

Dietary Factors and the Risk of Incident Kidney Stones in Younger Women

Nurses' Health Study II

Gary C. Curhan, MD, ScD; Walter C. Willett, MD, DrPH; Eric L. Knight, MD, MPH; Meir J. Stampfer, MD, DrPH

Background: In older women and men, greater intakes of dietary calcium, potassium, and total fluid reduce the risk of kidney stone formation, while supplemental calcium, sodium, animal protein, and sucrose may increase the risk. Recently, phytate has been suggested to play a role in stone formation. To our knowledge, no prospective information on the role of dietary factors and risk of kidney stone formation is available in younger women.

Methods: We prospectively examined, during an 8-year period, the association between dietary factors and the risk of incident symptomatic kidney stones among 96 245 female participants in the Nurses' Health Study II; the participants were aged 27 to 44 years and had no history of kidney stones. Self-administered food frequency questionnaires were used to assess diet in 1991 and 1995. The main outcome measure was an incident symptomatic kidney stone. Cox proportional hazards regression models were used to adjust simultaneously for various risk factors.

Results: We documented 1223 incident symptomatic kidney stones during 685 973 person-years of follow-up. After adjusting for relevant risk factors, a higher dietary calcium intake was associated with a reduced risk of kidney stones ($P = .007$ for trend). The multivariate rela-

tive risk among women in the highest quintile of intake of dietary calcium compared with women in the lowest quintile was 0.73 (95% confidence interval, 0.59-0.90). Supplemental calcium intake was not associated with risk of stone formation. Phytate intake was associated with a reduced risk of stone formation. Compared with women in the lowest quintile of phytate intake, the relative risk for those in the highest quintile was 0.63 (95% confidence interval, 0.51-0.78). Other dietary factors showed the following relative risks (95% confidence intervals) among women in the highest quintile of intake compared with those in the lowest quintile: animal protein, 0.84 (0.68-1.04); fluid, 0.68 (0.56-0.83); and sucrose, 1.31 (1.07-1.60). The intakes of sodium, potassium, and magnesium were not independently associated with risk after adjusting for other dietary factors.

Conclusions: A higher intake of dietary calcium decreases the risk of kidney stone formation in younger women, but supplemental calcium is not associated with risk. This study also suggests that some dietary risk factors may differ by age and sex. Finally, dietary phytate may be a new, important, and safe addition to our options for stone prevention.

Arch Intern Med. 2004;164:885-891

From the Channing Laboratory (Drs Curhan, Willett, Knight, and Stampfer) and the Renal Division (Drs Curhan and Knight), Department of Medicine, Brigham and Women's Hospital, Boston, Mass; and the Departments of Epidemiology (Drs Curhan, Willett, and Stampfer) and Nutrition (Drs Willett and Stampfer), Harvard Medical School, Harvard School of Public Health, Boston. The authors have no relevant financial interest in this article.

DIETARY FACTORS PLAY AN important role in kidney stone formation.¹⁻³ In older women and men, greater intakes of dietary calcium, potassium, alcohol, and total fluid are associated with a reduced risk of stone formation, while supplemental calcium, sodium, animal protein, and sucrose may be associated with an increased risk.^{1,2} To our knowledge, no prospective information has been published on the role of dietary factors and risk of kidney stone formation in younger women.

Recently, dietary phytate has been suggested to play a role in stone formation.^{4,5} Phytate (myoinositol hexaphosphate) binds tightly to doubly charged cations such as

calcium. Binding of calcium in the gastrointestinal tract may increase the absorption of dietary oxalate and thereby increase the risk of calcium oxalate stone formation.⁶ However, phytate also is a strong inhibitor of calcium oxalate crystal formation *in vitro*.⁵ Recent evidence^{4,7} suggests that ingested dietary phytate is absorbed and excreted in the urine. Thus, a higher intake of dietary phytate could reduce the risk of stone formation.

Because the effects of dietary factors may vary with age, results of studies from older women may not be generalizable to younger women. To examine associations between dietary factors and the risk of incident kidney stone formation among younger women, we conducted an 8-year

prospective analysis among 96 245 female participants in the Nurses' Health Study (NHS) II who had no history of kidney stones.

METHODS

STUDY POPULATION

In 1989, 116671 female registered nurses from 15 states, aged 25 to 42 years, completed and returned the initial questionnaire. These women constitute the NHS II. The cohort is followed up using biennial mailed questionnaires that inquire about lifestyle practices, other exposures of interest, and newly diagnosed disease. The average follow-up for the cohort exceeds 90%.

Dietary information was first collected in 1991; hence, the start time for the present study was 1991. The analysis was limited to those women who had completed at least 1 dietary questionnaire. We excluded women for whom the date of diagnosis of a reported stone could not be confirmed or for whom the diagnosis occurred before 1991. In addition, we excluded women with asymptomatic stones that were detected during the evaluation of another condition.

ASSESSMENT OF DIET

In 1991 and 1995, participants completed semiquantitative food frequency questionnaires that ascertained the average intake of specified foods and beverages during the past year. Nutrient intakes were determined based on the reported frequency of consumption of each specified unit of food or beverage and from published data on nutrient content of the specified portions.⁸ Information was also collected on the amount of supplemental calcium (such as calcium carbonate) ingested, either as separate supplements or as part of multivitamin preparations. The reproducibility and validity of the questionnaires completed by women in a similar cohort (NHS I) have been documented,^{8,9} and a similar questionnaire has been shown to be valid and reproducible in men.¹⁰

Nutrient values were adjusted for total caloric (energy) intake by taking the residuals of a linear regression model with total caloric intake as the independent variable and absolute nutrient intake as the dependent variable.^{8,11} Calorie-adjusted values reflect the nutrient composition of the diet independent of the quantity of food consumed. In addition, adjustment for calories reduces variation introduced by questionnaire responses that underreported or overreported intake, thereby improving the accuracy of nutrient measurements.^{8,11}

ASSESSMENT OF NONDIETARY FACTORS

Information on age, weight, and height was obtained on the baseline questionnaire, and age and weight were updated every 2 years. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Family history of kidney stones in a parent or sibling was reported on the 1997 questionnaire.

FOLLOW-UP AND ASCERTAINMENT OF CASES

Participants who reported the diagnosis of a kidney stone in 1991 (when dietary information was first collected) or later were mailed a supplementary questionnaire to confirm the diagnosis and to ascertain the date of occurrence, the type of symptoms, other relevant medical conditions, and, if known, the stone type. A validation study of self-reported diagnosis in similar cohorts (NHS I² and Health Professionals Follow-up Study¹) found that medical records confirmed the self-report in more than 97% of the cases.

Only cases of kidney stones that were diagnosed during the 8 years between the date on which the 1991 questionnaire was returned and May 31, 1999, were considered. After the exclusion of women for whom the date of the kidney stone fell outside the study period or could not be confirmed, 96245 women with no history of kidney stones remained in the study group.

STATISTICAL ANALYSIS

The study design was prospective, with information on diet collected before the onset of kidney stone symptoms. For each participant, person-months of follow-up were counted from the date on which the 1991 questionnaire was returned until the date a kidney stone was diagnosed, death, or May 31, 1999, whichever occurred first. Information on exposures of interest collected on the 1991 questionnaire was updated using responses to the 1995 questionnaire. We allocated person-months of follow-up according to exposure status at the start of each follow-up period (eg, quintile of dietary phytate intake). The division of the cohort into quintiles of nutrient intake allowed us to examine a wide range of nutrient intakes while maintaining enough participants in the highest and lowest categories. If complete information on diet was missing at the start of a time period, the participant was excluded for that period.

The relative risk (the incidence among women in a particular category of intake divided by the corresponding rate in the comparison group) was used as the measure of association.¹² Age-adjusted relative risks were calculated after the participants were stratified according to 5-year age categories. The Mantel extension test was used to evaluate linear trends across categories of intake.¹³ We used a Cox proportional hazards regression model to adjust simultaneously for several risk factors.¹⁴ Variables potentially related to stone formation that were considered in the models were age, body mass index (6 categories), alcohol intake (7 categories), vitamin B₆ intake (5 categories), vitamin C intake (5 categories), intake of supplemental calcium (0, 1-100, 101-500, and >500 mg/d), and dietary intakes of calcium, animal protein, potassium, sodium, sucrose, magnesium, phosphorus, phytate, and fluid (quintile groups). We calculated 95% confidence intervals for all relative risks. All *P* values are 2-tailed.

RESULTS

We documented 1223 incident symptomatic kidney stones during 685973 person-years of follow-up. The frequencies of self-reported characteristics from the supplementary questionnaire are shown in **Table 1**. Sixty-two (5.1%) of the women reported a systemic condition potentially related to stone formation. A urinary tract infection was reported present at the time of the stone event by 17.5% of the women; however, the stone was believed by the individual to be related to the infection in only 6.6% of the cases. A family history of kidney stones was reported by 36.4% of the women with stones. Pain was reported by 95.2% as the presenting symptom. Of the 439 women who reported information on stone type, 87.5% reported a calcium-containing stone.

The overall incidence of symptomatic kidney stones for the cohort was 178 cases per 100000 person-years. The incidence was highest for those aged 27 to 34 years, was lower for those aged 35 to 44 years, and then increased again in those 45 years and older (**Table 2**).

Characteristics of participants according to dietary calcium quintiles are presented in **Table 3**. We used the 1991 dietary data to present representative values for bound-

aries and medians. For our analyses, the updated dietary values were used for the respective time periods. The mean daily intake of animal protein; sodium; potassium; magnesium; phosphorus; vitamins B₆, C, and D; and fluid increased with increasing intake of dietary calcium. The mean daily intake of sucrose and alcohol decreased with increasing intake of dietary calcium. The mean daily intake of supplemental calcium and phytate was similar across the quintiles of dietary calcium intake.

A higher dietary calcium intake was strongly associated with a reduced risk of kidney stones after adjusting for age ($P < .001$ for trend) (Table 4). The age-adjusted relative risk among women in the highest quintile of dietary calcium intake compared with women in the lowest quintile was 0.54. After adjusting for age, body mass index, and intake of supplemental calcium, animal protein, sodium, potassium, sucrose, phytate, and total volume, the inverse association with dietary calcium was slightly attenuated but remained highly significant ($P = .007$ for trend). The multivariate relative risk among women in the highest quintile of intake of dietary calcium compared with women in the lowest quintile was 0.73. The results were essentially unchanged after further adjustment for total vitamin D intake. Similar results were found in a multivariate analysis that excluded the 62 women who reported a systemic disease that predisposes to stone formation and the 81 women who reported a urinary tract infection as the cause of stone formation.

The relation between the intake of supplemental calcium and the risk of kidney stones was examined as well. In contrast to intake of dietary calcium, we found that after adjusting for age and other potential confounders, intake of supplemental calcium was not significantly associated with risk of stone formation ($P = .60$ for trend) (Table 5). The relative risk among women who consumed 501 mg/d or more of supplemental calcium compared with women who did not take supplements was 1.13.

The multivariate results for other dietary factors are shown in Table 4. Animal protein was marginally associated with decreased risk of stone formation ($P = .05$ for trend). Phytate and total fluid intakes were significantly related to reduced risk of stone formation ($P < .001$ for trend). Compared with women in the lowest quintile of intake, the multivariate relative risks of stone formation in the highest quintiles were 0.84 for animal protein, 0.63 for phytate, and 0.68 for total fluid.

Sucrose intake was associated with an increased risk of stone formation ($P = .01$ for trend) (Table 4). Compared with women in the lowest quintile of sucrose intake, the multivariate relative risk for the highest quintile was 1.31. The intakes of sodium, potassium, magnesium, and phosphorus were not independently associated with risk after adjusting for other dietary factors (data not shown).

COMMENT

These findings support an important influence of dietary factors on the risk of kidney stone formation in younger women. In particular, greater consumption of

Table 1. Self-reported Characteristics of the 1223 Women With Incident Kidney Stones

Characteristic	No. (%) of Women
Medical conditions	
Inflammatory bowel disease	26 (2.1)
Hyperparathyroidism	7 (0.6)
Hyperthyroidism	29 (2.4)
Urinary tract infection at the time of stone formation	214 (17.5)
Stone believed to be due to a urinary tract infection	81 (6.6)
Family history	
Kidney stones	445 (36.4)
Gout	258 (21.1)
Symptoms and signs	
Pain	1164 (95.2)
Hematuria	892 (72.9)
Type of stone reported*	
Calcium	384 (87.5)
Uric acid	44 (10.0)
Struvite	7 (1.6)
Cystine	4 (0.9)

*This information was provided by 439 of the 1223 women.

Table 2. Incidence of Kidney Stones Between 1991 and 1999 Among 96 245 Women in the Nurses' Health Study II According to Age

Age Group, y	No. of Cases	No. of Person-years	Incidence, per 10 ⁵ Person-years
27-34	377	182 828	206
35-39	384	225 693	170
40-44	325	208 415	156
≥45	137	69 037	198

dietary calcium decreases the risk of incident kidney stones. These results are consistent with the findings previously reported in studies of older women² and men.^{1,3} Dietary calcium may act by binding dietary oxalate in the gut, leading to reduced oxalate absorption and urinary oxalate excretion.^{6,15,16} Alternatively, dairy products may be a source of some other, as yet unidentified, protective factor.

Calcium from supplements was associated with a slight and nonsignificant increase in risk; a small but significant increase in risk was observed in a study² of older women. In earlier studies,^{1,2} most individuals took their supplement without food or only with breakfast; thus, the supplemental calcium was not being consumed near the time of consumption of dietary oxalate. This would lead to increased calcium absorption and urinary excretion, and would have little or no impact on the absorption and excretion of oxalate. Thus, the apparent discrepancy between the effects of dietary and supplemental calcium suggests that the timing of ingestion may be important.

One other prospective observational study has examined the association between calcium intake and risk of stone formation. A study¹⁷ of 27 001 male Finnish smokers, aged 50 to 69 years, who participated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

Table 3. Age-Standardized Characteristics of the Nurses' Health Study II Participants According to Calorie (Energy)-Adjusted Intake of Dietary Calcium in 1991*

Characteristic	Intake of Dietary Calcium Quintile				
	1	2	3	4	5
Age, y	36.7	36.5	36.2	35.8	35.5
Body mass index†	24.6	24.7	24.6	24.6	24.5
Nutrient					
Calcium, mg/d					
Dietary‡	525	696	832	1008	1357
Supplemental§	130	127	125	129	133
Animal protein, g/d	58.5	61.1	63.0	65.5	72.0
Sodium, mg/d	1991	2149	2194	2210	2219
Potassium, mg/d	2632	2845	2952	3046	3205
Sucrose, g/d	53.6	49.6	48.1	46.6	42.9
Phytate, mg/d	725	786	811	813	777
Dietary fiber, g/d	17.3	18.9	19.4	19.4	18.6
Magnesium, mg/d	271	300	317	333	358
Phosphorus, mg/d	1132	1265	1361	1476	1704
Vitamin					
B ₆ , mg/d	7.2	8.1	8.4	8.8	8.8
C, mg/d	232	251	261	272	273
D, IU/d	257	312	367	436	568
Animal fat, g/d	34.8	35.0	34.6	34.7	35.4
Alcohol, g/d	3.6	3.7	3.3	2.9	2.2
Fluid, mL/d	1889	2008	2077	2226	2390

*Data are given as the mean. For illustrative purposes, the means for variables were derived from responses to the 1991 questionnaire, standardized according to the age distribution of the cohort. However, the period-specific quintile values were used for the 1991 to 1999 analyses. Nutrient values are adjusted for calorie intake.

†Calculated as weight in kilograms divided by the square of height in meters.

‡See Table 4 for ranges of intake for the dietary calcium quintiles.

§From supplements and multivitamin preparations.

found no association with dietary calcium intake. However, the median calcium intake in their referent group was 860 mg/d, which was substantially higher than the intake in the referent group in our studies. In our study, the largest reduction in risk occurred between the first and second quintiles of dietary calcium (≤ 626 and 627-763 mg/d, respectively). No increase in risk was observed even among men in the highest quartile of calcium intake (median, 1790 mg/d).¹⁷

Recently, Borghi and colleagues³ reported the results of a randomized controlled dietary intervention trial. They studied 120 male first-time calcium oxalate kidney stone formers with an elevated urine calcium level who were randomized to either a low-calcium (approximately 400-mg/d) diet or a "normal" calcium (approximately 1200-mg/d), low-animal protein, and low-sodium diet. During the 5-year study, men assigned to the latter diet had a 50% lower rate of first recurrence and also clinically and statistically significant reductions in urinary calcium and oxalate levels. Thus, there seems to be no justification for the recommendation of low-calcium diets for individuals with calcium-containing kidney stones.^{18,19}

In the present study, we observed a marginally significant inverse association between animal protein intake and risk of stone formation. This result conflicts with our a priori hypothesis and with previous findings in women² and men.¹ The ranges of animal protein intake in the present study (≤ 51 g/d in the lowest quintile and ≥ 78 g/d in the highest quintile) were quite similar to those

in the other studies. Interestingly, the Finnish researchers¹⁷ also found a reduced risk for animal protein; however, they did not control for all the potentially relevant dietary confounders. In a dietary intervention study²⁰ of 99 calcium oxalate stone formers, an increased risk of stone formation was observed in the intervention group assigned to a diet that included a reduced animal protein intake. In the study by Borghi et al,³ the independent effect of protein reduction could not be assessed. Previous physiologic studies^{21,22} have predicted an increased risk with higher animal protein intake, based on changes in urine chemistry results (ie, increased calcium and uric acid levels and decreased citrate level), but these studies have not focused on younger women. Evidently, the role of animal protein merits further study.

We observed a strong inverse association between phytate intake and risk of stone formation; women in the highest quintile of phytate intake had a 36% lower risk. Phytate is the most abundant form of phosphate in plants. Phytate forms insoluble complexes with calcium in the gastrointestinal tract and reduces calcium absorption and urinary calcium excretion, which consequently could reduce the risk of stone formation. However, this same action could result in increased oxalate absorption and urinary oxalate excretion, which would increase the risk. In vitro, phytic acid inhibits heterogeneous nucleation of calcium oxalate crystals, which would reduce the risk of stone formation. In a rat model of ethylene glycol-induced calcium oxalate nephrolithiasis, oral phytic acid reduced the number of calcifications on the papillary tips.⁵

Table 4. Age-Adjusted and Multivariate Relative Risks for Incident Kidney Stones According to Intake of Calcium (Dietary), Animal Protein, Sucrose, Phytate, and Fluid*

Variable	Intake Quintile				
	1	2	3	4	5
Calcium (Dietary)					
Intake range, mg/d	≤626	627-763	764-908	909-1128	≥1129
Quintile median, mg/d	540	696	831	1003	1300
No. of cases of stone formation	324	244	239	233	183
No. of person-years	135 085	136 660	137 320	138 105	138 803
Age-adjusted values					
RR	1.00	0.74	0.72	0.69	0.54
95% CI	Ref	0.63-0.87	0.61-0.84	0.58-0.80	0.45-0.63
Multivariate values†					
RR	1.00	0.85	0.85	0.87	0.73
95% CI	Ref	0.72-1.01	0.72-1.02	0.73-1.05	0.59-0.90
Animal Protein					
Intake range, g/d	≤51	52-60	61-68	69-77	≥78
Quintile median, g/d	44	56	64	72	85
No. of cases of stone formation	268	266	228	229	232
No. of person-years	136 748	137 230	137 180	137 418	137 396
Age-adjusted values					
RR	1.00	0.99	0.85	0.85	0.86
95% CI	Ref	0.83-1.17	0.69-1.01	0.71-1.01	0.72-1.03
Multivariate values†					
RR	1.00	0.97	0.85	0.84	0.84
95% CI	Ref	0.81-1.16	0.70-1.02	0.69-1.03	0.68-1.04
Sucrose					
Intake range, g/d	≤36	37-43	44-50	51-59	≥60
Quintile median, g/d	31	40	47	54	66
No. of cases of stone formation	210	209	263	223	318
No. of person-years	137 478	137 532	137 312	137 478	136 173
Age-adjusted values					
RR	1.00	0.99	1.24	1.05	1.51
95% CI	Ref	0.82-1.20	1.04-1.49	0.87-1.27	1.27-1.80
Multivariate values†					
RR	1.00	1.01	1.25	1.00	1.31
95% CI	Ref	0.83-1.23	1.04-1.51	0.82-1.23	1.07-1.60
Phytate					
Intake range, mg/d	≤596	597-697	698-797	798-938	≥939
Quintile median, mg/d	528	648	745	858	1071
No. of cases of stone formation	319	292	234	205	173
No. of person-years	136 878	136 892	136 952	137 419	137 833
Age-adjusted values					
RR	1.00	0.92	0.74	0.64	0.54
95% CI	Ref	0.78-1.08	0.63-0.88	0.54-0.76	0.45-0.65
Multivariate values†					
RR	1.00	0.98	0.80	0.73	0.63
95% CI	Ref	0.83-1.15	0.67-0.96	0.60-0.88	0.51-0.78
Fluid					
Intake range, mL/d	≤1431	1432-1850	1851-2252	2253-2768	≥2769
Quintile median, mL/d	1145	1650	2048	2479	3204
No. of cases of stone formation	312	271	239	211	190
No. of person-years	136 568	139 305	138 765	138 389	132 945
Age-adjusted values					
RR	1.00	0.85	0.76	0.67	0.63
95% CI	Ref	0.72-1.00	0.64-0.89	0.56-0.80	0.53-0.75
Multivariate values†					
RR	1.00	0.88	0.79	0.72	0.68
95% CI	Ref	0.75-1.04	0.66-0.94	0.60-0.86	0.56-0.83

Abbreviations: CI, confidence interval; Ref, referent group; RR, relative risk.

*For illustrative purposes, quintile cut points and medians for dietary variables were derived from responses to the 1991 dietary questionnaire. However, the period-specific quintile values were used for the 1991 to 1999 analyses. The RR is the risk for stone formation compared with the group that had the lowest intake. The χ values (P values for trend) for the age-adjusted RRs are as follows: calcium (dietary), $\chi = -6.47$ ($P < .001$); animal protein, $\chi = -2.26$ ($P = .02$); sucrose, $\chi = 4.66$ ($P < .001$); phytate, $\chi = -7.61$ ($P < .001$); and fluid, $\chi = -5.83$ ($P < .001$). The corresponding values for the multivariate RRs are as follows: calcium (dietary), $\chi = -2.70$ ($P = .007$); animal protein, $\chi = -1.98$ ($P = .05$); sucrose, $\chi = 2.48$ ($P = .01$); phytate, $\chi = -4.95$ ($P < .001$); and fluid, $\chi = -4.37$ ($P < .001$). A χ value greater than 1.96 denotes $P < .05$. The sign of the χ value indicates the direction of the trend.

†The multivariate model included age (in 5-year categories), body mass index (5 categories), family history of kidney stones, and intake of supplemental calcium (4 categories), dietary calcium, animal protein, potassium, sodium, sucrose, phytate, and fluid (quintile groups for the last 5 variables).

Table 5. Age-Adjusted and Multivariate Relative Risks for Incident Kidney Stones According to Intake of Supplemental Calcium*

Variable	Intake of Supplemental Calcium, mg/d			
	0	1-100	101-500	≥501
No. of cases of stone formation	790	85	228	120
No. of person-years	431 607	47 906	141 825	64 635
Age-adjusted values				
RR	1.00	0.96	0.87	1.02
95% CI	Ref	0.77-1.20	0.75-1.01	0.84-1.24
Multivariate values†				
RR	1.00	1.00	0.92	1.13
95% CI	Ref	0.80-1.25	0.79-1.07	0.92-1.36

Abbreviations: See Table 4.

*The RR is the risk for stone formation compared with the group that had the lowest intake of supplemental calcium. For the age-adjusted RR, $\chi = -0.99$ ($P = .32$ for trend); and for the multivariate RR, $\chi = 0.53$ ($P = .60$ for trend). A χ value greater than 1.96 denotes $P < .05$. The sign of the χ value indicates the direction of the trend.

†The variables included in the multivariate model are described in the third footnote to Table 4.

This suggests that phytate acts by inhibiting crystal formation in the urine. There are limited data on the quantity of phytic acid or its metabolites excreted in the urine. In a case-control study,⁴ urinary phytate levels were 40% lower in active calcium oxalate stone formers compared with healthy control subjects ($P < .05$). In healthy individuals, urinary phytate levels decreased by more than 50% after 36 hours of a phytate-free diet ($P < .05$),⁴ but they may be normalized with phytate supplements.²³ In our female cohort, the most common foods that contributed to phytate intake were cold cereal, dark bread, and beans. Apparently, phytate is absorbed from the diet and excreted in the urine and may, thus, be a modifiable dietary factor that could decrease the likelihood of stone recurrence.

Sucrose intake was associated with an increased risk that is consistent with the findings in an older female cohort.² A high sucrose intake increases urinary calcium excretion independent of calcium intake.²⁴ The mechanism by which this occurs is unknown.

Sodium intake was not associated with risk of stone formation. These findings are consistent with observations in men,¹ but differ from the increased risk found in women.² It is possible that sodium intake is not important in this age group. Another possibility is that the assessment of sodium intake was not sufficiently accurate to detect an association. The independent effect of sodium could not be determined in the Italian randomized trial.³

Surprisingly, we found no association with potassium, which differs from what was previously observed in men¹ and older women.² Magnesium was also not associated with risk after controlling for other dietary factors, similar to previous findings in men and women but in contrast to findings from the Finnish study.¹⁷ However, in the study from Finland, the only other dietary factors that were adjusted for in the multivariate model were fiber and alcohol. Given the high correlation be-

tween the intake of magnesium and other dietary factors such as potassium, it is possible that magnesium would not have been significantly associated with risk if these other dietary variables were included in the multivariate model.

The incidence of nephrolithiasis varied by age, and was highest in the youngest age group (27-34 years). When we compared the incidence rates in the present study with those in corresponding age groups from 10 years earlier in the NHS I,² the incidence of stone formation seems to be increasing among women. This is consistent with national trends.²⁵ Although the specific reasons for this increase are unknown, dietary and other lifestyle factors are probably important contributors.

The information on dietary factors was obtained before the kidney stone was diagnosed; thus, biased recall of dietary intake was avoided. Although there may be other unmeasured lifestyle factors that relate to stone formation, we included in our multivariate models those variables that are believed to be most strongly related to stone formation. Incomplete information on the oxalate content of foods precluded us from performing analyses on the association between dietary oxalate intake and stone formation. We do not have information on 24-hour urine chemistry results from the whole cohort.

These findings are most directly generalizable to women younger than 50 years. The findings for dietary calcium intake are quite consistent with the literature; however, the results for some of the other dietary factors that we studied are quite different from what was observed in older women and men. These results underscore that care should be taken when attempting to generalize results across age and sex groups and that more studies are needed. Because the pathophysiological features of stone formation are believed to remain the same regardless of a history of nephrolithiasis, it is likely that these results apply to young women with a history of kidney stones as well.

In summary, our findings indicate that a higher intake of dietary calcium decreases the risk of kidney stone formation in younger women. The lack of an increased risk with greater intake of calcium and the potential to increase the risk with calcium restriction reinforce that the routine restriction of dietary calcium in patients who have had a kidney stone is no longer justified. Supplemental calcium was not associated with risk in this study; however, the risk of supplements in women who have had a kidney stone should be considered on an individual basis. This study also suggests that some dietary risk factors may differ by age and sex. Finally, dietary phytate may be a new, important, and safe addition to our options for stone prevention.

Accepted for publication May 30, 2003.

This study was supported by grants CA50385 and DK59583 from the National Institutes of Health, Bethesda, Md.

Corresponding author: Gary C. Curhan, MD, ScD, Channing Laboratory, Brigham and Women's Hospital, 181 Longwood Ave, Boston, MA 02115 (e-mail: Gary.Curhan@channing.harvard.edu).

REFERENCES

1. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med.* 1993;328:833-838.
2. Curhan G, Willett W, Speizer F, Spiegelman D, Stampfer M. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Intern Med.* 1997;126:497-504.
3. Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med.* 2002;346:77-84.
4. Grases F, March JG, Prieto RM, Simonet BM, Garcia-Raja A, Conte A. Urinary phytate in calcium oxalate stone formers and healthy people: dietary effects on phytate excretion. *Scand J Urol Nephrol.* 2000;34:162-164.
5. Grases F, Garcia-Gonzalez R, Torres JJ, Llobera A. Effects of phytic acid on renal stone formation in rats. *Scand J Urol Nephrol.* 1998;32:261-265.
6. Lemann J Jr. Composition of the diet and calcium kidney stones. *N Engl J Med.* 1993;328:880-881.
7. Grases F, Simonet BM, March JG, Prieto RM. Inositol hexakisphosphate (InsP6) in urine: study of the relation between oral intake and urinary excretion. *BJU Int.* 2000;85:138-142.
8. Willett WC. *Nutritional Epidemiology.* 2nd ed. New York, NY: Oxford University Press Inc; 1998.
9. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semi-quantitative food frequency questionnaire. *Am J Epidemiol.* 1985;122:51-65.
10. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol.* 1992; 135:1114-1126.
11. Willett WC, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol.* 1986;124:17-27.
12. Rothman K. *Modern Epidemiology.* Boston, Mass: Little Brown & Co Inc; 1986.
13. Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. *J Am Stat Assoc.* 1963;58:690-700.
14. Cox D, Oakes D. *Analysis of Survival Data.* New York, NY: Chapman & Hall; 1984.
15. Larsson L, Tiselius H-G. Hyperoxaluria. *Miner Electrolyte Metab.* 1987;13:242-250.
16. Zaremski PM, Hodgkinson A. Some factors influencing the urinary excretion of oxalic acid in man. *Clin Chim Acta.* 1969;25:1-10.
17. Hirvonen T, Pietinen P, Virtanen M, Albanes D, Virtamo J. Nutrient intake and use of beverages and the risk of kidney stones among male smokers. *Am J Epidemiol.* 1999;150:187-194.
18. Bushinsky DA. Recurrent hypercalciuric nephrolithiasis: does diet help [comment]? *N Engl J Med.* 2002;346:124-125.
19. Coe FL, Parks JH, Favus MJ. Diet and calcium: the end of an era [comment]? *Ann Intern Med.* 1997;126:553-555.
20. Hiatt R, Ettinger B, Caan B, Quesenberry C Jr, Duncan D, Citron J. Randomized controlled trial of a low animal protein, high fiber diet in the prevention of recurrent calcium oxalate kidney stones. *Am J Epidemiol.* 1996;144:25-33.
21. Breslau N, Brinkely L, Hill K, Pak C. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. *J Clin Endocrinol Metab.* 1988; 66:140-146.
22. Coe FL, Moran E, Kavalich AG. The contribution of dietary purine overconsumption to hyperpuricosuria in calcium oxalate stone formers. *J Chronic Dis.* 1976;29:793-800.
23. Grases F, Simonet BM, Vucenik I, et al. Absorption and excretion of orally administered inositol hexaphosphate (IP(6) or phytate) in humans. *Biofactors.* 2001; 15:53-61.
24. Lemann J Jr, Piering WF, Lennon EJ. Possible role of carbohydrate-induced calciuria in calcium oxalate kidney-stone formation. *N Engl J Med.* 1969;280:232-237.
25. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. *Kidney Int.* 2003;63:1817-1823.