Urinary Stone Disease and Cardiovascular Disease Risk in a Rural Chinese Population

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Introduction: Urinary stone disease (USD) is associated with cardiovascular disease (CVD) in Western populations. However, the prevalence and relationship between USD and CVD risk have not been fully examined in the Chinese population.

Methods: We performed a cross-sectional study of 10,281 participants in rural China. All subjects underwent renal ultrasound to detect USD, brachial−ankle pulsewave velocity (baPWV) measurement to estimate arterial stiffness, and ankle−brachial index (ABI) examination to detect peripheral arterial disease (PAD) (defined as ABI <0.9 on at least 1 side of the body).

Results: Mean age of the study population was 55.4 ± 10.0 years; 47.1% were men. Among all participants, 5.7% (n = 582) had USD, mean baPWV was 15.6 ± 3.2 m/s, and 4.0% had PAD. The prevalence of USD increased in parallel with mean arterial pressure, albuminuria, Framingham risk score, and baPWV. In multivariate analyses after adjustment for demographic characteristics, USD was significantly associated with an increased risk of hypertension (odds ratio [OR]: 1.32; 95% confidence interval [CI]: 1.08−1.62), albuminuria (OR: 2.17; 95% CI: 1.74−2.69), chronic kidney disease (OR: 2.11; 95% CI: 1.70−2.62), increased arterial stiffness (OR: 1.24; 95% CI: 1.01−1.52), and PAD (OR: 1.50; 95% CI: 1.04−2.16).

Discussion: In rural China, USD was associated with a high prevalence of traditional CVD risk factors, increased arterial stiffness, and PAD. The presence of USD should increase physician awareness of the concomitant presence of CVD risk factors.

The prevalence of urinary stone disease (USD) is approximately 9% in the United States and has doubled in the past decade.[1,2] Associations between USD and cardiovascular events, including myocardial infarction,[3] coronary artery revascularization,[4–6] and stroke[4,7] have recently been reported. Furthermore, previous studies have revealed positive associations between USD and diabetic mellitus,[8,9] hypertension,[10,11] obesity,[12], chronic kidney disease (CKD),[13–15] and low bone mineral density.[16,17]

In China, the prevalence of USD is less clear, and several studies have estimated the prevalence of USD to be 2.2% to 6.4% in adults.[14,18,19] Most studies that link USD and cardiovascular disease (CVD) have examined Western populations, but whether associations exist between USD and CVD risk in the Chinese population is unknown.

Brachial−ankle pulsewave velocity (baPWV), as a measure of arterial stiffness, has emerged as an important surrogate marker of atherosclerosis,[20] yet studies have not robustly investigated the connection between baPWV and USD in non-Western populations. Similarly, the presence of peripheral arterial disease (PAD) has been linked to an increased risk of ischemic events, with a 2-fold increase in the risk of myocardial infarction and strokes, but the association of PAD with

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USD in Chinese people is unclear.[21,22] We report the prevalence of USD in a large population from rural China and their associated CVD risk in terms of baPWV and PAD.

MATERIALS AND METHODS

Study Participants

The study population consisted of 2 groups (cohort I and cohort II) of adults aged 35 years or older who were recruited during 2 different time periods from the Pinggu District, a suburb of Beijing. For both cohorts, 1 person per household was randomly selected to participate. Details of our sampling procedure were previously described.[23] In cohort I, participants from 20 villages were enrolled and underwent a first study examination between April 2008 and March 2009; many of these cohort I participants returned for a second examination in 2014 (Figure 1). Examination 1 for cohort II (a newly recruited cohort living in another town in the Pinggu District) also occurred in 2014. Because our study procedures evolved to standardized methods by the 2014 data collection period, the present cross-sectional study was based only on data collected from participants in cohort I at examination 2 and from newly recruited participants in cohort II at examination 1. The study was approved by the Ethics Committee of Peking Union Medical College Hospital (PUMCH), and written informed consent was obtained from each participant before any data were collected.
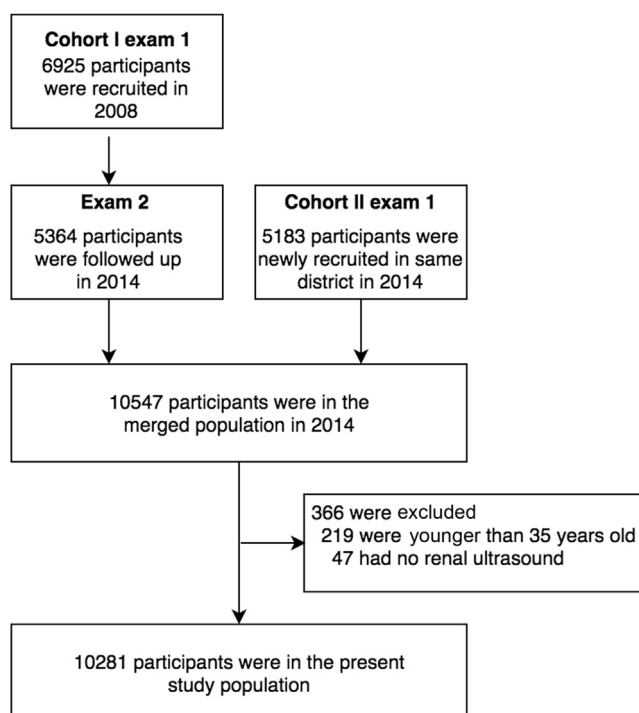
Figure 1. Flowchart of study population recruitment.

Anthropometric and Laboratory Measurement

All participants completed a questionnaire to document demographic information and self-reported smoking status, history of hypertension, diabetes, CVD, and medication history. Height, body weight, and circumference were measured by standardized methods and trained staff. Blood pressure (BP) was measured twice after at least 5 minutes of rest using a mercury sphygmomanometer. If the difference between the 2 measurements was >10 mm Hg, a third measurement was obtained, and the mean value of the BPs was calculated using the 2 closest values.

Venous blood samples were collected after overnight fasting of 8 to 12 hours. The concentration of fasting blood glucose, serum creatinine, serum inorganic ions (potassium, sodium, calcium, and phosphorous), uric acid, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and high-sensitivity C-reactive protein (hs-CRP) were measured using a Beckman Coulter AU5800 (Brea, CA), and serum creatinine was determined by an enzymatic method. Hemoglobin was measured by the SYSMEX-500 (Kobe, Japan). Plasma glycosylated hemoglobin (HbA_{1c}) was detected by VARIANT II Turbo (Hercules, CA).

First void morning urine was collected to detect the albumin-to-creatinine ratio (ACR) using a Beckman Coulter AU270. Urine albumin was measured with the immunoturbidimetric method, and urine creatinine (UCr) was measured with an enzymatic method. Calibrated UCr was used for ACR; 200 urine samples were retested by Jaffe's kinetic method, and the following calibration equation was approved ($R^2 = 0.997$): calibrated UCr (mmol/l) = 0.884 UCr (mmol/l) + 0.3355.

All blood and urine samples were transferred at 4°C in iceboxes and tested at the PUMCH laboratory.

Diabetes was defined as a fasting serum glucose of >7.0 mmol/l, HbA_{1c} >6.5%, or a previous diagnosis of diabetes.

Exposure Measures

Renal ultrasonography was used to define the presence of USD, including the location and number of urinary stones. The diagnosis of USD required demonstration of at least 1 hyperechoic structure that caused acoustic shadowing in the renal collecting system.

Outcome Measures

The mean arterial pressure (MAP) was calculated as diastolic pressure plus one-third of the difference between systolic pressure minus diastolic pressure. Hypertension was defined as a systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, a self-reported history of hypertension, or use of antihypertensive medications in the past 3 months.

CKD was defined as a decreased estimated glomerular filtration rate (eGFR; <60 ml/min/1.73 m^2) and/or albuminuria (ACR $\geq$30 mg/g).[24] The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[25]

Brachial–ankle pulsewave velocity and ankle–brachial index (ABI) were evaluated with a noninvasive and volume-plethysmographic apparatus (BP-203RPEIII, Omron Corporation, Kyoto, Japan) after at least 5 minutes of rest in the supine position. BP and pulsewave measurement cuffs were applied to all 4 limbs. The distance between the upper arm and ankle was calculated using linear regression from the subject's height. The transit time between the brachial and ankle waveform was defined as the pulsewaves of the time interval between the brachium and ankle. Brachial–ankle pulsewave velocity was calculated as the ratio of the distance between the brachial and the tibial artery divided by the transit time between these 2 arteries.[20,26] The ABI was calculated as the ratio of systolic pressure at the ankle divided by that of the arm. The baPWV and ABI were measured bilaterally in all participants, and the mean value of the right and left baPWVs and the lower value of ABI were used in the analysis. Abnormal baPWV was defined as a baPWV >18 m/s.[27] PAD was defined as an ABI <0.9 on at least 1 side of the body.[28]

Framingham Risk Score (FRS) was calculated based on the general cardiovascular risk algorithm.[29] Variables including age, sex, smoking status, serum total cholesterol and high-density lipoprotein cholesterol, diabetes, and systolic BP (treated vs. not treated) were used to compute the general CVD risk score in each participant without a history of cardiovascular events. Individuals with an FRS $>20\%$ were considered to have a high 10-year CVD risk.

Statistical Analysis

Characteristics of participants were expressed as mean $\pm$ SD for continuous variables and proportions for categorical variables. Characteristics of groups with and without USD were compared using the Student's t-test, Mann-Whitney U test, and χ^2 test, as appropriate. The Cochran-Armitage test for trend was performed to assess the linear trend in the proportions of USD subjects across quartiles of the outcome variables. The association between USD and dichotomous outcomes was explored with unadjusted and adjusted binary logistic regression models. We used demographic factors in the adjusted regression model. Variables that appeared different between groups with and without USD ($P < 0.001$; as shown in Table 1) were considered potential confounders and were included as covariates in the adjusted models. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina).

Table 1. Characteristics of participants according to the presence of USD

Variable	USD present		P value
	Yes (n = 582)	No (n = 9699)	
Age, yr	56.4 ± 9.8	55.3 ± 10.0	0.01
Men, %	64.8	46.1	<0.001
Current or past smoker, %	47.1	34.3	<0.001
BMI, kg/m^2	26.3 ± 3.8	26.3 ± 3.7	0.90
Serum glucose, mmol/l	6.4 ± 1.7	6.3 ± 1.8	0.25
Serum sodium, mmol/l	141.3 ± 2.0	141.3 ± 2.0	0.77
Serum calcium, mmol/l	2.3 ± 0.1	2.3 ± 0.1	0.94
Serum phosphorus, mmol/l	1.1 ± 0.2	1.2 ± 0.2	<0.001
Serum uric acid, µmol/l	301.7 ± 88.6	279.9 ± 80.5	<0.001
Triglycerides, mmol/l	1.5 ± 1.3	1.5 ± 1.5	0.92
LDL-C, mmol/l	3.0 ± 0.8	3.0 ± 0.8	0.38
Serum hsCRP, mg/l	1.0 (0.5–2.1)	0.9 (0.4–1.8)	0.02
Hemoglobin, g/l	151.5 ± 15.0	148.2 ± 15.6	<0.001
Diabetes, %	23.2	20.4	0.12

Sex, smoking status, and diabetes are expressed as proportions. The remaining data are expressed as mean ± SD or median (interquartile range).
BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; USD, urinary stone disease.

RESULTS

Demographic Characteristics

A total of 6925 participants were enrolled in cohort I at examination 1. Of these, 5364 participants from cohort I were followed again at examination 2 in 2014 and were included in the present cross-sectional study. A total of 5183 participants were enrolled in cohort II at examination 1. In all, 10,328 participants aged 35 years or older were included in the present study. Forty-seven participants (0.5%) with missing renal ultrasound data were excluded from analysis; thus, 10,281 participants were included in the final analysis (Figure 1).

The mean age of the entire Chinese study population was 55.4 $\pm$ 10.0 years; 47.1% were men, and 582 subjects (5.7%) had USD. The prevalence of CKD was 11.6%: reduced eGFR (<60 ml/min/1.73^2) was present in 1.2%, and albuminuria was present in 10.9%. The prevalence of PAD, as defined by an ABI <0.9, was 4.0%.

Characteristics of the participants according to the presence of USD are listed in Table 1. Those subjects with USD were more likely to be older, men, and current or past smokers. Serum phosphorus was lower, and the serum level of uric acid and hs-CRP were higher among subjects with USD compared with those without USD. Other characteristics such as body mass index and the proportion of participants with diabetes did not differ significantly between the groups.

Prevalence of USD and Risk Factors for CVD

Both MAP (109.6 $\pm$ 14.0 mm Hg vs. 107.4 $\pm$ 13.1 mm Hg; $P < 0.001$) and baPWV (16.1 $\pm$ 3.3 m/s vs.

15.5 ± 3.1 m/s; $P < 0.001$) were significantly higher in participants with USD compared with those without USD. Participants with USD also had a higher prevalence of PAD (5.9% vs. 3.9%; $P = 0.016$) and CKD (20.6% vs. 11.0%; $P < 0.001$) (Table 2).

As shown in Figure 2, the overall prevalence of USD paralleled the increase in baPWV, MAP, FRS, and ACR, and the decrease in eGFR. There was no significant difference in the prevalence of USD subgroups defined by quartiles of ABI. Both the highest quartile of ACR and the lowest quartile of eGFR included normal participants because they made up most of the subjects in this study.

In an unadjusted model (Table 2), participants with USD had a significantly higher prevalence of hypertension, albuminuria, CKD, increased FRS and baPWV, and PAD with a low ABI <0.9. In multivariate logistic regression, USD was significantly associated with hypertension with an odds ratio (OR) of 1.32 (95% confidence interval [CI]: 1.08−1.62) after adjustment for demographic characteristics (sex, smoking status, serum uric acid, serum phosphate, and hemoglobin levels; $P < 0.001$ in Table 1). The USD group also had a 1.50-fold increase in the odds of having a low ABI (95% CI: 1.04−2.16) and a 1.24-fold increase in the odds of having an elevated baPWV (95% CI: 1.01−1.52). The adjusted ORs of USD and risk for albuminuria (2.17; 95% CI: 1.74−2.69) and CKD (2.11; 95% CI: 1.70−2.62) compared with participants without USD were also higher, although the association between USD and decreased eGFR was not significant (OR: 1.75; 95% CI: 0.93−3.29). As shown in Supplementary Table S1, the risk of hypertension might have been higher in men than women; however, women were more likely to have a higher risk with decreasing eGFR. In the present study, 469 participants had a self-reported history of CVD, but USD was not significantly associated with self-reported CVD (OR: 1.32; 95% CI: 0.92−1.89).

DISCUSSION

In the present cross-sectional study of a rural Chinese population, the overall prevalence of USD was 5.7%. We found that study participants with USD demonstrated a parallel increase in the prevalence of important CVD risk factors, including hypertension, albuminuria, and CKD as well as a higher FRS compared with those without USD. Participants with USD also had increased arterial stiffness and a higher frequency of PAD as detected by an ABI <0.9. This study confirmed that a significant relationship between ultrasound-documented USD and increased CVD risk previously shown in Western populations also exists in this rural Chinese population.

The prevalence of USD confirmed by renal ultrasound in the present study was 2.6-fold higher than the prevalence reported in a community-based population from Shanghai, in the south of China in 2006 (2.2% of 2554 participants aged 18 years or older, also screened by renal ultrasound).[14] However, data collected from the Chinese National Health Examination Centers in 2008 showed that the overall prevalence of USD among urban inhabitants aged older than 20 years was 4.0% (n = 1,169,651).[18] The prevalence of USD in our study was similar to the age- and sex-adjusted national prevalence from 2013 to 2014 in China (5.7% vs. 5.8%).[19] The increasing trend of USD might be related to dietary and health trends, as previously noted in children,[30] but could also involve genetics, individual disease, or environmental factors that have yet to be elucidated.[31] These trends were somewhat consistent with data from the Health and Nutrition Examination Survey, which revealed that the prevalence of kidney stones rose from 3.8% in 1976 to 1980 to 5.2% in 1988 to 1994, and rose again to 8.8% in 2007 to 2010.[2]

Along with its high incidence and increasing prevalence, USD has been associated with CVD risk factors in the west. Our study added to data that was previously lacking in a Chinese population and documented

Table 2. Associations of urinary stone disease with risk factors of cardiovascular disease

Dichotomous outcomes[a]	USD present		Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]
	Yes (n = 582)	No (n = 9699)		
HTN	449 (77.3)	6800 (70.3)	1.44 (1.18−1.75)	1.32 (1.08−1.62)
CKD	118 (20.6)	1056 (11.0)	2.09 (1.69−2.59)	2.11 (1.70−2.62)
eGFR (<60 ml/min/1.73 m^2)	12 (2.1)	116 (1.2)	1.74 (0.95−3.17)	1.75 (0.933.29)
ACR (≥30 mg/g)	114 (19.9)	996 (10.4)	2.14 (1.73−2.66)	2.17 (1.74−2.69)
Framingham CVD risk score (>20%)	203 (41.2)	2701 (31.7)	1.51 (1.26−1.82)	1.14 (0.93−1.41)
baPWV (≥18 m/s)	131 (22.9)	1789 (18.8)	1.28 (1.05−1.57)	1.24 (1.01−1.52)
PAD	34 (5.9)	372 (3.9)	1.55 (1.08−2.23)	1.50 (1.04−2.16)

ACR, albumin-to-creatinine ratio; baPWV, brachial-ankle pulsewave velocity; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimate glomerular filtration rate; HTN, hypertension; OR, odds ratio; PAD, peripheral artery disease; USD, urinary stone disease.
[a]Outcomes are expressed as number (proportion); the calculated proportion may be based on slightly different sample sizes because of missing values for a particular outcome.
[b]Adjusted for sex, smoking, uric acid, hemoglobin, and phosphate.
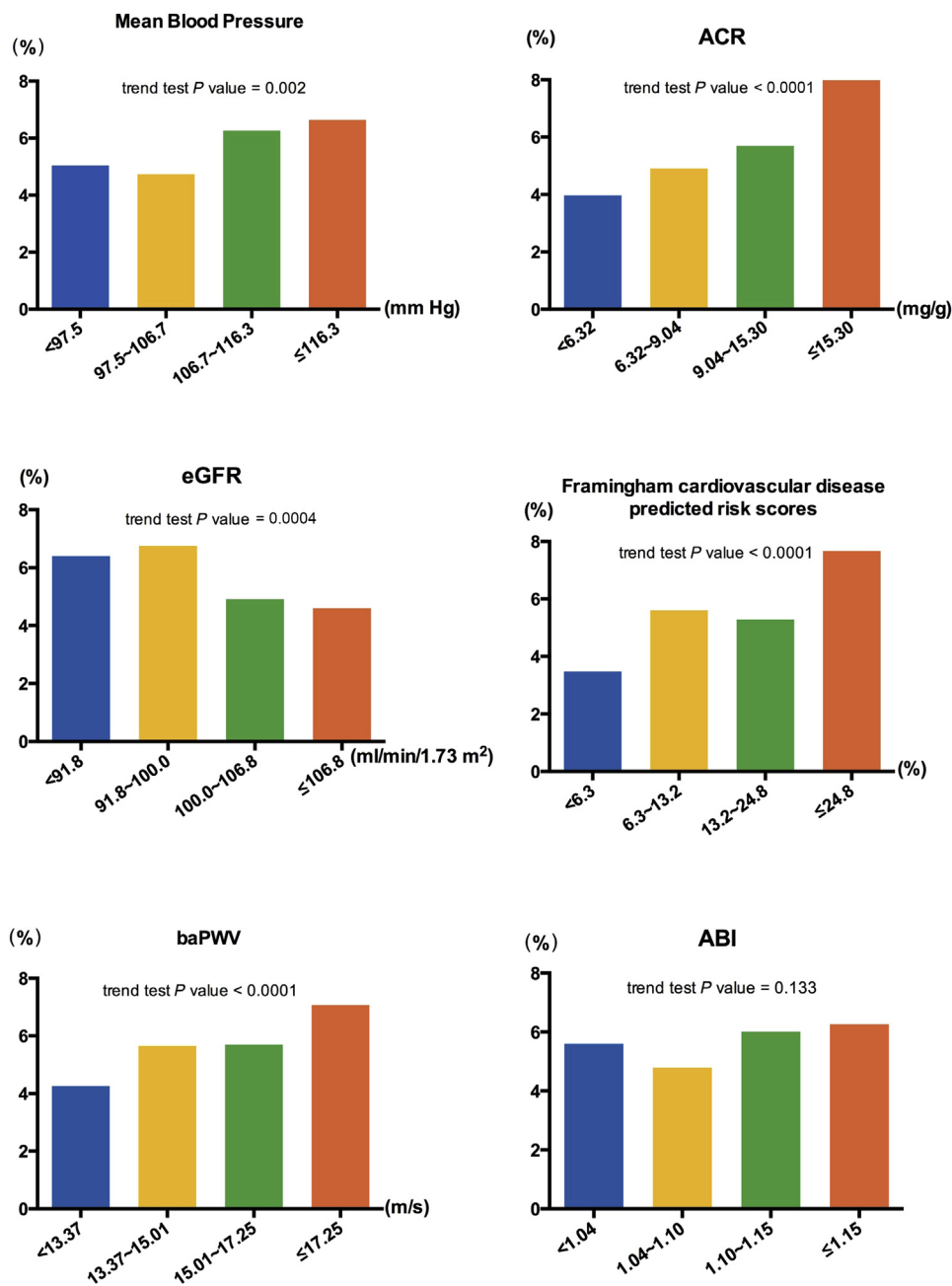
Figure 2. The prevalence of urinary stone disease in study participants grouped into quartiles by various outcomes measures. ABI, ankle−brachial index; ACR, albumin-to-creatinine ratio; baPWV, brachial-ankle pulsewave velocity; eGFR, estimated glomerular filtration rate.

similar findings to those reported in Western populations. Among Chinese subjects with USD, we detected a high prevalence of CVD risk factors, including older age, male sex, hypertension, hyperuricemia, high hs-CRP, albuminuria, and CKD. Not surprisingly, subjects with USD were 51% more likely to have a higher 10-year CVD risk (FRS >20%) compared with subjects without USD, and the prevalence of USD was increased at higher quartiles of FRS. In our study, we did not find a significant association between USD and self-reported CVD events as reported by others; that is, the presence of kidney stones was associated with an increased adjusted risk ratio of 1.23

(95% CI: 1.08−1.41) for coronary heart disease in North American and European populations. The reason might be that our study lacked the power to confirm an association or that the self-reporting nature of our data simply lacked precision. However, we did find significant associations between USD and well-known risk factors for CVD. Therefore, the presence of USD should alert the caring clinician to the concomitant presence of CVD risk.

In our study of Chinese participants, subjects who formed urinary stones had a 32% higher risk of having concomitant hypertension. A positive relationship between the presence of urinary stones and hypertension

was suggested by Western population studies. In a cross-sectional study in 1982 of 1,167,009 US participants aged older than 30 years, the OR for hypertension in those with a history of nephrolithiasis was 1.2 (adjusted for age and race; 95% CI 1.2–1.3).[10] The link with nephrolithiasis and hypertension was also confirmed in prospective studies of men in the Health Professionals Follow-up Study and in the women in the Nurses' Health Study.[11,32]

We also observed a strong association between USD and the presence of albuminuria and CKD; however, the relationship between USD and reduced eGFR was not significant. Consistent with our data, nephrolithiasis was not an independent risk factor for CKD overall in the Atherosclerosis Risk in Communities study.[33] In contrast, subjects who formed urinary stones had an increased risk for proteinuria (hazard ratio: 1.66; 95% CI: 1.20–2.29) defined by diagnosis codes, and the presence of urinary stones was associated with a significant increased risk of reduced GFR in Olmsted County (Olmsted, Minnesota).[15] Another registry cohort study in Canada[13] showed that subjects with a single kidney stone episode during follow-up had a significantly increased risk of renal adverse outcomes, including ESRD, and the adjusted risk of ESRD associated with stone episodes seemed to be greater for women than men (*P* value for interaction = 0.003). A prospective cohort study in the United Kingdom found that USD was a significant risk for ESRD in women (adjusted hazard ratio: 2.07; 95% CI: 1.34–3.19) but not in men,[34] which is in agreement with our results. USD was significantly associated with decreased eGFR (OR: 3.11; 95% CI: 1.27–7.58) only in women (shown in Supplementary Table S1). Because of the limited number of participants with decreased eGFR in our study, we had limited power to robustly examine the association between USD and decreased eGFR. The mechanisms of sex-specific effect modification was not fully clear and requires further investigation.

Our study added the novel finding that subjects with USD had a higher prevalence of increased baPWV (22.9% vs. 18.8%; *P* = 0.02) and PAD (5.9% vs. 3.9%; *P* = 0.02) compared with those who did not have stones in China. Moreover, we found that USD was independently associated with increased baPWV (OR: 1.24; 95% CI: 1.01–1.52) and PAD (OR: 1.50; 95% CI: 1.04–2.16) after adjustment for potential confounders. The dose–response pattern showed no significant trend of prevalence of USD over quartiles of ABI, in contrast to 1 previous study that suggested that the relationship of cardiovascular outcome by ABI level was described by a reverse J-shaped curve, in which the lowest level of risk was from 1.11 to 1.40.[35] Thus,

not only individuals with an ABI <0.9 (diagnosis for PAD), but also those with an ABI >1.40 might be at increased CVD risk. It will be necessary to confirm whether the prevalence of USD by an ABI level is described by a reverse J-shaped curve.

Brachial–ankle pulsewave velocity as a measure of arterial stiffness is commonly considered to reflect progression of arteriosclerosis and is an independent predictor for CVD onset. For example, each 1 m/s increase of baPWV has been associated with a 12% increase in the risk of CVD events.[26] Brachial–ankle pulsewave velocity has also been independently associated with FRS.[36] Brachial–ankle pulsewave velocity increases with age, hypertension, diabetes, metabolic syndrome, and CKD.[20] Previous studies that examined the association between the USD and arterial stiffness have been limited. A recent case–control study of 42 subjects with recurrent idiopathic calcium oxalate stones and 42 matched subjects without stones revealed that abnormal arterial stiffness (measured by carotid-radial and carotid-femoral pulsewave velocity) was more common among subjects with USD compared with those who did not form stones (36% vs. 12%; *P* = 0.01). The difference remained significant even after adjustment for potential confounders, which suggested that abnormal arterial stiffness might partially explain the higher CVD risk in those who form calcium stones.[37]

Another previous study showed an interactive relationship between arterial stiffness and PAD, which has been considered as the "end stage disease of arterial stiffening."[38] The prevalence of PAD in subjects with USD has only been described in a cohort study of 3,195,452 individuals aged older than 17 years registered in the Universal Healthcare System in Alberta, Canada.[4] Baseline data from that study showed that the prevalence of PAD in individuals with USD was significantly higher than in those without USD, both in the primary cohort (1.6% vs. 0.7%; *P* < 0.001) and in a subset of participants with serum creatinine (2.5% vs. 1.3%; *P* < 0.001).[4]

There were several plausible explanations for the mechanisms linking USD and increased CVD risk, including shared pathogenesis, shared risk factors, and shared genetic predispositions. Epidemiological studies provided evidence that individuals who formed urinary stones tended to have a higher prevalence of concomitant diseases (e.g., hypertension, diabetes, metabolic syndrome, and CKD) compared with those who did not form stones,[8,11,15,39] and these comorbidities not only might lead to stone disease but could also be triggered by it. Shared biological pathways might lead to vascular calcification and development of kidney stones through ectopic calcification. A recently published study[40] found that recurrent kidney stone

formation was associated with moderate or severe coronary artery calcification (CAC); moreover, the association demonstrated a stronger link with CAC severity than with CAC presence. Current theory about the formation of Randall's plaques at the tip of renal papillae indicates that the pathology is similar to the formation of calcified plaques in arteries and capillaries.[34] Further studies are needed to elucidate the exact mechanisms that link stone formation with vascular atherosclerosis.

Our study had several limitations. First, the diagnosis of PAD was based on the ABI criteria used to screen for PAD; however, we did not collect information about symptoms such as claudication or confirm PAD by angiography. Second, there was a high prevalence of hypertension (70.7%) in our population, whose mean age was 55.4 ± 10.0 years. According to a national survey (2009–2010), the prevalence of hypertension in individuals aged 45 to 59 and 60 years or older in the north of China was also very high (47.9% and 60.1%, respectively).[41] The higher prevalence of hypertension in this district might be due to high salt intake. Finally, because this was a cross-sectional study, we could not conclude whether a potential causal relationship existed between USD and CVD risk factors, which will require prospective studies to determine.

In conclusion, in the present study of >10,000 participants from rural China, we found that USD was associated with a higher prevalence of traditional CVD risk factors, such as hypertension, albuminuria, and CKD. Furthermore, USD was associated with a higher prevalence of nontraditional CVD risk factors, such as increased arterial stiffness and low ABI, which are indicators of PAD. Individuals with USD in China may be at higher risk of CVD events than individuals without USD. Additional studies to understand the biological link between USD and CVD are warranted.

DISCLOSURE

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

Table S1. Sex-specific associations of urinary stone disease with risk factors of cardiovascular disease.
Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Scales CD Jr., Smith AC, Hanley JM, et al. Prevalence of kidney stones in the United States. *Eur Urol*. 2012;62: 160–165.

2. Shoag J, Tasian GE, Goldfarb DS, et al. The new epidemiology of nephrolithiasis. *Adv Chronic Kidney Dis*. 2015;22: 273–278.

3. 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.

4. Alexander RT, Hemmelgarn BR, Wiebe N, et al. Kidney stones and cardiovascular events: a cohort study. *Clin J Am Soc Nephrol*. 2014;9:506–512.

5. Ferraro PM, Taylor EN, Eisner BH, et al. History of kidney stones and the risk of coronary heart disease. *JAMA*. 2013;310:408–415.

6. Cheungpasitporn W, Mao M, O'Corragain O, et al. The risk of coronary heart disease in patients with kidney stones: a systematic review and meta-analysis. *N Am J Med Sci*. 2014;6:580–585.

7. Lin SY, Lin CL, Chang YJ, et al. Association between kidney stones and risk of stroke: a nationwide population-based cohort study. *Medicine (Baltimore)*. 2016;95:e2847.

8. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int*. 2005;68:1230–1235.

9. Domingos F, Serra A. Nephrolithiasis is associated with an increased prevalence of cardiovascular disease. *Nephrol Dial Transplant*. 2010;26:864–868.

10. Soucie JM, Coates RJ, McClellan W, et al. Relation between geographic variability in kidney stones prevalence and risk factors for stones. *Am J Epidemiol*. 1996;143: 487–495.

11. Madore F, Stampfer MJ, Rimm EB, et al. Nephrolithiasis and risk of hypertension. *Am J Hypertens*. 1998;11:46–53.

12. Pigna F, Sakhaee K, Adams-Huet B, et al. Body fat content and distribution and urinary risk factors for nephrolithiasis. *Clin J Am Soc Nephrol*. 2014;9:159–165.

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

14. Chen N, Wang W, Huang Y, et al. Community-based study on CKD subjects and the associated risk factors. *Nephrol Dial Transplant*. 2009;24:2117–2123.

15. Rule AD, Bergstralh EJ, Melton LJ 3rd, et al. Kidney stones and the risk for chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4:804–811.

16. Denburg MR, Leonard MB, Haynes K, et al. Risk of fracture in urolithiasis: a population-based cohort study using the health improvement network. *Clin J Am Soc Nephrol*. 2014;9: 2133–2140.

17. Taylor EN, Feskanich D, Paik JM, et al. Nephrolithiasis and risk of incident bone fracture. *J Urol*. 2016;195:1482–1486.

18. Zeng Q, He Y. Age-specific prevalence of kidney stones in Chinese urban inhabitants. *Urolithiasis*. 2013;41:91–93.

19. Zeng G, Mai Z, Xia S, et al. Prevalence of kidney stones in China: an ultrasonography based cross-sectional study. *BJU Int*. 2017;120:109–116.

20. Munakata M. Brachial-ankle pulse wave velocity in the measurement of arterial stiffness: recent evidence and clinical applications. *Curr Hypertens Rev*. 2014;10:49–57.

21. Agnelli G, Cimminiello C, Meneghetti G, et al. Low ankle-brachial index predicts an adverse 1-year outcome after acute coronary and cerebrovascular events. *J Thromb Haemost*. 2006;4:2599–2606.

22. Malyar NM, Freisinger E, Meyborg M, et al. Low rates of revascularization and high in-hospital mortality in patients with ischemic lower limb amputation: morbidity and mortality of ischemic amputation. *Angiology*. 2016;67:860–869.

23. Cai J, Fan X, Mou L, et al. Association of reduced renal function with hepatitis B virus infection and elevated alanine aminotransferase. *Clin J Am Soc Nephrol*. 2012;7:1561–1566.

24. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39:S1–S266.

25. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.

26. Vlachopoulos C, Aznaouridis K, Terentes-Printzios D, et al. Prediction of cardiovascular events and all-cause mortality with brachial-ankle elasticity index: a systematic review and meta-analysis. *Hypertension*. 2012;60:556–562.

27. Takashima N, Turin TC, Matsui K, et al. The relationship of brachial-ankle pulse wave velocity to future cardiovascular disease events in the general Japanese population: the Takashima Study. *J Hum Hypertens*. 2014;28:323–327.

28. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.

29. D'Agostino RB Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.

30. Clayton DB, Pope JC. The increasing pediatric stone disease problem. *Ther Adv Urol*. 2011;3:3–12.

31. Scales CD Jr., Tasian GE, Schwaderer AL, et al. Urinary stone disease: advancing knowledge, patient care, and population health. *Clin J Am Soc Nephrol*. 2016;11:1305–1312.

32. Madore F, Stampfer MJ, Willett WC, et al. Nephrolithiasis and risk of hypertension in women. *Am J Kidney Dis*. 1998;32:802–807.

33. Kummer AE, Grams M, Lutsey P, et al. Nephrolithiasis as a risk factor for CKD: The Atherosclerosis Risk in Communities Study. *Clin J Am Soc Nephrol*. 2015;10:2023–2029.

34. 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.

35. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008;300:197–208.

36. Yamashina A, Tomiyama H, Arai T, et al. Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. *Hypertens Res*. 2003;26:615–622.

37. Fabris A, Ferraro PM, Comellato G, et al. The relationship between calcium kidney stones, arterial stiffness and bone density: unraveling the stone-bone-vessel liaison. *J Nephrol*. 2015;28:549–555.

38. Husmann M, Jacomella V, Thalhammer C, et al. Markers of arterial stiffness in peripheral arterial disease. *Vasa*. 2015;44:341–348.

39. Rendina D, De Filippo G, D'Elia L, et al. Metabolic syndrome and nephrolithiasis: a systematic review and meta-analysis of the scientific evidence. *J Nephrol*. 2014;27:371–376.

40. Hsi RS, Spieker AJ, Stoller ML, et al. Coronary artery calcium score and association with recurrent nephrolithiasis: the Multi-Ethnic Study of Atherosclerosis. *J Urol*. 2016;195:971–976.

41. Yongqing Z, Ming W, Jian S, et al. Prevalence, awareness, treatment and control of hypertension and sodium intake in Jiangsu Province, China: a baseline study in 2014. *BMC Public Health*. 2016;16:56.