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History of kidney stones and risk of coronary heart disease

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Abstract

Importance—Kidney stone disease is common and may be associated with an increased risk of coronary heart disease (CHD). However, 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—We examined the association between a history of kidney stones and the risk of CHD in three large prospective cohorts.

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Design, setting, and participants—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, 51,529 men aged 40–75 years followed since 1986), Nurses' Health Study (NHS) I (121,700 women aged 30–55 years followed since 1976) and II (116,430 women aged 25–42 years followed since 1989). The diagnoses of kidney stones and CHD were updated biennially during follow-up.

Main outcome measure—CHD was defined as fatal or non-fatal myocardial infarction (MI) or coronary revascularization. The outcome was identified by biennial questionnaires and confirmed through review of medical records (fatal and non-fatal MI).

Results—Out 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 compared with those without had an increased risk of CHD in NHS I (incidence rate (IR) 754 vs 514/100,000 person-years; multivariate HR 1.18, 95% CI 1.08 to 1.28) and NHS II (IR 144 vs 55/100,000 person-years; multivariate HR 1.48, 95% CI 1.23 to 1.78); there was no significant association in men (IR 1,355 vs 1,022/100,000 person-years; multivariate HR 1.06, 95% CI 0.99 to 1.13). Similar results were found when analyzing the individual end-points (fatal and non-fatal MI, revascularization).

Conclusions—Among two 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.

Introduction

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 a prevalence of a history of kidney stones of 10.6% for males and 7.1% for females.[1] The overall prevalence has increased from 3.8% in the 1976–1980 period[2] to 8.8% in the 2007–2010 period[1].

Associations between nephrolithiasis and systemic diseases have been recognized, including subclinical atherosclerosis,[3] hypertension,[4–10] diabetes,[11–13] metabolic syndrome,[14–16] and cardiovascular disease (CVD).[17–19] A single longitudinal study reported a 31% increased risk for myocardial infarction in stone-formers.[20] However, the other studies published so far 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 renal disease among stone formers[21], and abnormalities of calcium metabolism[22]. 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 three large prospective cohorts.

Methods

Study populations

The Health Professionals Follow-Up Study (HPFS) started in 1986 with the enrollment of 51,529 male health professionals aged 40–75 years, who filled out a questionnaire on lifestyle and medical history. The Nurses' Health Study (NHS I) started in 1976 with the enrollment of 121,700 female nurses aged 30–55 years, who completed a questionnaire on lifestyle and medical history. A second Nurses' Health Study cohort (NHS II) was started in 1989, consisting of 116,430 female nurses aged 25–42 years. In all three cohorts, information has been updated every two years.

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

The study was approved by the Partners Healthcare institutional review board, which accepts return of the questionnaires as implied consent in these cohorts.

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 two 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 ~97% of cases who completed the additional questionnaire in two separate validation studies in these populations.[23,24]

Assessment of coronary heart disease

The primary outcome was CHD, defined as a composite of non-fatal or fatal myocardial infarction or coronary revascularization procedure (coronary artery bypass graft or percutaneous transluminal coronary angioplasty). Secondary outcomes were non-fatal or fatal myocardial infarction and coronary revascularization examined separately. Fatal and non-fatal 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.[25]

Covariates

The following covariates were considered: race (white/non-white); 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; <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 kg/m^2); 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, beta blockers, angiotensin-converting-enzyme inhibitors, and other anti-hypertensive drugs; and daily intake of the following energy-adjusted nutrients (quintiles): calcium, potassium, magnesium, animal protein, total fat, vitamin D, and caffeine, and alcohol (0, 0.1–5.0, 5.0–9.9, 10.0–14.9, 15.0–29.9, ≥30.0 grams/day). For the NHS I and NHS II cohorts, information about menopausal status and post-menopausal 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 four years.[26,27] Race/ethnicity 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, since the majority of the participants were white, race/ethnicity was coded as white/non-white and included in the analysis since race/ethnicity seems to be associated with both kidney stones and cardiovascular disease.[2,28]

Finally, 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 lower risk of kidney stone formation[29] and cardiovascular disease[30].

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 (January 2010 for HPFS, June 2010 for NHS I, June 2009 for NHS II), whichever came first.

The crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the development of a CHD event in participants with compared with those without a history of kidney stones 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 one coronary event occurred in the same time 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 two-tailed p-value <0.05 was considered statistically significant. All analyses were performed with SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

After exclusions, a total of 242,105 participants 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 8,851 during follow-up). The median (25^{th}, 75^{th} 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 and 53.7 years in HPFS, 59.0 and 58.4 years in NHS I and 37.4 and 36.6 years in NHS II for participants with and without a reported history of kidney stones, respectively. High blood pressure, use of thiazides and elevated cholesterol were more prevalent among participants with a reported history of kidney stones in all three 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 among participants with and without a reported history of kidney stones were 1,355 and 1,022 in the HPFS cohort (rate difference 333/100,000 person-years), 754 and 514 in the NHS I cohort (rate difference 240/100,000 person-years) and 144 and 55 in the NHS II cohort (rate difference 89/100,000 person-years), respectively.

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

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

In age-adjusted analyses, there was a significant association between history of kidney stones and CHD in all the cohorts: the HRs and 95% CI were 1.18 (1.11, 1.25) for HPFS, 1.41 (1.30, 1.54) for NHS I and 2.19 (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 (NHS I: HR 1.23, 95% CI 1.07, 1.41; NHS II: 1.42, 95% CI 1.07, 1.90), and revascularization (NHS I: HR 1.20, 95% CI 1.09, 1.32; NHS II: HR 1.46, 95% CI 1.17, 1.81).

After pooling the NHS I and NHS II cohorts, females with a history of kidney stones had an increased risk of CHD (HR 1.30; 95% CI 1.04, 1.62), fatal and non-fatal 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 > 0.05 for all cohorts). The only significant interaction was with high blood pressure in HPFS (HR 0.98 and 1.12 for participants with and without high blood pressure, respectively; p = 0.04) and NHS II (HR 1.24 and 2.15 for participants with and without high blood pressure, respectively; p = 0.01). The results did not change after including the intake of calcium supplements in the analysis.

Discussion

We found a significantly higher independent risk of CHD in participants with self-reported history of kidney stones in both female cohorts (NHS I and NHS II), whereas no significant association was evident in the male cohort (HPFS).

One of the first reports of an association between nephrolithiasis and CVD was by Elmfeldt and colleagues in 1976, who 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.[18] The prevalence of kidney stones in the post-myocardial infarction group was 16.1%, compared with 7.8% of the general population (p = 0.01). However, the results were only adjusted for age.[18] Similar studies in the same time frame, however, did not confirm this finding.[31,32]

More recently, Domingos and Serra 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.[17] 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 SCORE risk scores, Aydin and colleagues 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 CVD and mortality.[33] The results suggested a higher predicted risk for both CVD (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 stones was by Rule and colleagues who compared the incidence of myocardial infarction in 4,564 patients with kidney stones with 10,860 age- and sex-matched individuals without history of kidney stones.[20] 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 developed a myocardial infarction. The multivariate-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[23] and with CVD in a direct manner.[34] 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,[35] 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 in the present 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,[11,12] hypertension,[5,6,8] metabolic syndrome[14–16] 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 mechanism 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[23,24,36] and hypertension,[37] one of the major risk factors 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 mechanism is related to deterioration of renal function related to kidney stones,[21,38,39] which in turn could cause an increase in cardiovascular morbidity and mortality.[40] Unfortunately, we could not analyze renal 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.[20]

Finally, an impairment of the regulation of physiologic calcification has been postulated. Osteopontin (OPN) is a glycoprotein involved in the formation and calcification of bone, and levels are increased in patients with CHD.[41] It is also an inhibitor of calcification in urine, and mice deficient for OPN have been shown to develop calcium oxalate stones after induction of hyperoxaluria.[42] A study in humans found significantly lower levels of urinary OPN in stone formers compared with non-stone formers.[22] However, such findings were not replicated in another study.[43]

Our findings of a positive association between history of kidney stones and subsequent coronary events might be explained by three possible scenarios: the presence of an unknown inherent metabolic state (or unknown risk factors) that cause both kidney stones and CHD; the presence of a stone per se might increase the risk independent of other known risk factors; and 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 the one that is more biologically sound. However, further studies are needed to explore this and other possibilities.

Our finding of no significant association in males yet increased risk in females, even though we could not determine whether this is due to sex or some other difference between the male and female cohorts, is difficult to explain. 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 found that, after adjusting for comorbidities, only females with history of nephrolithiasis had increased odds of previous myocardial infarction.[17] In the study by Hippisley-Cox et al., only females with a history of stone disease showed a significant increased risk of developing moderate to severe chronic kidney disease.[39] Furthermore, Ando et al. reported that the prevalence of diabetes in patients with kidney stones was significantly higher in females but not males[12] and the same has been reported for hypertension.[10] However, a large prospective study by Taylor and colleagues did not find a differential association by sex between history of kidney stones and incidence of diabetes.[11] Recently, Alexander and colleagues found a higher risk of developing adverse renal outcomes in female stone formers (HRs 3.36, 1.94 and 2.65 for end-stage renal disease, doubling of serum creatinine, or chronic kidney disease stages 3b-5, respectively) than in males (HRs 1.87, 1.67, 1.70).[21] Taken together, these findings suggest that females may be more likely exposed than males to unknown factors that could increase their cardiovascular and stone risk.

On the basis of a set of clinical and experimental evidence, Stoller and colleagues challenged the traditional hypothesis of stone formation in favor of a vascular etiology.44 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, becoming 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, since the majority of the participants were white and race has an impact on both nephrolithiasis (with whites being more prone to form stones compared with blacks and Hispanics)[2] and CHD (with blacks having a higher incidence of coronary heart disease)[28]. 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, and about laboratory parameters such as serum creatinine to account for renal function. The exclusion of individuals with a previous CHD event before baseline might have biased our findings toward the null. Finally, 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.

In conclusion, among two 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.

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References

1. Scales CD Jr, Smith AC, Hanley JM, Saigal CS. Urologic Diseases in America P. Prevalence of kidney stones in the United States. European urology. 2012; 62:160–165. [PubMed: 22498635]
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; 63:1817–1823. [PubMed: 12675858]
3. Reiner AP, Kahn A, Eisner BH, et al. Kidney stones and subclinical atherosclerosis in young adults: the CARDIA study. J Urol. 2011; 185:920–925. [PubMed: 21251678]
4. Tibblin G. A population study of 50-year-old men. An analysis of the non-participation group. Acta Med Scand. 1965; 178:453–459. [PubMed: 5838318]
5. Cirillo M, Laurenzi M. Elevated blood pressure and positive history of kidney stones: results from a population-based study. J Hypertens Suppl. 1988; 6:S485–S486. [PubMed: 3241240]
6. Cappuccio FP, Strazzullo P, Mancini M. Kidney stones and hypertension: population based study of an independent clinical association. BMJ. 1990; 300:1234–1236. [PubMed: 2354291]
7. Madore F, Stampfer MJ, Willett WC, Speizer FE, Curhan GC. Nephrolithiasis and risk of hypertension in women. Am J Kidney Dis. 1998; 32:802–807. [PubMed: 9820450]
8. Borghi L, Meschi T, Guerra A, et al. Essential arterial hypertension and stone disease. Kidney Int. 1999; 55:2397–2406. [PubMed: 10354288]
9. Cappuccio FP, Siani A, Barba G, et al. A prospective study of hypertension and the incidence of kidney stones in men. J Hypertens. 1999; 17:1017–1022. [PubMed: 10419076]
10. Gillen DL, Coe FL, Worcester EM. Nephrolithiasis and increased blood pressure among females with high body mass index. Am J Kidney Dis. 2005; 46:263–269. [PubMed: 16112044]
11. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. Kidney Int. 2005; 68:1230–1235. [PubMed: 16105055]
12. 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; 18:131–138. [PubMed: 21175865]
13. Chung SD, Chen YK, Lin HC. Increased risk of diabetes in patients with urinary calculi: a 5-year followup study. J Urol. 2011; 186:1888–1893. [PubMed: 21944094]
14. 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; 51:741–747. [PubMed: 18436084]
15. 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; 24:900–906. [PubMed: 18835844]
16. 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; 58:383–388. [PubMed: 21620546]
17. Domingos F, Serra A. Nephrolithiasis is associated with an increased prevalence of cardiovascular disease. Nephrol Dial Transplant. 2011; 26:864–868. [PubMed: 20709737]
18. 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; 29:221–231. [PubMed: 1270570]
19. 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; 12:859–863. [PubMed: 16323977]
20. Rule AD, Roger VL, Melton LJ 3rd, et al. Kidney stones associate with increased risk for myocardial infarction. J Am Soc Nephrol. 2010; 21:1641–1644. [PubMed: 20616170]

21. Alexander RT, Hemmelgarn BR, Wiebe N, et al. Kidney stones and kidney function loss: a cohort study. BMJ. 2012; 345:e5287. [PubMed: 22936784]
22. Yasui T, Fujita K, Hayashi Y, et al. Quantification of osteopontin in the urine of healthy and stone-forming men. Urol Res. 1999; 27:225–230. [PubMed: 10460890]
23. 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. [PubMed: 8441427]
24. 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; 126:497–504. [PubMed: 9092314]
25. Rimm EB, Giovannucci EL, Willett WC, et al. Prospective study of alcohol consumption and risk of coronary disease in men. Lancet. 1991; 338:464–468. [PubMed: 1678444]
26. 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. discussion 27–36. [PubMed: 1632423]
27. Feskanich D, Rimm E, Giovannucci E, et al. Reproducibility and validity of food intake measurements from a semi-quantitative food frequency questionnaire. J Am Diet Assoc. 1993; 93:790–796. [PubMed: 8320406]
28. CDC. National Vital Statistics Report. 2011; Vol. 59(Num 10) Table 17.
29. Taylor EN, Fung TT, Curhan GC. DASH-style diet associates with reduced risk for kidney stones. J Am Soc Nephrol. 2009; 20:2253–2259. [PubMed: 19679672]
30. 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; 168:713–720. [PubMed: 18413553]
31. Westlund K. Urolithiasis and coronary heart disease: a note on association. Am J Epidemiol. 1973; 97:167–172. [PubMed: 4692992]
32. Ljunghall S, Hedstrand H. Renal stones and coronary heart disease. Acta Med Scand. 1976; 199:481–485. [PubMed: 937074]
33. 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; 39:451–458. [PubMed: 21567159]
34. 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. 2011; 12:105–116. [PubMed: 22283597]
35. Reilly RF, Peixoto AJ, Desir GV. The evidence-based use of thiazide diuretics in hypertension and nephrolithiasis. Clin J Am Soc Nephrol. 2010; 5:1893–1903. [PubMed: 20798254]
36. 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; 164:885–891. [PubMed: 15111375]
37. McCarron DA, Morris CD, Stanton JL. Hypertension and calcium. Science. 1984; 226:386–393. [PubMed: 17799915]
38. Rule AD, Krambeck AE, Lieske JC. Chronic kidney disease in kidney stone formers. Clin J Am Soc Nephrol. 2011; 6:2069–2075. [PubMed: 21784825]
39. 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. [PubMed: 20565929]
40. US Renal Data System, USRDS 2010 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney; 2010. Atlas of chronic kidney disease and end-stage renal disease in the United States.
41. Ohmori R, Momiyama Y, Taniguchi H, et al. Plasma osteopontin levels are associated with the presence and extent of coronary artery disease. Atherosclerosis. 2003; 170:333–337. [PubMed: 14612215]

42. 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; 14:139–147. [PubMed: 12506146]

43. Kleinman JG, Wesson JA, Hughes J. Osteopontin and calcium stone formation. Nephron Physiol. 2004; 98:43–47.

Table 1

Age-adjusted baseline characteristics of the cohorts according to presence or absence of history of kidney stones

	HPFS		NHS I		NHS II	
	No stones (n = 42,231)	**Stones (n = 3,517)**	**No stones (n = 86,414)**	**Stones (n = 3,821)**	**No stones (n = 102,633)**	**Stones (n = 3,489)**
Age, years*	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, No. (%)	40,013(95)	3,342(95)	80,878(94)	3,594(94)	95,500(93)	3,293(94)
Family history of CHD, No. (%)	13,488(32)	1,211(33)	31,435(36)	1,527(39)	22,276(22)	892(25)
BMI (kg/m^2)						
<20.0, No. (%)	596(1)	44(1)	4,354(5)	193(6)	12,850(13)	391(12)
20.0–24.9, No. (%)	13,123(32)	968(28)	26,886(33)	1,004(28)	44,333(44)	1,311(40)
25.0–29.9, No. (%)	22,692(55)	1,954(57)	30,635(38)	1,302(36)	25,980(26)	912(26)
≥30.0, No. (%)	4,837(12)	482(14)	19,466(24)	1,096(31)	16,583(17)	775(22)
Smoking status						
Never, No. (%)	19,332(48)	1,620(49)	38,189(44)	1,589(42)	67,168(65)	2,197(64)
Past, No. (%)	17,125(42)	1,463(42)	34,708(40)	1,587(41)	22,807(22)	737(21)
Current, No. (%)	4,112(10)	302(9)	13,316(15)	638(17)	12,525(12)	551(16)
Physical activity (METS/week)						
<3, No. (%)	8,628(20)	762(22)	13,520(16)	656(17)	14,795(14)	541(15)
3–8, No. (%)	9,480(22)	839(24)	16,956(20)	769(20)	22,892(22)	779(22)
9–17, No. (%)	7,544(18)	614(17)	16,228(19)	721(19)	21,271(21)	740(21)
18–27, No. (%)	5,359(13)	465(13)	10,225(12)	424(11)	12,849(13)	357(10)
>27, No. (%)	11,220(27)	837(24)	16,907(20)	679(18)	23,502(23)	833(25)
Diabetes, No. (%)	1,122(3)	121(3)	4,418(5)	324(8)	977(1)	63(2)
High blood pressure, No. (%)	8,570(20)	932(25)	28,402(33)	1,605(41)	6,519(6)	394(10)
Gout, No. (%)	1,882(4)	319(8)	1,688(2)	144(4)	449(1)¶	83(1)¶

	HPFS		NHS I		NHS II	
	No stones (n = 42,231)	**Stones (n = 3,517)**	**No stones (n = 86,414)**	**Stones (n = 3,821)**	**No stones (n = 102,633)**	**Stones (n = 3,489)**
Elevated cholesterol, No. (%)	4,492(11)	466(13)	27,201(32)	1,346(35)	9,665(9)	472(13)
Aspirin use, No. (%)	11,434(27)	1,009(28)	20,410(24)	886(23)	11,428(11)	455(13)
Thiazide use, No. (%)	3,689(9)	450(12)	9,352(11)	536(14)	1,774(2)	155(4)
Loop diuretics use, No. (%)	331(1)	41(1)	1,428(2)¶	132(3)¶	424(0)	38(1)
Oral steroids use, No. (%)	268(1)¶	42(1)¶	1,536(2)¶	112(3)¶	1,089(1)¶	149(3)¶
Lipid-lowering drugs use, No. (%)	218(1)	21(1)	1,428(2)	71(2)	4,075(4)¶	385(7)¶
Calcium channel blockers use, No. (%)	406(1)	47(1)	1,601(2)	117(3)	1,604(2)¶	171(3)¶
Beta blockers use, No. (%)	3,244(8)	398(10)	5,957(7)	343(9)	2,128(2)	131(4)
ACE inhibitors use, No. (%)	2,509(11)¶	480(13)¶	1,745(2)	117(3)	2,921(3)¶	280(5)¶
Other anti-hypertensive drugs, No. (%)	1,238(3)	145(4)	1,434(2)	90(2)	1,438(1)	104(3)
Calcium intake, mg/day	798(399)	725(360)	800(382)	751(369)	879(399)	821(380)
Potassium intake, mg/day	3403(1114)	3220(1071)	3073(954)	2981(976)	2906(947)	2842(948)
Magnesium intake, mg/day	350(121)	330(115)	324(118)	311(116)	312(108)	301(106)
Animal protein intake, g/day	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 intake, g/day	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 intake, mg/day	234(230)	211(210)	266(222)	238(215)	238(215)	224(205)
Vitamin D intake, IU/day	398(302)	361(282)	359(257)	341(248)	379(253)	354(251)
DASH-score	24(5)	23(5)	24(5)	23(5)	24(5)	23(5)
Alcohol intake, g/day#	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)

	HPFS		NHS I		NHS II	
	No stones (n = 42,231)	**Stones (n = 3,517)**	**No stones (n = 86,414)**	**Stones (n = 3,821)**	**No stones (n = 102,633)**	**Stones (n = 3,489)**
Post-menopause, No. (%)	N.A.	N.A.	72,356(84)	3,324(85)	3,277(3)	200(5)
Post-menopausal hormone use						
Missing/pre-menopause, No. (%)	N.A.	N.A.	20,377(24)	784(22)	8,041(8)	266(8)
Never used, No. (%)	N.A.	N.A.	23,788(28)	1,059(27)	81,517(79)	2,575(75)
Past user, No. (%)	N.A.	N.A.	28,957(34)	1,279(33)	8,815(9)	399(11)
Current user, No. (%)	N.A.	N.A.	13,292(15)	699(18)	4,260(4)	249(7)
Region						
West, No. (%)	9,188(22)	688(20)	10,508(12)	375(10)	14,986(15)	438(13)
Midwest, No. (%)	11,530(27)	908(26)	16,163(19)	732(19)	34,323(33)	1,157(33)
South, No. (%)	11,253(27)	1,067(30)	9,251(11)	447(12)	17,515(17)	684(20)
Northeast, No. (%)	9,742(23)	809(23)	50,492(58)	2,267(59)	35,568(35)	1,205(35)

Values are means(SD) or percentages except where otherwise specified and are standardized to the age distribution of the study population.

*Value is not age-adjusted.

#Median (25^{th}, 75^{th} percentiles).

¶Baseline values not available, first available value reported. Some percentages may not add up to 100% due to rounding or missing values. ACE, angiotensin converting enzyme, N.A., not available. Time at risk goes from 1986 to 2010 for HPFS, 1991 to 2009 for NHS II, 1992 to 2010 for NHS I.

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Table 2

Hazard ratios and 95% confidence intervals of incident coronary heart disease by history of kidney stones in the Health Professional Follow-Up Study, Nurses' Health Study I and Nurses' Health Study II cohorts

	HPFS		NHS I		NHS II	
	No stones	**Stones**	**No stones**	**Stones**	**No stones**	**Stones**
Total CHD						
cases	7,365	1	6,594	561	949	135
person-years	720,427	91	1,282,236	74,404	1,732,190	93,785
Incidence rate*	1,022	1	514	754	55	144
age-adjusted HR	1.0	1.18 [1.11, 1.25]	1.0	1.41 [1.30, 1.54]	1.0	2.19 [1.83, 2.63]
multivariate 1 HR	1.0	1.09 [1.02, 1.16]	1.0	1.21 [1.11, 1.32]	1.0	1.56 [1.29, 1.87]
multivariate 2 HR	1.0	1.06 [0.99, 1.13]	1.0	1.18 [1.08, 1.28]	1.0	1.48 [1.23, 1.78]
Fatal and non-fatal MI						
cases	3,137	493	2,527	216	429	57
person-years	725,451	92,061	1,286,070	74,751	1,732,882	93,893
Incidence rate*	432	536	196	289	25	61
age-adjusted HR	1.0	1.11 [1.01, 1.23]	1.0	1.46 [1.27, 1.68]	1.0	2.10 [1.58, 2.78]
multivariate 1 HR	1.0	1.05 [0.95, 1.15]	1.0	1.26 [1.09, 1.45]	1.0	1.54 [1.15, 2.05]
multivariate 2 HR	1.0	1.01 [0.92, 1.11]	1.0	1.23 [1.07, 1.41]	1.0	1.42 [1.07, 1.90]
Revascularization						
cases	5,090	859	5,141	451	685	100
person-years	721,356	91,294	1,283,255	74,484	1,732,449	93,824
Incidence rate*	706	941	401	606	40	107
age-adjusted HR	1.0	1.18 [1.09, 1.27]	1.0	1.44 [1.31, 1.59]	1.0	2.22 [1.79, 2.73]
multivariate 1 HR	1.0	1.08 [1.00, 1.17]	1.0	1.23 [1.12, 1.36]	1.0	1.52 [1.22, 1.88]
multivariate 2 HR	1.0	1.06 [0.98, 1.14]	1.0	1.20 [1.09, 1.32]	1.0	1.46 [1.17, 1.81]

Multivariate 1 model adjusted for age, race, region of residence (5 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, beta blockers, angiotensin-converting-enzyme inhibitors, other anti-hypertensive drugs, menopausal status (NHS I and NHS II), post-menopausal hormone use (NHS I and NHS II), profession (HPFS). Multivariate 2 model further adjusted for smoking status (3 categories), BMI (13 categories), physical activity (6 categories), quintiles of

intake of calcium, potassium, magnesium, animal protein, total fat, vitamin D, caffeine, DASH score, alcohol. 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 MI and revascularization in the same time period.

* Incidence rate expressed as number of events per 100,000 person-years.