)	0.57 (0.46–0.70)	<0.001
multivariate RR[c] (95% CI)	1.0	0.81 (0.68–0.98)	0.72 (0.59–0.88)	0.81 (0.66–0.99)	0.69 (0.56–0.87)	0.01
≥60 years of age						
quintile median of dietary calcium (mg/d)	498	637	751	896	1218	
cases	96	96	105	95	91	
person-years	39,224	39,817	41,595	44,006	46,287	
age-adjusted RR (95% CI)	1.0	0.99 (0.74–1.31)	1.04 (0.79–1.37)	0.89 (0.67–1.18)	0.81 (0.60–1.07)	0.07
multivariate RR[c] (95% CI)	1.0	1.09 (0.81–1.45)	1.21 (0.91–1.62)	1.12 (0.83–1.52)	1.20 (0.87–1.66)	0.40

[a] For illustrative purposes, quintile medians for intake of dietary calcium were derived from responses to the 1994 dietary questionnaire. However, the period-specific quintile values were used for the 1986 to 2000 analyses. RR are for the risk for stone formation compared with the group that had the lowest intake of dietary calcium. RR, relative risk; CI, confidence interval.

[b] *P* value for interaction terms between dichotomized age and quintiles of calcium intake was 0.04. The *P* value for interaction between continuous age and quintiles of calcium intake was also 0.04.

[c] Results are adjusted for age; body mass index (six categories); use of thiazide diuretics (yes or no); volume intake (in quintiles); alcohol use (seven categories); calcium supplement use (four categories); and dietary intake of animal protein, potassium, sodium, vitamin C, and magnesium (all in quintiles).

Table 3. Total vitamin C intake and the RR of incident kidney stones[a]

	Vitamin C Intake (mg/d)					*P* for Trend
	<90 mg	90–249 mg	250–499 mg	500–999 mg	≥1000 mg	
Category median (mg/d)	72	165	326	700	1389	
Cases	128	705	245	197	198	
Person-years	36,978	219,302	94,272	65,542	61,606	
Age-adjusted RR (95% CI)	1.0	1.00 (0.83–1.21)	0.84 (0.67–1.04)	0.97 (0.77–1.21)	1.01 (0.81–1.22)	0.78
Multivariate RR[b] (95% CI)	1.0	1.22 (1.01–1.49)	1.20 (0.96–1.51)	1.36 (1.07–1.72)	1.41 (1.11–1.80)	0.01

[a] For illustrative purposes, category medians for intake of vitamin C were derived from responses to the 1994 dietary questionnaire. However, the period-specific quintile values were used for the 1986 to 2000 analyses. RR are for the risk for stone formation compared with the group that had the lowest intake of vitamin C.

[b] Results are adjusted for age; body mass index (six categories); use of thiazide diuretics (yes or no); volume intake (in quintiles); alcohol use (seven categories); calcium supplement use (four categories); and dietary intake of animal protein, calcium, potassium, sodium, and magnesium (all in quintiles).

BMI <25 kg/m^2 (*i.e.*, not overweight by World Health Organization criteria), the RR of developing an incident stone for those in the highest quintile of animal protein intake compared with the lowest quintile was 1.38 (95% CI, 1.05 to 1.81; *P* = 0.03 for trend). There was no association between animal protein intake and stones for men with a BMI of 25 kg/m^2 or

Table 4. Supplemental vitamin C intake and the RR of incident kidney stones[a]

| | Supplemental Vitamin C Intake (mg/d) | | | | | *P* for Trend |
	None	1–99 mg	100–499 mg	500–999 mg	≥1000 mg	
Category median (mg/d)	0	60	245	560	1120	
Cases	618	298	208	161	188	
Person-years	182,448	109,389	76,805	51,490	57,569	
Age-adjusted RR (95% CI)	1.0	0.91 (0.78–1.06)	0.85 (0.73–1.00)	1.01 (0.85–1.20)	1.02 (0.86–1.20)	0.58
Multivariate RR[b] (95% CI)	1.0	0.95 (0.81–1.12)	0.91 (0.78–1.07)	1.11 (0.93–1.34)	1.16 (0.97–1.39)	0.01

[a] For illustrative purposes, category medians for intake of vitamin C were derived from responses to the 1994 dietary questionnaire. However, the period-specific quintile values were used for the 1986 to 2000 analyses. RR are for the risk for stone formation compared with the group that had the lowest intake of vitamin C.

[b] Results are adjusted for age; body mass index (six categories); use of thiazide diuretics (yes or no); volume intake (in quintiles); alcohol use (seven categories); calcium supplement use (four categories); and dietary intake of animal protein, calcium, potassium, sodium, and magnesium (all in quintiles).

greater ($P = 0.25$ for interaction between dietary animal protein and continuous BMI).

Potassium and fluid intake was inversely associated with the risk of incident stone formation (Table 5). The RR for the men in the highest as compared with the lowest quintile group were 0.54 (95% CI, 0.42 to 0.68; $P <0.001$ for trend) for potassium and 0.71 (95% CI, 0.59 to 0.85; $P < 0.001$ for trend) for fluid intake.

The incidence rates of kidney stones in men in the highest quintiles of potassium and fluid intake were 1.78 per 1000 person-years and 2.15 per 1000 person-years, respectively. Each year, the numbers of additional incident kidney stones associated with potassium and fluid in the lowest four quintiles of intake were 0.77 per 1000 men and 0.96 per 1000 men, respectively.

Sodium, phosphorus, sucrose, phytate, vitamin B_6, vitamin D, and supplemental calcium were not associated with risk after adjusting for potential confounders. These results did not change with age or BMI.

Discussion

As in our previous study, we found that dietary calcium was associated with a lower risk of kidney stone formation. However, this association was limited to men younger than 60 yr.

The cause of this age-specific difference is unclear. Dietary calcium may bind to dietary oxalate in the intestine, thereby reducing oxalate absorption and the subsequent concentration of urinary oxalate (28–32). Even a small increase in urinary oxalate excretion increases the risk for calcium oxalate stones (13,14). Both vitamin D deficiency and a diminished ability to absorb dietary calcium are more prevalent in older people (6,33). Perhaps in older individuals, a greater proportion of dietary calcium remains in the intestine available to bind oxalate. After most of the oxalate is bound, additional dietary calcium would simply result in more calcium absorption and would not protect against calcium stones. We have also as-

sumed that the majority of kidney stones reported by our cohort consisted predominantly of calcium oxalate, as in the general population. If most kidney stones in older men were composed of uric acid or calcium phosphate, then we would not expect a protective effect from dietary calcium. However, the proportion of calcium oxalate stones in the elderly is probably similar to that of other age groups (34).

Although higher levels of dietary calcium intake did not reduce risk in older men, they also did not seem to increase risk. To date, no evidence suggests that dietary calcium restriction alone reduces the likelihood of actual kidney stone formation. Indeed, several observational studies and a randomized trial indicate that diets that contain low amounts of calcium are less effective in the prevention of calcium kidney stones than diets that contain higher amounts of calcium (2–4,22,35).

This is the first prospective study to show a significant association between the intake of vitamin C and the development of kidney stones. In the past, vitamin C ingestion in this cohort was not significantly associated with increased risk (11). However, the previous analysis had limited statistical power, especially for the highest category of vitamin C intake. In addition, the referent group's intake of vitamin C in our previous report was higher (up to 250 mg/d), which obscured the significant effect of vitamin C at levels between 90 and 250 mg/d.

The pharmakinetics of vitamin C may explain why the majority of the increased risk occurred at relatively low doses. Vitamin C plasma concentrations display sigmoid kinetics, with the steep portion of the curve occurring between 30 and 100 mg/d of intake (36). In one study, increasing the daily dose of vitamin C from 200 to 2500 mg increased the plasma concentration only from 12 to 15 mg/L (37). Evidence also suggests that tissue saturation occurs at relatively low plasma concentrations of vitamin C; in healthy volunteers, intracellular vitamin C concentrations peaked when daily vitamin C con-

Table 5. Intake of magnesium, animal protein, potassium, and fluid and the RR of incident kidney stones[a]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for Trend
Magnesium (mg/d)	<314	314–354	355–394	395–450	>450	
quintile median (mg/d)	287	335	374	419	499	
cases	437	322	263	246	205	
person-years	92,468	95,356	96,340	96,286	97,250	
age-adjusted RR (95% CI)	1.0	0.72 (0.63–0.83)	0.59 (0.51–0.69)	0.56 (0.48–0.66)	0.47 (0.40–0.56)	<0.001
multivariate RR[b] (95% CI)	1.0	0.85 (0.73–1.00)	0.78 (0.65–0.94)	0.80 (0.66–0.97)	0.71 (0.56–0.89)	0.01
Animal protein (g/d)	<47	47–55	56–63	64–74	>74	
quintile median (g/d)	40	52	60	68	81	
cases	278	285	314	304	292	
person-years	94,519	95,589	95,553	96,302	95,737	
age-adjusted RR (95% CI)	1.0	1.00 (0.85–1.18)	1.09 (0.93–1.28)	1.04 (0.89–1.23)	1.01 (0.86–1.19)	0.75
multivariate RR[b] (95% CI)	1.0	1.02 (0.86–1.20)	1.13 (0.96–1.33)	1.10 (0.93–1.30)	1.08 (0.91–1.29)	0.27
Potassium (mg/d)	<2914	2914–3254	3255–3569	3570–3958	>3958	
quintile median (mg/d)	2671	3096	3405	3743	4289	
cases	436	333	288	242	174	
person-years	92,553	95,418	96,151	96,543	97,036	
age-adjusted RR (95% CI)	1.0	0.75 (0.65–0.87)	0.66 (0.57–0.76)	0.56 (0.48–0.66)	0.42 (0.35–0.50)	<0.001
multivariate RR[b] (95% CI)	1.0	0.83 (0.71–0.97)	0.77 (0.64–0.91)	0.69 (0.56–0.84)	0.54 (0.42–0.68)	<0.001
Fluid (ml/d)	<1263	1263–1661	1662–2036	2037–2517	>2517	
quintile median (ml/d)	992	1474	1843	2251	2914	
cases	349	368	293	254	209	
person-years	91,658	96,007	96,184	97,200	96,651	
age-adjusted RR (95% CI)	1.0	0.98 (0.85–1.14)	0.78 (0.67–0.91)	0.67 (0.57–0.78)	0.53 (0.45–0.63)	<0.001
multivariate RR[b] (95% CI)	1.0	1.06 (0.91–1.23)	0.89 (0.76–1.04)	0.80 (0.68–0.95)	0.71 (0.59–0.85)	<0.001

[a] For illustrative purposes, quintile cutpoints and medians for intake of dietary factors were derived from responses to the 1994 dietary questionnaire. However, the period-specific quintile values were used for the 1986 to 2000 analyses. RR are for the risk for stone formation compared with the group that had the lowest intake.

[b] The multivariate model includes age; body mass index (six categories); use of thiazide diuretics (yes or no); fluid intake (in quintiles); alcohol use (seven categories); calcium supplement use (four categories); and dietary intake of animal protein, calcium, potassium, sodium, vitamin C, and magnesium (all in quintiles).

sumption reached 100 mg (36). In addition, the enzymatic generation of oxalate from vitamin C seems to be easily saturable (38). Therefore, escalating doses of vitamin C may have a relatively small effect on additional oxalate production.

The increase in risk at relatively low intakes of vitamin C may account for the modest association between supplemental vitamin C use and incident kidney stones. The median intake of dietary vitamin C in men who took no supplements was 150 mg/d. Therefore, it may have been difficult to detect an in-

crease in risk with the additional intake of vitamin C in the form of supplements.

It is possible that the weak association between supplemental vitamin C intake and risk indicates that the relation between total vitamin C intake and stone formation was confounded by an unmeasured dietary factor. Although we could not adjust for oxalate intake because reliable values were not available for the full range of foods on our questionnaire, foods that are known to contain both oxalate and vitamin C (*e.g.*, spinach)

contributed only small amounts to the total dietary vitamin C intake of the cohort (data not shown). Therefore, oxalate intake is unlikely to explain the association between vitamin C and the risk of stone formation.

Magnesium intake was associated with a reduced risk of stone formation. Although our original study did not detect a significantly reduced risk (2), the current analysis had increased statistical power because of the substantially higher number of stones. The importance of magnesium has been controversial; a controlled, randomized trial found supplementation with magnesium hydroxide to be ineffective in the prevention of recurrent calcium oxalate nephrolithiasis (39). However, this trial sustained a high dropout rate. Furthermore, trial participants were instructed to eat a low-oxalate diet and were not instructed to take magnesium hydroxide with meals. If magnesium reduces risk by inhibiting oxalate absorption in the gut, then its effectiveness would be diminished if administered between meals or in the setting of a low-oxalate diet.

We found that the risk associated with animal protein intake varied with BMI. Animal protein consumption increased the risk of kidney stone formation only in men with BMI <25 kg/m^2. In the previous study of this cohort, animal protein was marginally associated with an increased risk of stone formation, but stratified analyses were not performed (2). The reason for the lack of association in the overall cohort was because the average BMI increased over time (data not shown). It is unclear why animal protein intake increased risk only in men who were not overweight.

Unfortunately, few clinical trials have evaluated the effect of animal protein restriction on calcium oxalate stone formation. One randomized trial found a decreased risk with restriction, but dietary sodium was also tightly restricted (to <1.2 g/d), and the comparison group had a low intake of dietary calcium (4). Another randomized trial found an increased rate of recurrence with animal protein restriction, but the control group exhibited an unusually low rate of recurrence (1.2 per 100 person-years) (40).

The results for other dietary factors in this cohort are similar to those previously reported. Potassium intake was inversely associated with the risk of stone formation. Reduced levels of dietary potassium increase the excretion of urinary calcium, an effect that would increase the risk of stone formation (23). The beneficial effect of fluid intake on the dilution of lithogenic factors in the urine is well known, and increased fluid intake has been shown to decrease the recurrence of calcium stones (41). Differences in risk factors by gender continue to be observed. In contrast to the female cohorts that we have examined previously (3,42), sucrose and phytate were not associated with stone formation.

The limitations of this study deserve mention. An FFQ approximates actual nutrient intake. The resulting potential misclassification is likely to be random with respect to case status, however, and therefore would bias the study results toward the null. Another source of misclassification is error in the recollection of the date of a symptomatic incident kidney stone. However, we inquire about new diseases every 2 yr.

The generalizability of our results may be limited because this cohort is all male and largely white. In addition, these results may not be generalizable to men younger than 40 yr or to men who experience recurrent nephrolithiasis. However, most men experience their first stone after the age of 40 (7,43), and the pathophysiology of nephrolithiasis is not known to be different after a single stone has formed.

Our results confirm the importance of individual dietary factors in the development of symptomatic kidney stones. Foods that are high in calcium, potassium, and magnesium should be evaluated as part of a diet to reduce the risk of kidney stone recurrence. Although vitamin C intake is associated with an increased risk of stones, the high amount of potassium in vitamin C–rich foods suggests that limiting the intake of dietary vitamin C in men with calcium oxalate nephrolithiasis is unwarranted. However, we recommend that calcium oxalate stone formers abstain from consuming supplemental vitamin C. Our findings also show that the association between dietary factors and kidney stone formation varies with age and BMI. Clinical studies in the future need to account for the body size and age of their stone-forming participants, and more research is needed to identify the mechanism by which body size and age affect the risk of stone formation.

Acknowledgments

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