Association Between Kidney Stone History and Cardiovascular Event Risk in US Adults

Samir Bhattacharyya, Larry E. Miller, Silvia Proietti, Khurshid R. Ghani, Ben H. Chew, and Naeem Bhojani

OBJECTIVE To determine the association between kidney stone history and predicted 10-year risk of atherosclerotic cardiovascular disease (CVD) events in a nationally representative US adult sample without existing CVD.

METHODS This was a cross-sectional study of the 2017-2020 National Health and Nutrition Examination Survey that included a nationally representative sample of 3842 adults aged 40-79 free from CVD. Kidney stone history was assessed through self-reporting. The 10-year risk of an atherosclerotic CVD event was predicted using the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations.

RESULTS The weighted prevalence of kidney stones was 12.2% (95% CI: 10.5% to 14.1%). In unadjusted analysis, the odds of borderline or higher (≥5%) atherosclerotic CVD risk were higher in stone formers (odds ratio = 1.56; 95% CI 1.01-2.40; P = .046). This association persisted after adjustment for demographics and clinical covariates (adjusted odds ratio = 1.57; 95% CI = 1.02 to 2.43; P = .04). A significant interaction by biological sex was identified (P = .002), with excess risk conferred by kidney stones in males but not females.

CONCLUSION Kidney stone history was independently associated with increased 10-year predicted atherosclerotic CVD event risk, with excess risk observed among males but not females. Intensified CVD screening may be warranted among stone formers given their increased cardiovascular risk. UROLOGY 194: 121–126, 2024. © 2024 Published by Elsevier Inc.

Kidney stones affect approximately 10% of the population during their lifetime.[1] Prior studies have reported associations between kidney stones and obesity, diabetes mellitus, and cardiovascular disease (CVD).[2-5] Proposed mechanisms linking these conditions include systemic inflammation, endothelial dysfunction, vascular calcification, and metabolic abnormalities.[6] However, the association between kidney stones and subsequent cardiovascular events remains unclear. While several meta-analyses reported modestly higher CVD risk among stone formers,[2-4] the included studies varied considerably in design and subject demographics, and the small number of studies in these reviews precluded a detailed analysis of confounding factors that may influence CVD risk. Further, evidence from population-based studies examining the association of kidney stone history and CVD risk is limited. An analysis of the 2007-2012 National Health and Nutrition Examination Survey (NHANES) found no association between stone history and 10-year predicted risk of atherosclerotic cardiovascular disease (ASCVD) events overall or by sex.[7] However, non-Hispanic Black participants with a history of stones had over twice the predicted ASCVD risk compared to those without a history of stones. Given the rising prevalence of kidney stones in the population over the past decade [8] and the discordant findings between nationally representative samples[7] and meta-analyses,[2-4] a re-evaluation of this relationship using contemporary national data is warranted. This study evaluated the association between self-reported history of kidney stones and predicted 10-year ASCVD event risk using contemporary data from a nationally representative sample of US adults with no prior history of CVD. We hypothesized that adults with a history of kidney stones would have a significantly higher predicted 10-year risk of an ASCVD event compared to those without a history of kidney stones.

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MATERIAL AND METHODS

Study Population

This cross-sectional observational study utilized data from the 2017-March 2020 NHANES, a recurring national survey conducted in the US by the National Center for Health Statistics. The NHANES employs a complex, multistage probability sampling design to provide nationally representative estimates for the noninstitutionalized civilian US population. Trained personnel collected data using standardized interviews, questionnaires, and physical examinations. The current study sample was restricted to males and nonpregnant females aged 40-79 without a history of CVD, specifically congestive heart failure, coronary heart disease, myocardial infarction, angina, or stroke. This age range and health criteria match the sample used to derive the Pooled Cohort Equations, which were used to predict the 10-year risk of an ASCVD event (described in Section 2.2). De-identified participant data were publicly accessible from the National Center for Health Statistics.[9] Written informed consent was obtained from all NHANES participants. The Ethics Review Committee of the National Center for Health Statistics approved the study. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[10]

10-Year ASCVD Event Risk Calculation

The primary outcome was the predicted 10-year risk of experiencing a first ASCVD event, defined as nonfatal myocardial infarction, coronary heart disease death, or fatal or nonfatal stroke. This risk was calculated using the Pooled Cohort Equations developed by the joint American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines.[11] These equations were derived from multiple racially and geographically diverse cohort studies of participants aged 40-79 without CVD at baseline and using adjudicated clinical outcome data with at least 12 years of active surveillance, including the ARIC (Atherosclerosis Risk in Communities) study,[12] the Cardiovascular Health Study,[13] the CARDIA (Coronary Artery Risk Development in Young Adults) study,[14] and the Framingham Original and Offspring Study cohorts.[15,16] These equations accurately predict the 10-year ASCVD risk for both males and females, as well as for different racial groups.[17] The predictor variables in the equations comprise traditional cardiac risk factors including age, sex, race, systolic and diastolic blood pressure, antihypertensive medication use, total and high-density lipoprotein cholesterol, diabetes mellitus, and current smoking status.

Kidney Stone History and Covariates

The exposure variable was a lifetime history of kidney stones, assessed by the self-reported survey question, "Have you ever had kidney stones?" Ten variables from the NHANES database were used to calculate 10-year ASCVD risk scores. Age, sex, and race/ethnicity were self-reported. Systolic and diastolic blood pressure were calculated as the mean of 3 measurements obtained during the physical examination. Antihypertensive medication use was determined by the question, "Because of your high blood pressure/hypertension, are you now taking prescribed medicine?" among those with a self-reported history of hypertension. Total and high-density lipoprotein cholesterol were measured from fasted blood samples collected during the physical examination. Diabetes mellitus diagnosis was established based on affirmative responses to the question, "Have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" or self-reported current use of insulin or oral diabetes medication. Current smokers were identified through self-reported smoking on some days or every day during a typical week, along with a lifetime history of at least 100 cigarettes smoked. Additional variables evaluated as potential effect modifiers of the association between kidney stone prevalence and ASCVD risk were chronic kidney disease, arthritis, and obesity (body mass index ≥30 kg/m^2).

Statistical Analysis

Statistical analyses accounted for the complex multistage cluster sampling design of NHANES by applying sampling weights, strata, and primary sampling units. Survey weights adjusted for oversampling of specific subgroups and survey nonresponse, enabling post-stratification adjustments to generate nationally representative estimates. Standard errors were estimated using Taylor series linearization to account for the complex sampling design. The 10-year predicted ASCVD event risk probabilities were calculated using the ACC/AHA Pooled Cohort Equations [11] and modeled as categorical variables based on the following clinical risk thresholds: < 5% low risk; 5%-7.4% borderline risk; 7.5%-19.9% intermediate risk; and ≥20% high risk. Multivariable logistic regression models were constructed to determine the independent association between kidney stone history and having at least borderline risk (ASCVD event risk ≥5%), which is the recommended lower threshold for considering moderate-intensity statin therapy in individuals with risk-enhancing factors.[18] An unadjusted model quantified the crude association between kidney stone history and predicted 10-year ASCVD event risk, reported as the odds ratio and 95% confidence interval. Adjusted models controlled for demographics (ie, age, sex, and race/ethnicity), with additional adjustment for clinical covariates (chronic kidney disease, arthritis, and obesity). Interaction terms between kidney stone history and age, sex, and race/ethnicity were evaluated to assess potential demographic effect modification. Statistical analyses were conducted using Stata v18 (StataCorp; College Station, TX, USA). Statistical significance was defined as a 2-sided *P*-value of less than .05.

RESULTS

Among the 15,560 participants in the 2017-March 2020 NHANES, 11,718 were excluded from the analysis through a 2-stage process. The first stage excluded 10,727 participants who did not meet demographic and medical history criteria. Among the non-mutually exclusive reasons for exclusion, 9809 were outside the 40-79 age range, 487 had a history of stroke, 432 had myocardial infarction, 423 had coronary heart disease, 361 had congestive heart failure, 240 had angina, and 87 were pregnant. During the second stage, 991 participants were excluded due to missing data necessary to determine kidney stone history or to predict ASCVD event risk.

Among the 3842 participants included in the analysis, 396 reported a lifetime history of kidney stones, corresponding to a weighted population prevalence of 12.2% (95% CI: 10.5 to 14.1%). Compared to those without a history of kidney stones, stone formers were of similar mean age (57 vs 56 years), and more likely male (56.8% vs 46.0%), White (74.5% vs 66.1%), taking antihypertensive medication (38.4% vs 29.4%), obese (50.0% vs 42.8%), and having arthritis (44.6% vs 34.0%) (Table 1).

Overall, participants with a history of kidney stones more frequently had at least borderline ASCVD event risk (60.9% vs 50.0%). A greater proportion of stone formers versus non-stone formers had borderline (19.2% vs 12.5%), intermediate (29.5% vs 26.8%), or high (12.2 vs 10.8%) ASCVD event risk (Fig. 1). In the unadjusted analysis, kidney stone history was associated with 56% higher odds of having at least borderline (≥5%) predicted 10-year ASCVD event risk compared to those without a history of stones (odds ratio = 1.56; 95% CI = 1.01 to 2.40; P = .046). This association persisted after adjustment for demographics (adjusted odds ratio = 1.65; 95% CI = 1.13 to 2.41; P = .01) and additional adjustment for clinical covariates (adjusted odds ratio = 1.57; 95% CI = 1.02 to 2.43; P = .04) (Table 2).

Table 1. Participant characteristics of adults aged 40 to 79 years by kidney stone history.[a].

	Stone history	
Variable	Yes (n = 396)	No (n = 3446)
ASCVD Risk Factors		
Male sex	56.8%	46.0%
Age, y	57.3 (0.7)	56.3 (0.4)
Race		
White	74.5%	66.1%
Black	5.1%	10.8%
Asian	3.2%	5.6%
Mexican American	7.0%	6.9%
Hispanic	7.1%	6.8%
Other race	3.1%	3.8%
Total cholesterol (mg/dl)	192 (3)	197 (1)
HDL cholesterol (mg/dl)	52 (1)	55 (1)
Systolic blood pressure (mmHg)	126 (1)	125 (1)
Hypertension medication	38.4%	29.4%
Diabetes mellitus	16.1%	14.1%
Current smoker	14.4%	14.9%
Additional Factors		
Obesity (BMI ≥30 kg/m^2)	50.0%	42.8%
Arthritis	44.6%	34.0%
Kidney disease	3.8%	2.4%
Myocardial infarction	0%	0%
Stroke	0%	0%
Coronary heart disease	0%	0%
Congestive heart failure	0%	0%
Angina	0%	0%

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HDL, high-density lipoprotein.

[a] Values are population-weighted percentages or mean (standard error).

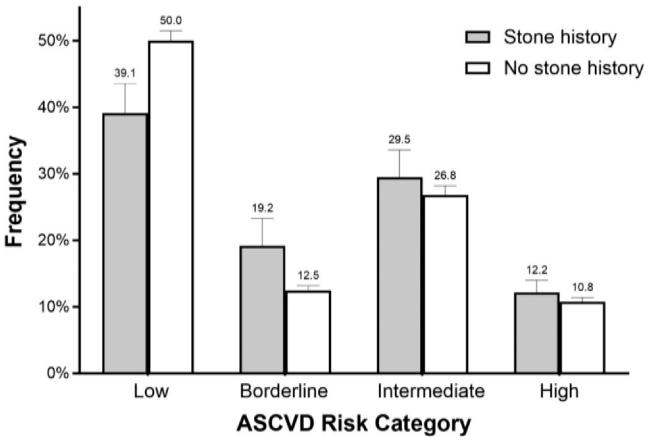

Figure 1. ASCVD risk category frequencies in adults aged 40 to 79 years by kidney stone history. Plotted values are population-weighted percentages (standard error). ASCVD, atherosclerotic cardiovascular disease.

Kidney stones were associated with elevated ASCVD event risk across most age groups, except those aged 70-79 where background risk was already high (Supplement Figure 1). The elevated risk of ASCVD conferred by kidney stones was consistent across most racial/ethnic groups (Supplement Figure 2). No significant interactions were observed between kidney stone history and age or race/ethnicity. However, a significant interaction was found between sex and kidney stone history (P = .002). Kidney stones were associated with higher cardiovascular risk in males but not females (Fig. 2), primarily in the 40-59 age groups (Supplement Tables 1 and 2). In analyses stratified by age and sex, while the elevated stone-associated ASCVD risk among males was identified in the 40-59 age groups, females with a history of kidney stones in these age groups tended to have lower ASCVD event risk compared to females without kidney stones (Supplement Figure 3).

COMMENT

Assessment of CVD risk is essential for guiding clinical decisions regarding preventive care, as major practice guidelines endorse using 10-year ASCVD event risk prediction to inform treatment approaches for aspirin, antihypertensive, and statin therapy.[18] Our analysis of contemporary data from the nationally representative

Table 2. Association between kidney stone history and other patient factors with elevated (≥5%) 10-year risk of ASCVD in adults aged 40 to 79 years.

Model	Odds ratio	95% CI	*P*-value
Independent variables			
Kidney stone history	1.56	1.01, 2.40	.046
Age, per 10-year increase	7.39	6.23, 8.76	< .001
Sex, male versus female	2.85	2.22, 3.65	< .001
Race			< .001
White	Ref.	—	
Black	1.79	1.43, 2.24	
Other races	0.80	0.64, 1.00	
Obesity (≥30 kg/m^2)	1.32	1.08, 1.60	.008
Arthritis	2.41	1.87, 3.09	< .001
Kidney disease	2.04	0.98, 4.23	.06
Multivariable model			
Kidney stone history	1.56	1.01, 2.40	.046
Adjusted for age, sex, and race	1.65	1.13, 2.41	.01
Adjusted for age, sex, race, obesity, arthritis, and kidney disease	1.57	1.02, 2.43	.04

ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein.

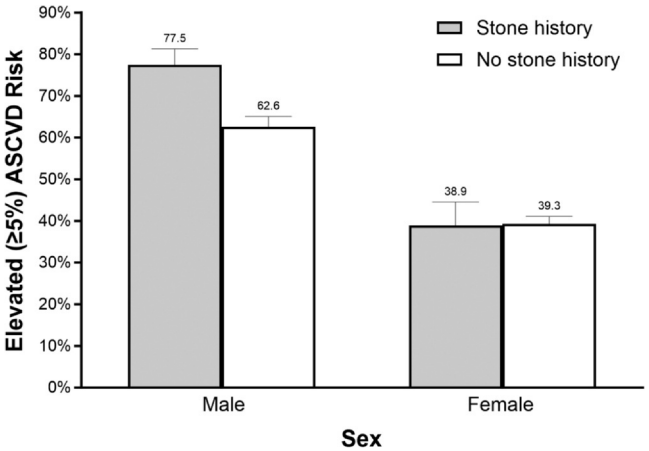

Figure 2. Frequency of elevated (≥5%) 10-year risk of ASCVD by kidney stone history and sex. Plotted values are population-weighted percentages (standard error). ASCVD, atherosclerotic cardiovascular disease.

NHANES survey demonstrated an independent association between self-reported lifetime kidney stone history and elevated predicted 10-year ASCVD event risk in US adults aged 40-79 without existing CVD. Adults with a history of kidney stones had 57% higher adjusted odds of having at least borderline ASCVD risk compared to those without kidney stones after controlling for demographics and clinical risk factors. This increased cardiovascular risk was most pronounced among males, suggesting a potential sex-specific interaction between stone pathogenesis and CVD risk profiles.

Our findings demonstrated an association between a lifetime history of kidney stones and elevated 10-year predicted ASCVD risk, particularly among males aged 40-59. Current ACC/AHA guidelines advise initiating ASCVD risk estimation at age 40.[19,20] However, the strong influence of age in the Pooled Cohort Equations somewhat limits their ability to identify independent cardiovascular risk factors in certain age groups. For example, adults in their 40s typically have very low 10-year ASCVD event risk regardless of underlying risk profiles, while those in their 70s tend to have high predicted risk driven solely by advanced age. Thus, estimating long-term (eg, 30 years) risk may better identify emerging risks in younger adults.[21] In contrast, for older adults with already high ASCVD risk, which may be overestimated due to the suboptimal performance of the Pooled Cohort Equations in these individuals,[22] estimation of excess risk from specific conditions like kidney stones is unlikely to add prognostic value. Instead, a 3- to 5-year risk assessment could facilitate more informed risk/benefit discussions about preventive therapies in this age group.[23]

Arterial calcification may partially explain the potential link between kidney stone formation and increased ASCVD risk. Individuals with a history of kidney stones have a higher incidence of calcification in key vascular areas such as the carotid arteries, splenic arteries, and abdominal aorta.[24-26] This association suggests that the pathophysiological mechanisms underlying kidney stone formation, including disturbances in mineral metabolism, oxidative stress, and inflammatory responses, might similarly influence the development of vascular calcification.[6] Furthermore, shared risk factors like hypertension and diabetes may contribute to the parallel development of kidney stones and atherosclerotic plaque. Consequently, the metabolic abnormalities associated with kidney stones may predispose individuals to urolithiasis and vascular calcification, thereby elevating their ASCVD risk. Given the increasing prevalence of kidney stones in the population,[8] further investigation of these shared pathogenic pathways may improve understanding of their implications for cardiovascular health.

A previous NHANES analysis by Glover et al[7] found no overall association between stone history and ASCVD. A key difference between these studies was their use of a ≥20% ASCVD risk threshold to inform their prediction models, whereas we used a more sensitive threshold of ≥5%, based on guidelines recommending the consideration of moderate-intensity statin therapy at this risk level in those with additional risk-enhancing factors.[18] The disparity in these results

suggests that nephrolithiasis may be a more significant ASCVD risk factor in individuals at borderline to intermediate risk, as other factors may dominate its contribution in high-risk individuals.

Considerable variability exists in the literature regarding whether biological sex mediates the association between kidney stones and ASCVD risk. While we demonstrated that males with a kidney stone history have a considerably higher risk of ASCVD, others have reported that this excess cardiovascular risk was more pronounced in younger adults [27] and females.[27,28] Wide variability in participant age ranges among studies likely partially explains these divergent findings. Further studies should clarify the independent and cumulative effects of kidney stone history on long-term cardiovascular outcomes across patient subgroups.

Despite the utilization of contemporary data from a large nationally representative US population-based survey, several limitations of this study warrant discussion. First, the cross-sectional design cannot establish causality between kidney stone prevalence and ASCVD risk. Second, self-reported data may introduce inaccuracies due to potential recall and response bias. Specifically, kidney stone prevalence tends to be overestimated in patient surveys compared to confirming with medical records,[29] which may influence the study results. Third, the study did not measure all factors that might influence the association between kidney stones and ASCVD risk. Thus, the possibility of residual confounding from unmeasured variables remains. Fourth, the Pooled Cohort Equations to predict the 10-year risk of a first ASCVD event were derived using data from non-Hispanic African Americans and non-Hispanic Whites aged 40-79. While the ACC/AHA Task Force states that these equations may be used in other populations, race/ethnicity-specific risk algorithms are unavailable, and their use may have introduced inaccuracies in ASCVD risk prediction in other populations, mainly Asian Americans and Hispanics.[11] Fifth, there is a potential temporal disconnect in the study data since the timing of kidney stone occurrence relative to the reported risk factors was unreported. Finally, while adjusting for demographics allowed us to isolate the independent association between kidney stones and ASCVD risk, age, sex, and race are components of the Pooled Cohort Equations for risk prediction. Controlling for components of the outcome model in regression risks over adjustment bias and should be considered when interpreting the study results.[30] Additionally, the ability to statistically detect an independent contribution from kidney stones to ASCVD risk may only be feasible among adults with moderate baseline risk. In younger or older adults, the overwhelming influence of age-related baseline risk may outweigh any marginal risk contributed by kidney stones or other factors.

CONCLUSION

Kidney stone history was independently associated with increased 10-year predicted ASCVD event risk, with excess risk observed among males but not females. Intensified CVD screening may be warranted among stone formers given their increased ASCVD risk profile. Urologists should consider discussing modifiable cardiovascular risk factors with kidney stone patients as part of their overall care.

CRediT Authorship Contribution Statement

Samir Bhattacharyya: Writing—review and editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. Larry E Miller: Writing—original draft, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Silvia Proietti: Writing—review and editing, Validation, Resources, Methodology, Investigation. Khurshid R Ghani: Writing—review and editing, Resources, Methodology, Investigation. Ben H Chew: Writing—review and editing, Validation, Resources, Methodology, Investigation, Conceptualization. Naeem Bhojani: Writing—review and editing, Validation, Resources, Methodology, Investigation, Conceptualization.

Declaration of Competing Interest

S. Bhattacharyya reports employment with Boston Scientific, related to this work; L. Miller reports consultancy with Boston Scientific, related to this work; S. Proietti reports consultancy with Boston Scientific, unrelated to this work; K. Ghani reports consultancy with Boston Scientific (unrelated to this work), Coloplast, Olympus, and Ambu; B. Chew reports consultancy with Boston Scientific, unrelated to this work; N. Bhojani reports consultancy with Boston Scientific, unrelated to this work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.urology.2024.08.062.

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