Original Investigation

History of Kidney Stones and the Risk of Coronary Heart Disease

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IMPORTANCE Kidney stone disease is common and may be associated with an increased risk of coronary heart disease (CHD). Previous studies of the association between kidney stones and CHD have often not controlled for important risk factors, and the results have been inconsistent.

OBJECTIVE To examine the association between a history of kidney stones and the risk of CHD in 3 large prospective cohorts.

DESIGN, SETTING, AND PARTICIPANTS A prospective study of 45 748 men and 196 357 women in the United States without a history of CHD at baseline who were participants in the Health Professionals Follow-up Study (HPFS) (45 748 men aged 40-75 years; follow-up from 1986 to 2010), Nurses' Health Study I (NHS I) (90 235 women aged 30-55 years; follow-up from 1992 to 2010), and Nurses' Health Study II (NHS II) (106 122 women aged 25-42 years; follow-up from 1991 to 2009). The diagnoses of kidney stones and CHD were updated biennially during follow-up.

MAIN OUTCOMES AND MEASURES Coronary heart disease was defined as fatal or nonfatal myocardial infarction (MI) or coronary revascularization. The outcome was identified by biennial questionnaires and confirmed through review of medical records.

RESULTS Of a total of 242 105 participants, 19 678 reported a history of kidney stones. After up to 24 years of follow-up in men and 18 years in women, 16 838 incident cases of CHD occurred. After adjusting for potential confounders, among women, those with a reported history of kidney stones had an increased risk of CHD than those without a history of kidney stones in NHS I (incidence rate [IR], 754 vs 514 per 100 000 person-years; multivariable hazard ratio [HR], 1.18 [95% CI, 1.08-1.28]) and NHS II (IR, 144 vs 55 per 100 000 person-years; multivariable HR, 1.48 [95% CI, 1.23-1.78]). There was no significant association in men (IR, 1355 vs 1022 per 100 000 person-years; multivariable HR, 1.06 [95% CI, 0.99-1.13]). Similar results were found when analyzing the individual end points (fatal and nonfatal MI and revascularization).

CONCLUSIONS AND RELEVANCE Among the 2 cohorts of women, a history of kidney stones was associated with a modest but statistically significantly increased risk of CHD; there was no significant association in a separate cohort of men. Further research is needed to determine whether the association is sex-specific.

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Nephrolithiasis is a common condition, with the prevalence varying by age and sex. A recent estimate from the National Health and Nutrition Examination Survey, a representative sample of the US population, reported the prevalence of a history of kidney stones of 10.6% in men and 7.1% in women.[1] The overall prevalence has increased from 3.8% (1976-1980)[2] to 8.8% (2007-2010).[1]

Associations between nephrolithiasis and systemic diseases have been recognized, including subclinical atherosclerosis,[3] hypertension,[4-6] diabetes,[7,8] metabolic syndrome,[9] and cardiovascular disease.[10-12] One longitudinal study reported a 31% increased risk for myocardial infarction in patients with a history of kidney stones.[13] However, the other previously published studies either were cross-sectional, did not confirm clinical events, or did not take into account potential confounding by important risk factors such as dietary habits. Possible reasons for such association include shared risk factors, an increased incidence of kidney disease among patients with a history of kidney stones,[14] and abnormalities of calcium metabolism.[15] Therefore, we analyzed the relation between kidney stones and risk of incident coronary heart disease (CHD) for individuals with a history of kidney stones in 3 large prospective cohorts.

Methods

Study Populations

These studies were approved by the Partners HealthCare institutional review board, which accepts return of the questionnaires as implied consent in these cohorts. The Health Professionals Follow-up Study (HPFS) started in 1986 with the enrollment of 51 529 male health professionals aged 40 to 75 years who filled out a questionnaire on lifestyle and medical history. The Nurses' Health Study I (NHS I) started in 1976 with the enrollment of 121 700 female nurses aged 30 to 55 years who completed a questionnaire on lifestyle and medical history. Nurses' Health Study II (NHS II) was started in 1989, consisting of 116 430 female nurses aged 25 to 42 years. In all 3 cohorts, information has been updated every 2 years until the end of follow-up: January 2010 for HPFS, June 2010 for NHS I, and June 2009 for NHS II.

Participants with a baseline self-reported history of myocardial infarction, coronary revascularization, or cancer (except nonmelanoma skin cancer) were excluded from the analysis. Participants who developed cancer during the follow-up were censored.

Assessment of Kidney Stones

Questions about history of kidney stones were first asked in 1986 for the HPFS cohort, in 1992 for the NHS I cohort, and in 1991 for the NHS II cohort. Subsequent biennial questionnaires asked about history of kidney stones in the previous 2 years. Participants reporting an incident kidney stone were asked to complete a supplementary questionnaire asking about the date of occurrence and symptoms such as pain or hematuria from the event. The self-reported diagnosis was confirmed in approximately 97% of participants who completed the additional questionnaire in 2 separate validation studies in these populations.[16,17]

Assessment of CHD

The primary outcome was CHD, defined as a composite of nonfatal or fatal myocardial infarction, fatal coronary heart disease, or coronary revascularization procedure (coronary artery bypass grafting surgery or percutaneous transluminal coronary angioplasty). For simplicity, we defined fatal myocardial infarction as documented fatal myocardial infarction or fatal coronary heart disease determined by deaths identified from state death certificates or the National Death Index or reported by the participant's next of kin or the postal system. Fatal coronary heart disease was confirmed by an examination of hospital or autopsy records or if coronary heart disease was listed as the cause of death on the death certificate and the physician reviewers determined that coronary heart disease was the underlying and most plausible cause. Secondary outcomes were nonfatal or fatal myocardial infarction, and coronary revascularization, examined separately. Fatal and nonfatal myocardial infarction events were confirmed through medical record review and required characteristic symptoms with either diagnostic electrocardiographic changes or positive myocardial enzymes; revascularization was self-reported but has been found to be virtually 100% specific in the HPFS.[18]

Covariates

The following covariates were considered: race (white/nonwhite); region of residence (West, Midwest, Northeast, South); family history of heart disease (yes/no); smoking status (never smoked, past smoker, current smoker); body mass index (BMI, calculated as weight in kilograms divided by height in meters squared; <20.0, 20.0-20.9, 21.0-21.9, 22.0-22.9, 23.0-23.9, 24.0-24.9, 25.0-26.9, 27.0-28.9, 29.0-29.9, 30.0-31.9, 32.0-34.9, 35.0-39.9, ≥40.0); physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27.0 metabolic equivalents/week); diabetes (yes/no); hypertension (yes/no); gout (yes/no); elevated cholesterol (yes/no); use of the following drugs (yes/no): aspirin, thiazide diuretics, loop diuretics, oral steroids, lipid-lowering drugs, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, and other antihypertensive drugs; and daily intake of the following energy-adjusted nutrients (quintiles): calcium, potassium, magnesium, animal protein, total fat, vitamin D, caffeine, and alcohol (0, 0.1-5.0, 5.0-9.9, 10.0-14.9, 15.0-29.9, ≥30.0 g/d). For the NHS I and NHS II cohorts, information about menopausal status and postmenopausal hormone use was considered. For the HPFS cohort, information on profession was included. Dietary information was derived from a validated food-frequency questionnaire administered every 4 years.[19,20] Race was self-designated: each participant could choose among the following ancestries: Southern European/Mediterranean, Scandinavian, other Caucasian, Afro-American, Asian/Oriental, or other with an open option. For the purpose of the analysis, because the majority of the participants were white, race was coded as white/nonwhite and included in the analysis since race seems to be associated with both kidney stones and cardiovascular disease.[2,21]

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To adjust for dietary patterns, we added the Dietary Approaches to Stop Hypertension (DASH) score to the model. Previous studies have shown that the DASH score is associated with a lower risk of kidney stone formation[22] and cardiovascular disease.[23]

Statistical Analysis

The time at risk started when history of kidney stones was first asked on the biennial questionnaires: 1986 for HPFS, 1992 for NHS I, and 1991 for NHS II. We calculated the person-years of follow-up for each participant from the start of the time at risk to the date of death, development of the outcome, or end of follow-up, whichever came first.

The crude and adjusted hazard ratios (HRs) and 95% CIs for the development of a CHD event in participants with a history of kidney stones compared with those without were estimated with Cox proportional hazards regression models with biennial updating of history of kidney stones and covariates. For the composite CHD outcome, we used the first event when more than 1 coronary event occurred in the same period.

Interaction terms for history of kidney stones and age (≤50 or >50 years), BMI (<25 or ≥25), diabetes, and hypertension were included in separate models to explore possible effect modification. Furthermore, we analyzed whether including the intake of calcium supplements altered the association in a separate model.

Post hoc pooling of the results for the NHS I and NHS II cohorts was performed with random-effects meta-analysis.

A 2-tailed *P*-value less than .05 was considered statistically significant. All analyses were performed with SAS, version 9.3 (SAS Institute).

Results

After exclusions, a total of 242 105 participants (45 748 men and 196 357 women) were included in the analysis, contributing 3 994 120 person-years of follow-up. Of these, 19 678 had a history of kidney stones (10 827 at baseline and 8851 during follow-up). The median (25th-75th percentiles) follow-up times were 9.8 (5.3-15.8) years for HPFS, 8.2 (4.1-12.1) years for NHS I and 8.9 (4.9-13.1) years for NHS II. The overall number of participants developing incident CHD was 16 838.

The baseline characteristics of participants by cohort and exposure status are shown in **Table 1**. The mean ages were 55.8 years for participants with a history of kidney stones and 53.7 years for participants without a history of kidney stones in HPFS; 59.0 years for participants with and 58.4 years for participants without in NHS I; and 37.4 years for participants with and 36.6 years for participants without in NHS II. High blood pressure, use of thiazides, and elevated cholesterol were more prevalent among participants with a reported history of kidney stones in all 3 cohorts, as well as diabetes in NHS I and gout in HPFS and NHS I. Intakes of calcium, caffeine, and vitamin D were lower in participants with a reported history of kidney stones.

The crude incidence rates of CHD per 100 000 person-years were 1355 among participants with and 1022 among participants without a history of kidney stones in the HPFS cohort (rate difference, 333/100 000 person-years); 754 among participants with and 514 among participants without in the NHS I cohort (rate difference, 240/100 000 person-years); and 144 among participants with and 55 among participants without in the NHS II cohort (rate difference, 89/100 000 person-years).

The crude incidence rates of myocardial infarction per 100 000 person-years were 536 among participants with and 432 among participants without a history of kidney stones in the HPFS cohort (rate difference, 104/100 000 person-years); 289 among participants with and 196 among participants without in the NHS I cohort (rate difference, 93/100 000 person-years); and 61 among participants with and 25 among participants without in the NHS II cohort (rate difference, 36/100 000 person-years).

The crude incidence rates of coronary revascularization per 100 000 person-years were 941 among participants with and 706 among participants without a history of kidney stones in the HPFS cohort (rate difference, 235/100 000 person-years); 605 among participants with and 401 among participants without in the NHS I cohort (rate difference, 204/100 000 person-years); and 107 among participants with and 40 among participants without in the NHS II cohort (rate difference, 67/100 000 person-years).

In age-adjusted analyses, there was a significant association between history of kidney stones and CHD in all the cohorts: HR, 1.18 (95% CI, 1.11-1.25) for HPFS; HR, 1.41 (95% CI, 1.30-1.54) for NHS I; and HR, 2.19 (95% CI, 1.83-2.63) for NHS II.

After multivariable adjustment, there was no significant association between history of kidney stones and CHD in the HPFS cohort (HR, 1.06 [95% CI, 0.99-1.13]), whereas there was a significantly increased risk in the NHS I (HR, 1.18 [95% CI, 1.08-1.28]) and NHS II (HR, 1.48 [95% CI, 1.23-1.78]) cohorts (**Table 2**).

Multivariable-adjusted analysis of individual outcomes confirmed an association in NHS I and NHS II participants between history of kidney stones and myocardial infarction (HR, 1.23 [95% CI, 1.07-1.41] for NHS I; HR, 1.42 [95% CI, 1.07-1.90] for NHS II), and revascularization (HR, 1.20 [95% CI, 1.09-1.32] for NHS I; HR, 1.46 [95% CI, 1.17-1.81] for NHS II).

After pooling the NHS I and NHS II cohorts, women with a history of kidney stones had an increased risk of CHD (HR, 1.30 [95% CI, 1.04-1.62]), fatal and nonfatal myocardial infarction (HR, 1.26 [95% CI, 1.11-1.43]), and revascularization (HR, 1.29 [95% CI, 1.07- 1.55]).

There was no significant interaction between history of kidney stones and age, BMI, or diabetes and the risk of CHD (*P* for interaction >.05 for all cohorts). The only significant interaction was with high blood pressure in HPFS (HR, 0.98 for participants with high blood pressure vs HR, 1.12 for participants without high blood pressure; $P = .04$) and NHS II (HR, 1.24 for participants with high blood pressure vs HR, 2.15 without high blood pressure; $P = .01$). The results did not change after including the intake of calcium supplements in the analysis.

Discussion

We found that a self-reported history of kidney stones was associated with a statistically significant increased risk of CHD in both cohorts of women (NHS I and NHS II), whereas no significant association was evident in the cohort of men (HPFS).

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Table 1. Age-Adjusted Baseline Characteristics of the Cohorts According to Presence or Absence of a History of Kidney Stones

	No. of Participants (%)					
	Health Professionals Follow-up Study		Nurses' Health Study I		Nurses' Health Study II	
	No Kidney Stones (n = 42 231)	Kidney Stones (n = 3517)	No Kidney Stones (n = 86 414)	Kidney Stones (n = 3821)	No Kidney Stones (n = 102 633)	Kidney Stones (n = 3489)
Age, mean (SD), y[a]	53.7 (9.7)	55.8 (9.4)	58.4 (7.1)	59.0 (7.0)	36.6 (4.6)	37.4 (4.5)
White race	40 013 (95)	3342 (95)	80 878 (94)	3594 (94)	95 500 (93)	3293 (94)
Region						
West	9188 (22)	688 (20)	10 508 (12)	375 (10)	14 986 (15)	438 (13)
Midwest	11 530 (27)	908 (26)	16 163 (19)	732 (19)	34 323 (33)	1157 (33)
South	11 253 (27)	1067 (30)	9251 (11)	447 (12)	17 515 (17)	684 (20)
Northeast	9742 (23)	809 (23)	50 492 (58)	2267 (59)	35 568 (35)	1205 (35)
Family history of CHD	13 488 (32)	1211 (33)	31 435 (36)	1527 (39)	22 276 (22)	892 (25)
BMI						
<20.0	596 (1)	44 (1)	4354 (5)	193 (6)	12 850 (13)	391 (12)
20.0-24.9	13 123 (32)	968 (28)	26 886 (33)	1004 (28)	44 333 (44)	1311 (40)
25.0-29.9	22 692 (55)	1954 (57)	30 635 (38)	1302 (36)	25 980 (26)	912 (26)
≥30.0	4837 (12)	482 (14)	19 466 (24)	1096 (31)	16 583 (17)	775 (22)
Smoking status						
Never	19 332 (48)	1620 (49)	38 189 (44)	1589 (42)	67 168 (65)	2197 (64)
Past	17 125 (42)	1463 (42)	34 708 (40)	1587 (41)	22 807 (22)	737 (21)
Current	4112 (10)	302 (9)	13 316 (15)	638 (17)	12 525 (12)	551 (16)
Physical activity (MET/wk)						
<3	8628 (20)	762 (22)	13 520 (16)	656 (17)	14 795 (14)	541 (15)
3-8	9480 (22)	839 (24)	16 956 (20)	769 (20)	22 892 (22)	779 (22)
9-17	7544 (18)	614 (17)	16 228 (19)	721 (19)	21 271 (21)	740 (21)
18-27	5359 (13)	465 (13)	10 225 (12)	424 (11)	12 849 (13)	357 (10)
>27	11 220 (27)	837 (24)	16 907 (20)	679 (18)	23 502 (23)	833 (25)
Diabetes	1122 (3)	121 (3)	4418 (5)	324 (8)	977 (1)	63 (2)
High blood pressure	8570 (20)	932 (25)	28 402 (33)	1605 (41)	6519 (6)	394 (10)
Gout	1882 (4)	319 (8)	1688 (2)	144 (4)	449 (1)[b]	83 (1)[b]
Elevated cholesterol	4492 (11)	466 (13)	27 201 (32)	1346 (35)	9665 (9)	472 (13)
Drug use						
Aspirin	11 434 (27)	1009 (28)	20 410 (24)	886 (23)	11 428 (11)	455 (13)
Thiazide	3689 (9)	450 (12)	9352 (11)	536 (14)	1774 (2)	155 (4)
Loop diuretics	331 (1)	41 (1)	1428 (2)[b]	132 (3)[b]	424 (0)	38 (1)
Oral steroids	268 (1)[b]	42 (1)[b]	1536 (2)[b]	112 (3)[b]	1089 (1)[b]	149 (3)[b]
Lipid-lowering drugs	218 (1)	21 (1)	1428 (2)	71 (2)	4075 (4)[b]	385 (7)[b]
Calcium channel blockers	406 (1)	47 (1)	1601 (2)	117 (3)	1604 (2)[b]	171 (3)[b]
β-Blockers	3244 (8)	398 (10)	5957 (7)	343 (9)	2128 (2)	131 (4)
ACE inhibitors	2509 (11)[b]	480 (13)[b]	1745 (2)	117 (3)	2921 (3)[b]	280 (5)[b]
Other antihypertensive drugs	1238 (3)	145 (4)	1434 (2)	90 (2)	1438 (1)	104 (3)
Intake, mean (SD), mg/d						
Calcium	798 (399)	725 (360)	800 (382)	751 (369)	879 (399)	821 (380)
Potassium	3403 (1114)	3220 (1071)	3073 (954)	2981 (976)	2906 (947)	2842 (948)
Magnesium	350 (121)	330 (115)	324 (118)	311 (116)	312 (108)	301 (106)
Animal protein	67.1 (25.7)	64.5 (24.4)	59.8 (22.0)	59.0 (22.2)	63.3 (23.6)	63.4 (24.0)
Total fat, g/d	71.6 (27.9)	71.6 (28.2)	61.3 (22.5)	61.8 (23.2)	62.7 (22.3)	63.6 (22.8)
Caffeine	234 (230)	211 (210)	266 (222)	238 (215)	238 (215)	224 (205)
Vitamin D, IU/d	398 (302)	361 (282)	359 (257)	341 (248)	379 (253)	354 (251)
Alcohol, median (25th-75th percentiles), g/d	6.0 (0.9-15.0)	4.4 (0.0-13.0)	1.1 (0.0-6.0)	0.9 (0.0-4.4)	0.9 (0.0-3.5)	0.9 (0.0-2.8)
DASH score, mean (SD)	24 (5)	23 (5)	24 (5)	23 (5)	24 (5)	23 (5)
Postmenopause	NA	NA	72 356 (84)	3324 (85)	3277 (3)	200 (5)

(continued)

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Table 1. Age-Adjusted Baseline Characteristics of the Cohorts According to Presence or Absence of a History of Kidney Stones (continued)

	No. of Participants (%)					
	Health Professionals Follow-up Study		Nurses' Health Study I		Nurses' Health Study II	
	No Kidney Stones (n = 42 231)	Kidney Stones (n = 3517)	No Kidney Stones (n = 86 414)	Kidney Stones (n = 3821)	No Kidney Stones (n = 102 633)	Kidney Stones (n = 3489)
Postmenopausal hormone use						
Missing/premenopause	NA	NA	20 377 (24)	784 (22)	8041 (8)	266 (8)
Never used	NA	NA	23 788 (28)	1059 (27)	81 517 (79)	2575 (75)
Past user	NA	NA	28 957 (34)	1279 (33)	8815 (9)	399 (11)
Current user	NA	NA	13 292 (15)	699 (18)	4260 (4)	249 (7)

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CHD, coronary heart disease; DASH, Dietary Approaches to Stop Hypertension; MET, metabolic equivalent; NA, not available.

[a] Value is not age-adjusted.

[b] Baseline values not available, first available value reported. Some percentages may not add up to 100% due to rounding or missing values.

Table 2. Incident Coronary Heart Disease by History of Kidney Stones in the Health Professionals Follow-up Study, Nurses' Health Study I, and Nurses' Health Study II Cohorts

	Health Professionals Follow-up Study		Nurses' Health Study I		Nurses' Health Study II	
	No Kidney Stones	Kidney Stones	No Kidney Stones	Kidney Stones	No Kidney Stones	Kidney Stones
Total CHD						
Cases	7364	1235	6594	561	949	135
Person-years	720 427	91 118	1 282 236	74 404	1 732 190	93 785
Incidence rate[a]	1022	1355	514	754	55	144
Age-adjusted HR (95% CI)	1 [Reference]	1.18 (1.11-1.25)	1 [Reference]	1.41 (1.30-1.54)	1 [Reference]	2.19 (1.83-2.63)
Multivariable 1 HR (95% CI)[b]	1 [Reference]	1.09 (1.02-1.16)	1 [Reference]	1.21 (1.11-1.32)	1 [Reference]	1.56 (1.29-1.87)
Multivariable 2 HR (95% CI)[c]	1 [Reference]	1.06 (0.99-1.13)	1 [Reference]	1.18 (1.08-1.28)	1 [Reference]	1.48 (1.23-1.78)
Fatal and nonfatal myocardial infarction						
Cases[d]	3137	493	2527	216	429	57
Person-years	725 451	92 061	1 286 070	74 751	1 732 882	93 893
Incidence rate[a]	432	536	196	289	25	61
Age-adjusted HR (95% CI)	1 [Reference]	1.11 (1.01-1.23)	1 [Reference]	1.46 (1.27-1.68)	1 [Reference]	2.10 (1.58-2.78)
Multivariable 1 HR (95% CI)[b]	1 [Reference]	1.05 (0.95-1.15)	1 [Reference]	1.26 (1.09-1.45)	1 [Reference]	1.54 (1.15-2.05)
Multivariable 2 HR (95% CI)[c]	1 [Reference]	1.01 (0.92-1.11)	1 [Reference]	1.23 (1.07-1.41)	1 [Reference]	1.42 (1.07-1.90)
Revascularization						
Cases[d]	5090	859	5141	451	685	100
Person-years	721 356	91 294	1 283 255	74 484	1 732 449	93 824
Incidence rate[a]	706	941	401	605	40	107
Age-adjusted HR (95% CI)	1 [Reference]	1.18 (1.09-1.27)	1 [Reference]	1.44 (1.31-1.59)	1 [Reference]	2.22 (1.79-2.73)
Multivariable 1 HR (95% CI)[b]	1 [Reference]	1.08 (1.00-1.17)	1 [Reference]	1.23 (1.12-1.36)	1 [Reference]	1.52 (1.22-1.88)
Multivariable 2 HR (95% CI)[c]	1 [Reference]	1.06 (0.98-1.14)	1 [Reference]	1.20 (1.09-1.32)	1 [Reference]	1.46 (1.17-1.81)

Abbreviations: HR, hazard ratio.

[a] Incidence rate expressed as number of events per 100 000 person-years.

[b] Multivariable 1 model adjusted for age, race, region of residence (4 categories), family history of heart disease, diabetes, hypertension, gout, elevated cholesterol, use of aspirin, thiazide diuretics, loop diuretics, oral steroids, lipid-lowering drugs, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, other antihypertensive drugs, menopausal status (Nurses' Health Study I and II), postmenopausal hormone use (Nurses' Health Study I and II), and profession (Health Professionals Follow-up Study).

[c] Multivariable 2 model further adjusted for smoking status (3 categories), body mass index (13 categories), physical activity (5 categories), quintiles of intake of calcium, potassium, magnesium, animal protein, total fat, vitamin D, caffeine, Dietary Approaches to Stop Hypertension score, and alcohol.

[d] The number of cases for the secondary outcomes does not add up to the number of cases for the primary outcome because of some participants experiencing both myocardial infarction and revascularization in the same period.

One of the first reports of an association between nephrolithiasis and cardiovascular disease was by Elmfeldt and colleagues[11] in 1976, which compared the prevalence of self-reported history of kidney stones between 299 male survivors of myocardial infarction and a sample of the general population in Göteborg, Sweden.

The prevalence of kidney stones in the post-myocardial infarction group was 16.1% compared with 7.8% of the general population (P = .01). However, the results were only adjusted for age.[11] Similar studies in the same time frame, however, did not confirm this finding.[24,25]

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More recently, Domingos and Serra[10] published the results of a cross-sectional study in which 23 346 Portuguese individuals older than 15 years were asked to fill out a questionnaire with information on previous health conditions. After adjusting for age and BMI, there was a statistically significant association between self-reported history of kidney stones and myocardial infarction (odds ratio [OR], 1.34 [95% CI, 1.00-1.79]) and stroke (OR, 1.33 [95% CI, 1.02-1.74]). After multivariable adjustment, however, the relationship remained significant only for myocardial infarction in women (OR, 1.57 [95% CI, 1.00-2.45]).

Using the Framingham and Systematic Coronary Risk Evaluation (SCORE) risk scores, Aydin and colleagues[26] used demographic, clinical, and laboratory characteristics of 200 patients with calcium oxalate nephrolithiasis and 200 age- and sex-matched controls to calculate the 10-year risk of cardiovascular disease and mortality. The results suggested a higher predicted risk for both cardiovascular disease (OR, 8.36 [95% CI, 3.81-18.65) and mortality (OR, 3.02 [95% CI, 1.30-7.02]) for individuals with a history of kidney stones compared with controls.

To date, the only longitudinal study published on the risk of CHD in patients with kidney stones was by Rule and colleagues,[13] which compared the incidence of myocardial infarction in 4564 patients with kidney stones with 10 860 age- and sex-matched individuals without history of kidney stones. The diagnosis of kidney stones was based on diagnostic codes and that of myocardial infarction was confirmed through review of medical records. After a mean follow-up of 9 years, 96 individuals with kidney stones and 166 without kidney stones developed a myocardial infarction. The multivariable-adjusted HR of developing myocardial infarction for individuals with stones compared with controls was 1.31 (95% CI, 1.02-1.69). The model was adjusted for many covariates but not for potentially important dietary risk factors or medications. For example, intake of calcium has been shown to be independently associated with incidence of kidney stones in an inverse manner[16] and with cardiovascular disease in a direct manner.[27] Also, potential confounding by drugs such as thiazides, which reduce calciuria and hence reduce the risk of developing kidney stones and also lower blood pressure thus potentially reducing the risk of CHD,[28] could not be ruled out. Even though the authors included alcohol dependence in their analysis, this could not be enough to rule out the possible confounding effect of moderate intake of alcohol. Furthermore, the number of outcomes was far lower than those in our study and only myocardial infarction was a study outcome.

A potential explanation for the association between kidney stones and CHD is the relatively higher prevalence and incidence of cardiovascular risk factors in patients with stones, such as diabetes,[7,29] hypertension,[5,30,31] metabolic syndrome,[9,32,33] and subclinical atherosclerosis.[3] However, even after adjusting for high blood pressure, diabetes, elevated cholesterol, and BMI in our analysis, the risk of developing CHD remained higher in individuals with a history of stones.

Another proposed explanation may be the common influence of dietary factors (such as a low intake of calcium, which has been linked with both an increased risk of developing kidney stones[16,17,34] and hypertension[35]—a major risk factor for CHD). Again, the adjustment for dietary factors attenuated, but did not eliminate, the association in women, suggesting that this may not be the only explanation.

A third possible explanation is related to the deterioration of kidney function related to kidney stones,[14,36,37] which in turn could cause an increase in cardiovascular morbidity and mortality.[38] We could not analyze kidney function in our analysis; however, the relation between history of nephrolithiasis and CHD remained significant after adjusting for chronic kidney disease in the analysis by Rule et al.[13]

Finally, an impairment of the regulation of physiologic calcification has been postulated. Osteopontin is a glycoprotein involved in the formation and calcification of bone, and levels are increased in patients with CHD.[39] It is also an inhibitor of calcification in urine, and mice deficient in osteopontin have been shown to develop calcium oxalate stones after induction of hyperoxaluria.[40] A study in humans found significantly lower levels of urinary osteopontin in participants with a history of kidney stones compared with those without.[15] However, such findings were not replicated in another study.[41]

Our findings of a positive association between history of kidney stones and subsequent coronary events might be explained by 3 possible scenarios: (1) the presence of an unknown inherent metabolic state (or unknown risk factors) that cause both kidney stones and CHD; (2) the presence of a stone might increase the risk independent of other known risk factors; and (3) residual confounding. We feel that the first scenario, namely kidney stones being an earlier marker of a common metabolic state or of shared risk factors that might subsequently lead to coronary events, is more biologically sound. However, further studies are needed to explore this and other possibilities.

Our finding of no significant association between history of kidney stones and risk of CHD in men but an increased risk in women is difficult to explain, even though we could not determine whether this was due to sex or some other difference between the male and female cohorts. However, differences by sex are not infrequent in studies analyzing the association between nephrolithiasis and either CHD or risk factors for CHD. For example, Domingos and Serra[10] found that, after adjusting for comorbidities, only women with a history of nephrolithiasis had increased odds of previous myocardial infarction. In the study by Hippisley-Cox and Coupland,[37] only women with a history of stone disease showed a significant increased risk of developing moderate to severe chronic kidney disease.

Furthermore, Ando and colleagues[29] reported that the prevalence of diabetes in patients with kidney stones was significantly higher in women but not men, and the same has been reported for hypertension.[6] However, a large prospective study by Taylor and colleagues[7] did not find a differential association by sex between history of kidney stones and incidence of diabetes. Recently, Alexander and colleagues[14] found a higher risk of developing adverse kidney outcomes in women with a history of kidney stones (HRs: 3.36 for end-stage renal disease; 1.94, doubling of serum creatinine; and 2.65, chronic kidney disease stages 3b-5) than in men with a history of kidney stones (HRs: 1.87 for end-stage renal disease; 1.67, doubling of

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serum creatinine; and 1.70, chronic kidney disease stages 3b-5). Taken together, these findings suggest that women may be more likely exposed than men to unknown factors that could increase their cardiovascular and kidney stone risk.

On the basis of a set of clinical and experimental evidence, Stoller and colleagues[42] challenged the traditional hypothesis of stone formation in favor of a vascular etiology. The authors hypothesized that the site of the initial lesion may be the vascular bed at the tip of the renal papilla, where vascular injury may give rise to calcification, which in turn may grow and erode through the papillary epithelium and become a nidus for stone formation. However, the lack of association in men does not support this hypothesis.

A limitation of our study may be the lack of generalizability, because the majority of the participants were white and race has an influence on both nephrolithiasis (with white populations being more prone to form stones compared with black and Hispanic populations)[2] and CHD (with higher incidence among black populations).[21] Also, we did not have information about stone composition for the majority of participants with a reported history of kidney stones, which could help establish etiological hypotheses, nor information about laboratory parameters such as serum creatinine to account for kidney function. The exclusion of individuals with a previous CHD event before baseline might have biased our findings toward the null. Additionally, many of the conditions included in the analysis (such as high blood pressure) were self-reported, though these have been validated and found to be reliable.

Conclusion

In conclusion, among 2 large cohorts of women, a history of kidney stones was associated with a modest but statistically significant increased risk of CHD; there was no significant association in a separate cohort of men. Further research is needed to determine whether the association is sex-specific and to establish the pathophysiological basis of this association.

ARTICLE INFORMATION

Author Contributions: Dr Ferraro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ferraro, Taylor, Eisner, Gambaro, Curhan.
Acquisition of data: Taylor, Mukamal, Curhan.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Ferraro, Eisner.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Ferraro, Taylor, Eisner, Curhan.
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Administrative, technical, or material support: Ferraro, Mukamal, Curhan.
Study supervision: Gambaro, Curhan.

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REFERENCES

1. Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. *Eur Urol*. 2012;62(1):160-165.

2. 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(5):1817-1823.

3. Reiner AP, Kahn A, Eisner BH, et al. Kidney stones and subclinical atherosclerosis in young adults: the CARDIA study. *J Urol*. 2011;185(3):920-925.

4. Madore F, Stampfer MJ, Willett WC, Speizer FE, Curhan GC. Nephrolithiasis and risk of hypertension in women. *Am J Kidney Dis*. 1998;32(5):802-807.

5. Borghi L, Meschi T, Guerra A, et al. Essential arterial hypertension and stone disease. *Kidney Int*. 1999;55(6):2397-2406.

6. Gillen DL, Coe FL, Worcester EM. Nephrolithiasis and increased blood pressure among females with high body mass index. *Am J Kidney Dis*. 2005;46(2):263-269.

7. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int*. 2005;68(3):1230-1235.

8. Chung SD, Chen YK, Lin HC. Increased risk of diabetes in patients with urinary calculi: a 5-year follow-up study. *J Urol*. 2011;186(5):1888-1893.

9. West B, Luke A, Durazo-Arvizu RA, Cao G, Shoham D, Kramer H. Metabolic syndrome and self-reported history of kidney stones: the National Health and Nutrition Examination Survey (NHANES III) 1988-1994. *Am J Kidney Dis*. 2008;51(5):741-747.

10. Domingos F, Serra A. Nephrolithiasis is associated with an increased prevalence of cardiovascular disease. *Nephrol Dial Transplant*. 2011;26(3):864-868.

11. Elmfeldt D, Vedin A, Wilhelmsson C, Tibblin G, Wilhelmsen L. Morbidity in representative male survivors of myocardial infarction compared to representative population samples. *J Chronic Dis*. 1976;29(4):221-231.

12. Hamano S, Nakatsu H, Suzuki N, Tomioka S, Tanaka M, Murakami S. Kidney stone disease and risk factors for coronary heart disease. *Int J Urol*. 2005;12(10):859-863.

13. Rule AD, Roger VL, Melton LJ III, et al. Kidney stones associate with increased risk for myocardial infarction. *J Am Soc Nephrol*. 2010;21(10):1641-1644.

14. Alexander RT, Hemmelgarn BR, Wiebe N, et al; Alberta Kidney Disease Network. Kidney stones and kidney function loss: a cohort study. *BMJ*. 2012;345:e5287.

15. Yasui T, Fujita K, Hayashi Y, et al. Quantification of osteopontin in the urine of healthy and stone-forming men. *Urol Res*. 1999;27(4):225-230.

16. 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(12):833-838.

17. Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. 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(7):497-504.

18. Rimm EB, Giovannucci EL, Willett WC, et al. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet*. 1991;338(8765):464-468.

19. 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(10):1114-1126.

20. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc*. 1993;93(7):790-796.

21. Centers for Disease Control and Prevention. National Vital Statistics Report, Vol. 59, No. 10: Table I-7: Number of deaths, death rates, and age-adjusted death rates for ages 15 years and over, by marital status and sex: United States, 2008.

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http://www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_10_tables.pdf. Accessed June 24, 2013.

22. Taylor EN, Fung TT, Curhan GC. DASH-style diet associates with reduced risk for kidney stones. *J Am Soc Nephrol*. 2009;20(10):2253-2259.

23. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. *Arch Intern Med*. 2008;168(7):713-720.

24. Westlund K. Urolithiasis and coronary heart disease: a note on association. *Am J Epidemiol*. 1973;97(3):167-172.

25. Ljunghall S, Hedstrand H. Renal stones and coronary heart disease. *Acta Med Scand*. 1976;199(6):481-485.

26. Aydin H, Yencilek F, Erihan IB, Okan B, Sarica K. Increased 10-year cardiovascular disease and mortality risk scores in asymptomatic patients with calcium oxalate urolithiasis. *Urol Res*. 2011;39(6):451-458.

27. Wang L, Manson JE, Sesso HD. Calcium intake and risk of cardiovascular disease: a review of prospective studies and randomized clinical trials. *Am J Cardiovasc Drugs*. 2012;12(2):105-116.

28. Reilly RF, Peixoto AJ, Desir GV. The evidence-based use of thiazide diuretics in hypertension and nephrolithiasis. *Clin J Am Soc Nephrol*. 2010;5(10):1893-1903.

29. Ando R, Suzuki S, Nagaya T, et al. Impact of insulin resistance, insulin and adiponectin on kidney stones in the Japanese population. *Int J Urol*. 2011;18(2):131-138.

30. Cirillo M, Laurenzi M. Elevated blood pressure and positive history of kidney stones: results from a population-based study. *J Hypertens Suppl*. 1988;6(4):S485-S486.

31. Cappuccio FP, Strazzullo P, Mancini M. Kidney stones and hypertension: population based study of an independent clinical association. *BMJ*. 1990;300(6734):1234-1236.

32. Rendina D, Mossetti G, De Filippo G, et al. Association between metabolic syndrome and nephrolithiasis in an inpatient population in southern Italy: role of gender, hypertension and abdominal obesity. *Nephrol Dial Transplant*. 2009;24(3):900-906.

33. Jeong IG, Kang T, Bang JK, et al. Association between metabolic syndrome and the presence of kidney stones in a screened population. *Am J Kidney Dis*. 2011;58(3):383-388.

34. Curhan GC, Willett WC, Knight EL, Stampfer MJ. Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. *Arch Intern Med*. 2004;164(8):885-891.

35. McCarron DA, Morris CD, Stanton JL. Hypertension and calcium. *Science*. 1984;226(4673):386-393.

36. Rule AD, Krambeck AE, Lieske JC. Chronic kidney disease in kidney stone formers. *Clin J Am Soc Nephrol*. 2011;6(8):2069-2075.

37. Hippisley-Cox J, Coupland C. Predicting the risk of chronic kidney disease in men and women in England and Wales: prospective derivation and external validation of the QKidney Scores. *BMC Fam Pract*. 2010;11:49-61.

38. US Renal Data System. USRDS 2010 Annual Data Report: Atlas of chronic kidney disease and end-stage renal disease in the United States. http://www.usrds.org/2010/view/. Accessed June 24, 2013.

39. Ohmori R, Momiyama Y, Taniguchi H, et al. Plasma osteopontin levels are associated with the presence and extent of coronary artery disease. *Atherosclerosis*. 2003;170(2):333-337.

40. Wesson JA, Johnson RJ, Mazzali M, et al. Osteopontin is a critical inhibitor of calcium oxalate crystal formation and retention in renal tubules. *J Am Soc Nephrol*. 2003;14(1):139-147.

41. Kleinman JG, Wesson JA, Hughes J. Osteopontin and calcium stone formation. *Nephron Physiol*. 2004;98(2):43-47.

42. Stoller ML, Meng MV, Abrahams HM, Kane JP. The primary stone event: a new hypothesis involving a vascular etiology. *J Urol*. 2004;171(5):1920-1924.

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