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Dietary and Lifestyle Risk Factors Associated with Incident Kidney Stones in Men and Women

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Abstract

Purpose—Several dietary and lifestyle factors are associated with a higher risk of developing kidney stones. We estimated the population attributable fraction (PAF) and number needed to prevent (NNTP) for modifiable risk factors including body mass index (BMI), fluid intake, DASH-style diet, dietary calcium intake and intake of sugar-sweetened beverages.

Materials and methods—We used data from the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Studies (NHS) I and II cohorts. Information was obtained from validated questionnaires. Poisson regression models adjusted for potential confounders were used to estimate the association of each risk factor with development of incident kidney stones and to compute PAF and NNTP.

Results—The study included 192,126 participants who contributed a total of 3,259,313 person-years of follow-up, during which 6,449 participants developed an incident kidney stone. All the modifiable risk factors were independently associated with incident stones in each of the cohorts. The PAF ranged from 4.4% for higher sugar-sweetened beverages intake to 26.0% for lower fluid intake; the PAF for all the five risk factors combined was 57.0% in HPFS, 55.2% in NHS I and 55.1% in NHS II. NNTP over 10 years ranged from 67 for lower fluid intake to 556 for lower dietary calcium intake.

Conclusions—Five modifiable risk factors accounted for more than 50% of incident kidney stones in three large prospective cohorts. Assuming a causal relation, our estimates suggest that preventive measures aimed at reducing those factors could substantially reduce the burden of kidney stones in the general population.

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Keywords

attributable fraction; cohort studies; nutrition; obesity; urolithiasis

Introduction

Kidney stones are common, with an estimated lifetime prevalence in the U.S. of about 9% in women and 19% in men,[1] and a high economic burden in excess of $4.5 billion annually.[2] The heritability of the risk of stones was estimated to be 56% in a twin study, which implies that about half of the stone events could be prevented by acting on modifiable risk factors. In fact, modifiable factors, especially environmental and dietary, have been reported to be associated with risk of stones, including overweight and obesity,[3] amount and composition of fluid intake,[4–6] DASH-style diet (a diet high in fruits, vegetables and low-fat dairy products),[7] and amount of dietary calcium intake[8–10]. To date, no study has estimated the proportion of incident kidney stones that could be attributable to these modifiable risk factors simultaneously and thus potentially preventable. In this study, we estimated the population attributable fraction (PAF) and number needed to prevent (NNTP) for several modifiable risk factors for kidney stones and combinations thereof in three large prospective cohorts, the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Studies (NHS) I and II.

Methods

Study population

NHS I was established in 1976, when 121,700 female nurses aged 30–55 years completed a self-administered questionnaire on risk factors for cancer and other diseases. NHS II began in 1989, when 116,430 female nurses aged 25–42 years completed and returned a baseline questionnaire. HPFS comprises 51,529 male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians aged 40–75 years at baseline in 1986. In each cohort, information from the questionnaires was updated every 2 years for the main questionnaire and every 4 years for the food frequency questionnaires (FFQ). These studies were approved by the Partners HealthCare institutional review board.

Assessment of modifiable risk factors

We chose five modifiable risk factors with a well-established association with incident kidney stones: body mass index (BMI)[3], fluid intake[5], DASH-style diet[7], dietary calcium intake[8–10] and intake of sugar-sweetened beverages (SSB)[4,6]. Information about BMI was obtained from the main questionnaire, in which participants were requested to report their height and weight; self-reported weights from 123 men in HPFS and 140 women in NHS I were highly correlated with values obtained by technicians who visited the participants at home (r=0.97).[11] All the other risk factors were obtained from the FFQ, which asked about the average use of more than 130 individual foods and 22 beverages during the previous year. The FFQ was validated in the HPFS and NHS I cohorts using food records, and estimated intakes were found to be reasonably correlated with actual intakes.[12,13]

Definition of risk groups

For PAF and NNTP calculations, we categorized the risk factors of interest: three categories for BMI (<25, 25–29, ≥30 kg/m^2), fluid intake (<1, 1–1.9, ≥2 liters/day) and SSB (<4, 4–6, ≥7 servings/week), and cohort-specific quintiles for DASH-style diet and dietary calcium. Cutpoints were chosen based on the WHO criteria for BMI and on previous publications for the other risk factors.[6–8,10]

Assessment of kidney stones

The primary end point was an incident kidney stone accompanied by pain or hematuria. Individuals who reported a new kidney stone were sent a supplementary questionnaire asking for additional information on the event such as date of occurrence and accompanying symptoms. The diagnosis of kidney stones was confirmed through review of medical records in 95%, 96% and 98% of 582 men in HPFS, 194 women in NHS I, and 858 women in NHS II; among those with a stone composition report available, 86% of participants in the HPFS, 77% of participants in the NHS I, and 79% of participants in the NHS II cohort had a stone containing ≥50% calcium.[7]

Assessment of other covariates

Other variables included in the analysis were age, race, use of thiazide diuretics, history of diabetes and history of hypertension; information on all those variables was derived from the main questionnaires.

Statistical analysis

We computed incidence rates for kidney stones for each risk factor category calculating person-time from the date of return of the baseline FFQ (1986 for HPFS and NHS I, 1991 for NHS II) to 2012 for HPFS and NHS I and 2011 for NHS II. Adjusted incidence rates were estimated using Poisson regression models with multivariable adjustment for age, race, geographic area, use of thiazide diuretics, history of diabetes, history of hypertension and the other risk factors (DASH-score was not adjusted for dietary calcium and SSB intake because those items were already included in its calculation). Estimates of association for each risk factor were expressed as incidence rate ratios (IRR). Simple time updating was adopted for time-varying variables to use the most recent information available on risk factors and covariates from follow-up questionnaires.

PAF is an estimate of the percentage of new stone cases occurring in these populations that could hypothetically have been prevented if all participants had been in the low-risk group (assuming a causal and independent relation between the risk factor and kidney stones). It was calculated using the Bruzzi method which allows for estimation of PAFs for polytomous risk factors,[14] as well as for summary PAFs that are not the sum of individual PAFs.[15] Although other methods have been reported for PAF estimation in cohort studies,[16] those would only allow the analysis of binary risk factors.

NNTP is interpreted as the number of participants who were not in the low-risk category who would have to adopt the low-risk category characteristic over a period of 10 years to hypothetically prevent the development of 1 stone case. NNTP was calculated by first computing adjusted incidence rate differences for each category of exposure; rate differences were then used to compute absolute risk differences at 10 years. Finally, NNTP was obtained by dividing 100 by the absolute risk differences. A summary NNTP was obtained by comparing the adjusted rates for those participants in the all-high and those in the all-low risk group. A similar approach has been previously used in the same cohorts.[17]

Results

The analysis included 192,126 participants, whose baseline characteristics are reported in Table 1. At baseline, mean age was 54.2 ± 9.7 years for HPFS, 52.9 ± 7.1 years for NHS I and 36.6 ± 4.6 years for NHS II, and mean BMI was 25.5 ± 3.4 kg/m^2 for HPFS, 25.2 ± 4.7 kg/m^2 for NHS I and 24.6 ± 5.3 kg/m^2 for NHS II. Participants contributed a total of 3,259,313 person-years of follow-up, during which 6449 incident kidney stones developed. Median (25^{th}, 75^{th} percentile) follow-up times were 11.5 (6.5, 16.7) years for HPFS, 12.1 (7.9, 20.0) years for NHS I and 11.3 (5.1, 16.0) years for NHS II.

The multivariable adjusted estimates of association between each risk factor and incident kidney stones are reported in Table 2. In all the cohorts, the modifiable risk factors were each independently associated with risk of stones.

Estimates of PAF and NNTP are reported in Table 3. In the HPFS cohort, the highest PAF was for lower fluid intake, which accounted for 26.0% (95% CI 20.8 to 30.7%) of all the incident stones in the cohort; the corresponding NNTP over 10 years was 67 (95% CI 65 to 85). In the NHS cohorts, the highest PAF was for higher BMI, which accounted for 21.8% (95% CI 16.7 to 26.3%) of all the incident stones in the NHS I and for 18.9% (95% CI 15.5 to 22.2%) in the NHS II; the corresponding NNTP over 10 years was 164 (95% CI 134 to 213) in the NHS I and 112 (95% CI 94 to 137) in the NHS II. The summary PAF was 57.0% (95% CI 34.2 to 71.4%) in the HPFS cohort, 55.2% (95% CI 29.7 to 70.9%) in the NHS I cohort and 55.1% (95% CI 37.8 to 67.3%) in the NHS II cohort; the corresponding NNTP over 10 years was 19 (95% CI 16 to 23) for the HPFS cohort, 37 (95% CI 32 to 45) for the NHS I cohort and 24 (95% CI 21 to 27) for the NHS II cohort.

Discussion

In our study of three large prospective cohorts, maintaining a normal BMI, drinking an adequate amount of fluid, eating a diet high in fruits, vegetables and low-fat dairy products with an adequate intake of calcium, and avoiding frequently drinking SSB were associated with a clinically meaningful lower risk of incident kidney stones during follow-up. Assuming that these associations are causal, lifestyle interventions aimed at modifying risk factors could substantially prevent a large proportion of kidney stones in the general population and have a profound impact on public health, considering that kidney stone disease is common and associated with high costs.

All the modifiable risk factors included in our analysis have been previously reported to be associated with kidney stones in observational and/or interventional studies. Higher BMI has been associated with increased risk of stones in these cohorts: a BMI of ≥30 kg/m^2 was associated with a 30% to 109% higher risk of stones compared with a BMI of 21–22.9

kg/m^2.[3,18] The association between BMI and risk of stones was also confirmed in the Women's Health Initiative cohort.[19] Intake of higher volume of fluids has been associated with a lower risk of stones in these cohorts[20,21] and also shown to reduce the risk of stone recurrence by about 56% in a randomized controlled trial that enrolled idiopathic calcium stone formers.[5] Following a diet high in fruits, vegetables and low-fat dairy products was associated with up to a 45% lower risk of stones.[7] Consuming an adequate amount of dietary calcium has been associated with a 27 to 35% lower risk of stones among women and 44% among men;[8–10] this finding was later confirmed in another cohort[22] and by a randomized controlled trial in which individuals affected with idiopathic calcium stones assigned a diet with adequate calcium (about 1,200 mg per day), low animal protein and low sodium diet had a 51% reduction in stone recurrence compared with those assigned to a low calcium (about 400 mg per day) diet.[23] Finally, we previously reported that more frequent consumption of SSB (soda and punch) was associated with a 30–40% higher risk of stones.[6] Also, a randomized controlled trial showed that the rate of stone recurrence was about 6.4% lower among stone formers assigned to refrain from consuming soft drinks.[4]

In our study, we found that the categories of risk factors associated with the highest risk of incident stones varied by cohort. In the HPFS cohort, total fluid intake of less than two liters per day was associated with the highest risk. Conversely, in the NHS I and NHS II cohorts, the strongest risk factor was a higher BMI. Such differences were likely related to differences in sex and age across cohorts, which would in turn modify the association between individual risk factors and risk of stones. Differences across cohorts in terms of prevalence of risk factors (Table 1) and strengths of association with incident stones (Table 3) could also be reflected in different PAF estimates, given that PAF is computed based on those values. Overall, our data suggest that moving from low-risk to high-risk groups would lead to a halving in the number of cases of kidney stones, which is consistent with previously published data that the relative weight of environmental risk factors for stones was about 50%.[24] Estimates obtained from our study will be useful to inform future decision analyses aimed at evaluating the cost-effectiveness of primary prevention measures for kidney stones.

Our study has limitations. First, we needed to categorize the risk factors rather than model them continuously to calculate PAF and NNTP estimates. Although modeling some of the risk factors continuously would have been preferable, there is not an available method to estimate PAF using continuous variables. Using a published equation, we were able to obtain estimates for more than one cutpoint per risk factor; we were not able to increase the number of cutpoints further than those presented without producing unstable estimates due to the reduced number of participants in the low-risk group. Second, information used to classify the participants based on the presence and degree of risk factors was self-reported; however, validated questionnaires were used. Third, the PAF and NNTP estimates rely on the assumption of a causal relation between risk factors and outcomes; however, most of the risk factors analyzed have been proven to play a role in stone disease in an interventional setting. Fourth, some of the risk factors analyzed could partly share their causal pathways to development of kidney stones; however, we found an independent association for each risk factor even after adjusting for all the other risk factor and for additional confounders (Table 2). Fifth, in our study we analyzed risk factors for a first symptomatic stone event; our results may not necessarily apply to recurrence in patients with a history of stones. Finally, the PAF estimates are computed assuming complete change in the risk factors from the highest to lowest risk category, which is an optimistic scenario; however, future decision analyses might incorporate variable degrees of efficacy of preventive measures and also formally establish a threshold of efficacy for an intervention to be deemed cost-effective.

In conclusion, in three large prospective cohorts, adherence to low-risk dietary and lifestyle factors was associated with more than a 50% reduction in the incidence of kidney stones, thus suggesting that a substantial proportion of kidney stones is potentially preventable.

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PMF and GCC designed the study; PMF conducted the statistical analysis; PMF and GCC drafted the manuscript; ENT, GG and GCC reviewed the manuscript for important intellectual content.

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Table 1

Baseline characteristics of the study cohorts

	HPFS (n = 41,937)	**NHS I (n = 59,740)**	**NHS II (n = 90,449)**
Age, years (mean ± SD)	54.2 ± 9.7	52.9 ± 7.1	36.6 ± 4.6
BMI, kg/m^2 (mean ± SD)	25.5 ± 3.4	25.2 ± 4.7	24.6 ± 5.3
White race (%)	94.9	94.5	93.8
History of diabetes (%)	3.0	3.4	1.0
History of hypertension (%)	21.4	24.5	6.3
Use of thiazide diuretics (%)	9.0	13.5	1.7
Higher BMI (%)	53.1	42.2	34.1
Lower fluid intake (%)	57.1	52.9	48.0
Lower DASH-style diet (%)	80.3	79.1	81.1
Lower dietary calcium intake (%)	79.4	79.9	79.8
Higher SSB intake (%)	27.1	19.3	32.0

BMI, body mass index; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; SD, standard deviation; SSB, sugar-sweetened beverages.

Table 2

Multivariable adjusted estimates of association between modifiable risk factors and incidence of kidney stones

	HPFS		NHS I		NHS II	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
BMI						
- < 25 kg/m^2	1.00		1.00		1.00	
- 25–29 kg/m^2	1.26	1.14, 1.39	1.40	1.25, 1.57	1.34	1.23, 1.47
- ≥ 30 kg/m^2	1.44	1.23, 1.67	1.80	1.57, 2.05	1.71	1.56, 1.88
Fluid intake						
- ≥ 2 liters/day	1.00		1.00		1.00	
- 1.9–1 liters/day	1.53	1.37, 1.69	1.29	1.15, 1.44	1.30	1.20, 1.41
- < 1 liter/day	1.86	1.58, 2.14	1.86	1.58, 2.18	1.75	1.56, 1.97
DASH-style diet						
- Fifth quintile	1.00		1.00		1.00	
- Fourth quintile	1.06	0.90, 1.25	0.98	0.82, 1.17	1.18	1.04, 1.34
- Third quintile	1.21	1.04, 1.42	1.22	1.03, 1.44	1.09	0.96, 1.24
- Second quintile	1.36	1.17, 1.59	1.32	1.12, 1.56	1.33	1.18, 1.51
- First quintile	1.53	1.31, 1.78	1.47	1.25, 1.73	1.37	1.21, 1.55
Dietary calcium intake						
- Fifth quintile	1.00		1.00		1.00	
- Fourth quintile	1.09	0.94, 1.27	1.16	0.98, 1.37	1.06	0.93, 1.20
- Third quintile	1.02	0.87, 1.19	1.07	0.90, 1.27	1.13	1.00, 1.27
- Second quintile	1.14	0.98, 1.32	1.17	0.99, 1.39	1.18	1.04, 1.33
- First quintile	1.18	1.01, 1.37	1.21	1.02, 1.44	1.27	1.12, 1.44
SSB intake						
- <4 servings/week	1.00		1.00		1.00	
- 4–6 servings/week	1.23	1.09, 1.38	1.18	1.03, 1.37	1.19	1.07, 1.32
- ≥7 servings/week	1.41	1.23, 1.62	1.31	1.10, 1.56	1.51	1.37, 1.66

Models adjusted for age, race, geographic area, use of thiazide diuretics, history of diabetes, history of hypertension and all the other risk factors (DASH-score was not adjusted for dietary calcium and SSB intake). BMI, body mass index; CI, confidence interval; HPFS, Health Professionals Follow-up Study; IRR, incidence rate ratio; NHS, Nurses' Health Study; SSB, sugar-sweetened beverages

Table 3

Population attributable fraction and number needed to prevent for modifiable risk factors for incident kidney stones

	HPFS		NHS I		NHS II	
	Est.	95% CI	Est.	95% CI	Est.	95% CI
Higher BMI						
- PAF %	14.0	8.4, 18.9	21.8	16.7, 26.3	18.9	15.5, 22.2
- NNTP	115	85, 182	164	134, 213	112	94, 137
Lower fluid intake						
- PAF %	26.0	20.8, 30.7	18.1	11.9, 23.3	16.8	12.8, 20.5
- NNTP	67	55, 85	164	129, 228	109	90, 139
Lower DASH-style diet						
- PAF %	20.3	9.2, 30.0	17.6	5.2, 28.0	17.0	7.9, 25.2
- NNTP	148	101, 278	371	239, 910	233	162, 417
Lower dietary calcium intake						
- PAF %	8.2	0, 18.8	11.2	0, 22.7	11.8	2.1, 20.1
- NNTP	358	162, NE	556	295, 10,001	345	205, 1,001
Higher SSB intake						
- PAF %	7.5	4.1, 10.5	4.4	1.2, 7.3	9.1	6.3, 11.6
- NNTP	117	84, 193	323	205, 770	150	117, 209
Summary						
- PAF %	57.0	34.2, 71.4	55.2	29.7, 70.9	55.1	37.8, 67.3
- NNTP	19	16, 23	37	32, 45	24	21, 27

BMI, body mass index; CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; NNTP, number needed to prevent over 10 years; PAF, attributable fraction; SSB, sugar-sweetened beverages. For some risk factors with non-positive incidence rate ratios the NNTP was not estimable (NE)