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Kidney stone and risk of cardiovascular diseases: a cross-sectional study in the southeast of Iran

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Abstract

Background Since the prevalence of kidney stones and cardiovascular diseases (CVD) is increasing globally and also in Iran, it is vital to assess the associations between both disorders. The current study aimed to investigate the association between kidney stones and the risk of CVD.

Methods This study was cross-sectional in design, which used the data of the Rafsanjan cohort study (RCS), a population-based Prospective epidemiological research study in Iran (PERSIAN) that recruited 10,000 participants of both genders aged 35–70 years from four urban and suburban areas of Rafsanjan. Demographic factors, medical history, personal habits, biochemical parameters including Fasting blood sugar (FBS), glomerular filtration rate (GFR), creatine (Cr), Blood urea nitrogen (BUN), urine specific gravity (USG), and lipids of the participants were collected according to standard protocols.

Results The results showed that the risk of CVD was higher in men (51.02%) than in women (48.98%). Also, the results showed the highest risk of CVD development for age ≥ 56 years old. The results were presented in about 31% of patients with kidney stones, 19.5% of patients with abnormal urine tests, 9.84% with Proteinuria, more than 33% with abnormal USG, and more than 94% of patients with abnormal GFR had CVD. The odds of CVD were increased in patients with kidney stones (22%), female (25%), and age ≥ 56 years old (24%).

Conclusions There was a high prevalence of kidney stones and CVD risk factors, such as gender, age, and kidney stones that increased the risk of cardiovascular disease.

Keywords Kidney stone, Cardiovascular diseases, Rafsanjan cohort study (RCS), GFR, Prospective epidemiological research studies in Iran (PERSIAN)

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Introduction

As a common urological disease, kidney stones are becoming a significant clinical and financial burden worldwide [1]. There are many risk factors leading to kidney stone such as obesity, diabetes mellitus, metabolic syndrome and atrial hypertension [2–4]. In addition, demographic characteristics such as sex, race, occupation, habits (smoking, opioid and alcohol consumption), physical activity and sedimentary life style can be associated with increased incidence of kidney stones [5]. Various types of kidney stones are classified based on the stones' material, although more than 80% of kidney stones are related to calcium oxalate and phosphate, either alone or combined [6]. Increasingly evident in recent epidemiological studies have linked the disturbance of kidney stones with cardiovascular diseases (CVD) [7–10]. Hypocitraturia as one of the most common finding in kidney stone could be led to cardiovascular diseases [11]. There is strong evidence of an association between CVD, coronary artery disease (CAD) and the presence of albuminuria in urinary stone disease [12]. Although the relation between glomerular filtration rate (GFR) levels, as a major factor in measuring the kidney function, and CVD in kidney stones are controversial, some studies have reported a decrease of GFR in CVD [10, 12, 13]. In addition, proteinuria has been introduced an independent risk factor for renal disease as well as for CVD [14, 15]. Hematuria as a considerable issue in renal injuries, has been showed a significantly risk factor of cardiovascular death particularly in men [16]. Studies that included gender-based analyses showed that the relationship between kidney stones and CAD is significant for both men and women, but this connection is 1.20 times stronger for women [17]. However, lower urinary excretion of citrate aggregates the calcium-oxalate crystals and activates uric acid supersaturating following lithogenesis which can cause abdominal aortic calcification [18]. Furthermore, magnesium can increase the possibility of kidney stone disease through the development of calcium-oxalate stones and coronary artery calcification lead to cardiovascular disease and mortality [19]. Another critical risk factor involved in the growth of kidney stones and also in cardiovascular disease pathology is inflammation and oxidative stress [20]. According to an updated National Health and Nutrition Examination Survey (NHANES), overall prevalence of kidney stones in 2014 was estimated about 10.1% [21]. Epidemiological studies in southern Iran have reported a prevalence of kidney stone in the adult population about 21.11% [22]. Since the prevalence of urinary stones and CVDs are increasing globally and also in Iran, it is vital to assess the associations between both disorders. In this regard, the current study aimed to investigate the association between kidney stones and risk of cardiovascular diseases.

Methods

The study design and population

This study was cross-sectional in design, which used the data of the Rafsanjan cohort study (RCS), which is a part of the large Prospective Epidemiological Studies in Iran (PERSIAN) [23]. Detailed protocol of the RCS was reported previously [24]. In summary, the RCS was started in 2015 with the aim of investigating the factors predicting chronic non-communicable diseases in Rafsanjan located in the southeast of Iran. Adult RCS is a population-based prospective cohort that recruited a total of 10,000 participants of both genders aged 35–70 years from four urban and suburban areas of Rafsanjan. Individuals were randomly selected by systematic clustering based on household number. About 9991 people (67.42% participation rate) were enrolled in the study. Informed consent was obtained from all participants in the RCS. For present study, after excluding58 subjects due to incomplete data on CVD history, a total of 9933subjects finally included in the study. The questionnaires used in this study were developed for RCS and have previously been published in other papers [25]. The Ethics Committee of Rafsanjan University of medical sciences, Rafsanjan, Iran approved the protocol of the study (code: IR.RUMS.REC.1402.033).

Data collection

Demographic factors, medical history, and personal habits of the participants in the study were collected by trained interviewers and physicians during face-to-face interviews using the validated questionnaires by the PERSIAN Cohort Study [23]. Also, blood and urine samples were collected according to standard protocols.

The used information in the present study included demographic characteristics (age, gender, education, wealth score index (WSI), physical activity, Body Mass Index (BMI), medical history such as diabetes, hypertension, CVD, kidney stone, urinary problems, biochemical parameters including Fasting blood sugar (FBS), glomerular filtration rate (GFR), and lipids, and personal habits including smoking, consumption of alcohol, and opium [24].

WSI was measured using the method of Principal Component Analysis (PCA). This index is based on variables related to assets of participants. Then, the participants were categorized to low, low-middle, middle-high and high groups based on 25th, 50th, and 90th percentiles.

Also, physical activity was measured by the International Physical Activity Questionnaire (IPAQ) and expressed as metabolic equivalent hour per day (MET. h/day).Accordingly, the participants were classified in to three categories based on the 25th and 75th percentiles: low (MET ≤ 35.29), moderate (35.30-40.32), and heavy (MET ≥ 40.32).

History of CVD was positive if the disease was previously diagnosed by a physician. The answer was yes or no. CVD history included coronary heart disease or myocardial infarction or stroke. Hypertensin was defined as SBP_140 mmHg or more, or DBP_90 mmHg or more, or taking antihypertensive drugs [26]. Diabetes was described as: FBG ≥ 126 mg/dL or receiving the antidiabetic drugs [27]. According to the Third Report of the National Cholesterol Education Program (NCEP-Adult Treatment Panel III), dyslipidemia was defined as LDL ≥ 130 mg/ dL, or TC ≥ 200 mg/dL, or HDL ≤ 40 mg/ dL in men, and 50 mg/dl in women or TG ≥ 150 mg/dL and or using lipid-lowering medications [28].

Data on the personal habits (cigarette smoking, opium use, and alcohol consumption) was self-reported. Subjects who consumed beer about 200 ml or liquor about 45 ml, once a week for at least six months during their lifetime were defined as alcohol drinkers [23]. Subjects who consumed opium, once a week for at least six months during their lifetime were defined as opium users [29].

Biochemical measurements

FBS, lipid parameters (total cholesterol (TC), low-density lipoprotein cholesterol (LDL cholesterol), high-density lipoprotein cholesterol (HDL cholesterol), and triglycerides (TG), Blood urea nitrogen (BUN) and creatine (Cr) were measured by a biotechnical analyzer (BT 1500, Italy) at the Central Laboratory in the cohort center.

Outcome assessment

The history of kidney stone disease was based on the self-declaration of the participants [25]. Also, the medical documents (such as ultrasound, documents related to surgery) were checked using the cohort team. GFR was determined by MDRD formula:

GFR (ml/min/1.73 m2) = 186 × Cr (mg/dl)-1.154 × age-0.203 × 0.742 (if woman).

GFR was classified as normal (GFR ≥ 90), mild (GFR 60–89), moderate (GFR 45–59) and severe (GFR < 45). This classification was derived from the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Working Group [30].

Abnormal urine test was asked using this question: Having ever had an abnormal urine test (Including a urinalysis positive for RBC, WBC, blood, and etc. or positive urine culture). Hematuria was considered as the presence of RBC ≥ 3 in urine [31]. Proteinuria was considered the presence of protein ≥ 1 + in the urine [31]. The Urine specific gravity (USG) level was divided into three categories: <1.008 g/ml, 1.008–1.020 g/ml and > 1.020 g/ml. Serum Cr and BUN levels higher than 1.4 mg/dl and 23 mg/dl were considered as elevated Cr and BUN, respectively according to the laboratory's reference range in the Cohort center.

Statistical analyses

Characteristics of participants were expressed as either the mean ± standard deviation or median and interquartile ranges (IQR) as appropriate for continuous variables and frequency (%) for categorical variables and baseline characteristics were compared across the groups of our study (CVD/non-CVD) using chi-square (χ^2) for categorical variables and t-test for normally distributed quantitative variables and Mann–Whitney U test for no normally distributed quantitative variables. The assumption of normality of the distribution of continuous variables between two groups of CVD and non CVD was tested using normal probability plots (skewness and kurtosis index).

In addition, we used bivariate (Crude) and multiple logistic regression analysis to assess the association between CVD with kidney stone, genders and age categories as dependent and in-depended variables, respectively. Crude and three adjusted models were used in the regression analysis. Based on subject matter knowledge and epidemiological research we identified Confounder's variables. Potential confounding variables were sequentially entered into models according to their hypothesized strengths of association with kidney stone and CVD. Then, variables with a p-value < 0.05 were selected as confounders. The baseline model (crude model) has been stratified on CVD.

Adjusted model 1 included basic sociodemographic characteristics (age, gender, education, WSI). Adjusted model 2 adjusted for cigarette smoking, alcohol consumption, opium consumption, physical activity level, first-degree family history of CVD, and BMI. The adjusted model 3 is adjusted for confounding variables in adjusted model 1, 2 and Diabetes, Hypertension, LDL, TG, and HDL. The adjusted model 4 is adjusted for confounding variables in adjusted model 1, 2, 3 and GFR, Hematuria, Proteinuria, BUN and SG. In multivariable logistic regression models, the multi-collinearity of the variables was examined using the option of collinear in Stata. However, we again checked the correlation between the independent variables. The findings indicated that there is no high correlation between the independent variables.

Results

This study included 9933 participants, 4624 men (46.55%) and 5310 women (53.45%) with the mean age of 49.94 ± 9.56 years. The details of the demographic characteristics, Physical activity, habits, distribution of risk factors by CVD and no CVD have presented in Table 1.

Table 1 Baseline characteristics of 9933 subjects stratified by Baseline Cardiovascular Disease (CVD) status

characteristic	Total	CVD	No-CVD	*P*-Value
	(*n* = 9933)	(*n* = 1031)	(*n* = 8902)	
Age- yr. n (%)				< 0.001
35–45	3697(37.22)	80(7.76)	3617(40.63)	
46–55	3060(30.81)	263(25.51)	2797(31.42)	
≥ 56	3176(31.97)	688(66.73)	2488(27.95)	
Mean ± SD	49.94 ± 9.56	57.79 ± 7.64	49.03 ± 9.35	< 0.001
Gender- n (%)				0.002
Male	4624(46.55)	526(51.02)	4098(46.03)	
Female	5310(53.45)	505(48.98)	4805(53.97)	
Education-n (%)				< 0.001
≤ 5 years	3484(35.09)	529(51.36)	2955(33.21)	
6–12 years	4820(48.54)	394(38.25)	4426(49.74)	
≥ 13 years	1625(16.37)	107(10.39)	1518(17.06)	
Median (IQR)	9(5–12)	5(2–12)	9(5–12)	< 0.001
Physical activity (%)				< 0.001
Low	2541(25.58)	393(38.12)	2148(24.13)	
Moderate	4908(49.41)	450(43.65)	4458(50.07)	
Heavy	2485(25.02)	188(18.23)	2297(25.80)	
Median (IQR)	37.63(35.2-40.33)	36.08(34.08–39.28)	37.78(35.4-40.47)	< 0.001
WSI- n (%)				< 0.001
Low	2335(23.53)	282(27.38)	2053(23.08)	
Low-middle	2850(28.72)	339(32.91)	2511(28.23)	
Middle-high	3975(40.05)	357(34.66)	3618(40.67)	
High	765(7.71)	52(5.05)	713(8.02)	
Mean ± SD	-0.002 ± 1.00	-0.188 ± 0.994	0.019 ± 0.999	< 0.001
BMI- n (%)				0.050
< 25	2868(28.89)	275(26.67)	2593(29.14)	
25-29.99	4070(41)	413(40.06)	3657(41.10)	
≥ 30	2990(30.12)	343(33.27)	2647(29.75)	
Median (IQR)	27.48(24.54–30.78)	27.92(24.75–31.23)	27.44(24.52–30.72)	0.016
Alcohol consumption- n (%)				0.918
No	8921(89.98)	925(89.89)	7996(89.99)	
Yes	993(10.02)	104(10.11)	889(10.01)	
Cigarette smoking- n (%)				< 0.001
Never	7371(74.35)	688(66.86)	6683(75.22)	
Current	1679(16.94)	187(18.17)	1492(16.79)	
Former	864(8.71)	154(14.97)	710(7.99)	
Opium consumption- n (%)				< 0.001
No	7569(76.35)	671(65.21)	6898(77.64)	
yes	2345(23.65)	358(34.79)	1987(22.36)	
Hypertension- n (%)				< 0.001
No	7438(74.90)	499(48.45)	6939(77.97)	
yes	2492(25.10)	531(51.55)	1961(22.03)	
Diabetes- n (%)				< 0.001
No	7612(76.93)	570(55.50)	7042(79.41)	
yes	2283(23.07)	457(44.50)	1826(20.59)	
Dyslipidemia- n (%)				< 0.001
No	2635(26.66)	134(13.07)	2501(28.23)	
Yes	7248(73.34)	891(86.93)	6357(71.77)	
Kidney stone- n (%)				< 0.001
No	7541(75.91)	712(69.06)	6829(76.70)	
yes	2393(24.09)	319(30.94)	2074(23.30)	
First-degree family history of cardiac ischemic				< 0.001

Table 1 (continued)

characteristic	Total	CVD	No-CVD	*P*-Value
	(*n* = 9933)	(*n* = 1031)	(*n* = 8902)	
No	6458(65.01)	593(57.52)	5865(65.87)	
yes	3476(34.99)	438(42.48)	3038(34.12)	
Abnormal urine test- n (%)				0.047
No	8217(82.72)	830(80.50)	7387(82.97)	
yes	1717(17.28)	201(19.50)	1516(17.03)	
Proteinuria- n (%)				< 0.001
No	9406(95.09)	925(90.16)	8481(95.66)	
yes	486(4.91)	101(9.84)	385(4.34)	
Hematuria- n (%)				0.442
No	9719(98.25)	1005(97.95)	8714(98.29)	
yes	173(1.75)	21(2.05)	152(1.71)	
Urine specific gravity- n (%)				< 0.001
< 1.008 g/ml	305(3.08)	26(2.53)	279(3.15)	
1.008–1.020 g/ml	5596(56.57)	685(66.76)	4911(55.39)	
> 1.020 g/ml	3991(40.35)	315(30.70)	3676(41.46)	
GFR- n (%)				< 0.001
Normal	625(6.32)	54(5.26)	571(6.44)	
Mild	7695(77.78)	673(65.59)	7022(79.19)	
Moderate	1427(14.42)	245(23.88)	1182(13.33)	
Sever	146(1.48)	54(5.26)	92(1.04)	
Mean ± SD	71.28 ± 12.24	66.47 ± 13.62	71.84 ± 11.95	< 0.001
BUN- n (%)				< 0.001
Normal	9753(98.58)	983(95.81)	8770(98.91)	
Elevated	140(1.42)	43(4.19)	97(1.09)	
Cr- n (%)				< 0.001
Normal	9670(97.75)	963(93.86)	8707(98.20)	
Elevated	223(2.25)	63(6.14)	160(1.80)	
Cholesterol				< 0.001
Mean ± SD	198.66 ± 38.04	185.12 ± 44.83	200.23 ± 36.86	
Triglyceride				0.180
Median (IQR)	145(106–199)	144(111–200)	145(105–199)	
HDL				< 0.001
Mean ± SD	57.74 ± 10.87	55.22 ± 11.11	58.04 ± 10.80	
LDL				< 0.001
Mean ± SD	108.17 ± 30.28	96.88 ± 36.02	109.48 ± 29.27	
Fasting blood sugar (FBS)				< 0.001
Median (IQR)	101(94–113)	110(99–137)	101(94–111)	

Abbreviations: Cardiovascular disease (CVD); Glomerular Filtration Rate (GFR); High-density lipoprotein (HDL); Low-density lipoprotein (LDL); Blood urea nitrogen (BUN); Creatinine (Cr), Wealth Score Index (WSI), Interquartile ranges (IQR).

The results showed that the mean age of CVD group was significantly higher than no-CVD group ($P < 0.001$). Also, results presented that the prevalence of CVD was significantly higher in males (51.02%), education ≤ 5 years (51.36%), moderate physical activity (43.65%) and Middle to high WSI (34.66%) groups compared to control groups. In addition, we compared the distribution of lifestyle related variables, as well as, cigarette smoking, alcohol and opium consumption between the two groups. There were no significant differences in alcohol consumption between the groups ($P = 0.918$). While a significant difference was observed in the consumption of cigarettes and opium between the two groups, and prevalence of cigarette smoking and opium consumption was higher in the CVD group than no-CVD group ($P < 0.001$).

Among CVD group, 531 patients were hypertensive (51.55%), 457 patients had diabetes mellitus (44.50%), 891 patients had dyslipidemia (86.93%), 319 patients had kidney stone (30.94%), 438 patients had first-degree family history of cardiac ischemic (42.48%), 201 patients had abnormal urine test (19.50%), and 101 patients had Proteinuria (9.84%), and compared with the control group (no-CVD), there were significant differences ($P < 0.001$). In addition, the USG, GFR, BUN, Cr, cholesterol, HDL,

Table 2 The kidney stone and odds ratio of Cardiovascular disease (CVD).

CVD	Crude Model	Adjusted Model 1	Adjusted Model 2	Adjusted Model 3	Adjusted Model 4
Total population by Kidney stone					
No	1	1	1	1	1
Yes	1.47(1.28–1.69)*	1.32(1.14–1.53)*	1.32(1.14–1.54)*	1.23(1.05–1.43)*	1.22(1.05–1.43)*
Male by Kidney stone					
No	1	1	1	1	1
Yes	1.37(1.13–1.66)*	1.29(1.05–1.58)*	1.32(1.07–1.63)*	1.21(0.97–1.50)	1.19(0.96–1.48)
Female by Kidney stone					
No	1	1	1	1	1
Yes	1.55(1.26–1.91)*	1.35(1.08–1.67)*	1.32(1.06–1.64)*	1.25(1.01–1.56)*	1.25(1.01–1.56)*
Age groups by Kidney stone					
No	1	1	1	1	1
35–45	1.39(0.85–2.29)	1.33(0.81–2.20)	1.31(0.79–2.17)	1.15(0.69–1.93)	1.15(0.68–1.92)
46–55	1.43(1.09–1.89)*	1.38(1.05–1.83)*	1.41(1.06–1.87)*	1.27(0.95–1.70)	1.25(0.93–1.67)
≥ 56	1.33(1.11–1.60)*	1.29(1.07–1.56)*	1.32(1.09–1.60)*	1.27(1.04–1.54)*	1.24(1.02–1.51)*

The crude model is stratified on the status of CVD.

The adjusted model 1 is adjusted for confounding variables Age (continuous variable), Gender (male/ female), Education (continuous variable), WSI (continuous variable).

The adjusted model 2 is adjusted for confounding variables in adjusted model 1 and cigarette smoking (never, current, former), alcohol consumption (yes/no), opium consumption (yes/no), physical activity level (continuous variable), first-degree family history of CVD (yes/no), and BMI (continuous variable).

The adjusted model 3 is adjusted for confounding variables in adjusted model 1, 2 and diabetes (yes/ no), hypertension (yes/no), and dyslipidemia (yes/no).

The adjusted model 4 is adjusted for confounding variables in adjusted model 1, 2, 3 and GFR (continuous variable), Hematuria (yes/no), Proteinuria (yes/no), BUN (continuous variable) and USG (continuous variable).

* Significant odds ratios, $P < 0.05$.

Abbreviations: CVD: Cardiovascular disease.

LDL and FBS showed a significant difference between two groups ($P < 0.001$) (Table 1).

Table 2 represents the association of kidney stone and CVD, using the unadjusted and four adjusted model.

In the crude regression model, the odds of CVD significantly increased in participants who had kidney stone (OR: 1.47; 95% CI 1.28 to 1.69), in male (OR: 1.37; 95% CI 1.13 to 1.69), in female (OR: 1.55; 95% CI 1.26 to 1.91), age 46–55 years old (OR: 1.43; 95% CI 1.09 to 1.89), and age ≥ 56 years old (OR: 1.33; 95% CI 1.11 to 1.60), compared with the normal subjects.

Additionally, after adjusting for confounders (age, gender, education and WSI) in model 1, the obtained results showed that kidney stone about 32%, in male about 29%, in female about 35%, age 46–55 years old about 38% and age ≥ 56 years old about 29% increased odds of CVD.

Adjusted model 2 included all variables considered in adjusted model 1, plus cigarette smoking, alcohol and opium consumption, physical activity, first-degree family history of CVD, and BMI. In model 2, the results showed that this relationship remained significant and the factors of kidney stone about 32%, in male about 32%, in female about 32%, age 46–55 years old about 41%, and age ≥ 56 years old about 32%, increased the odds of CVD.

Adjusted model 3 included all variables considered in adjusted model 1 and 2, plus diabetes, hypertension, and dyslipidemia. In model 3, the results showed that this relationship remained significant and the factors of kidney stone about 23%, in female about 25%, and age ≥ 56 years old about 27%, increased the odds of CVD.

Finally, adjusted model 4 included all variables considered in adjusted model 1, 2, and 3 plus GFR, Hematuria, Proteinuria, BUN and USG. However, after adjusting for all variables, this association remained stable in population with kidney stone (OR: 1.22; 95% CI 1.05 to 1.43), in female (OR: 1.25; 95% CI 1.01 to 1.56), and age ≥ 56 years old (OR: 1.24; 95% CI 1.02 to 1.51), although it decreased slightly.

Discussion

According to the obtained results, significant differences were observed when comparing the CVD and the no-CVD groups based on some demographic variables. The results showed that the risk of CVD was higher in men (51.02%) than in women (48.98%). Also, our results showed the highest risk of CVD development for age ≥ 56 years old. The results were presented about 31% of patients with kidney stones, 19.5% of patients with abnormal urine tests, 9.84% of patients with Proteinuria, more than 33% of patients with abnormal USG and more than 94% of patients with abnormal GFR had CVD. The risk of CVD was increased in patients with kidney stones about 22%, in female about 25%, and age ≥ 56 years old about 24%.

Aune in 2018 showed that there was a significant variation in the prevalence of kidney stones in Asia ranging from 1 to 5% to 7–15% in North America [32]. Prevalence

of kidney stones in southeast of Iran was 24.08% (Rafsanjan) and 21.11% (Kharameh) and it was higher in men than women [25, 33]. Other studies also showed that the prevalence of kidney stones is increasing in Iran [34].

Xiaohong Fan et al. in 2017 showed that in some regions of China, urinary stone disease was associated with a high prevalence of CVD risk factors, increased arterial stiffness, and peripheral arterial disease [12]. The result of this study is in line with our study, and the results show that kidney stones increase the risk of CVD. Stone formation risk factors including age, high blood pressure, diabetes, proteinuria, abnormal GFR, were significantly higher in CVD group, which can suggest that the same risk factors that play a role in cardiovascular diseases are also effective in the formation of urinary stones.

A recent review study found that kidney stones are linked to various types of cardiovascular diseases, including CAD and strokes, independently of common risk factors. This study indicated that there might be abnormal calcification pathways and damage-inflammatory responses that serve as shared mechanisms leading to vascular calcification and/or stone formation, even when common risk factors are present. Their study's findings showed that risk factors for kidney stone formation are also involved in the development of cardiovascular diseases, and as a result, individuals with kidney stones are more likely to develop cardiovascular disease [17]. They also showed that the relationship between kidney stones and CAD for women was 1.20 times greater than for men [17]. Our study's results also confirm these findings, showing that having kidney stones increases the odds of CVD by 1.22 times, and this risk is significantly higher in women compared to men.

A study by Yuanyuan Zhao conducted in 2021 confirmed that kidney stones may lead to pathological processes that include coronary atherosclerosis and cardiomyopathy. Additionally, high blood pressure was identified as a risk factor that affects both kidney stones and cardiovascular disease [35]. High blood pressure in the group of cardiovascular diseases with kidney stones has been reported in different studies [36, 37]. In our study, it was also shown that more than 50% of people with high blood pressure are in the group of cardiovascular diseases, and more than 30% of them had kidney stones.

A meta-analysis study in 2021 showed that patients with kidney stones may be at risk of stroke, especially the likelihood of ischemic strokes increasing [38]. Our results also indicated that the odds of CVD, which includes strokes and chronic heart disease, increased in individuals with kidney stones.

It seems that the risk factors initially cause the stone formation and cardiovascular diseases, but if primary kidney involvement occurs, it can probably cause heart involvement by intensifying the risk factors of the heart secondarily, also primary heart disease can be caused by disruption of the blood supply system of the kidneys. It causes or aggravates kidney diseases, including stones, which can happen under different conditions in each of these scenarios, and the investigation of each of the proposed scenarios can be done in future studies.

The strength of the present study is that the subjects were participants in a large nationwide screening program. The large sample size in this study was 10,000 people, which is a part of the large Persian cohort study. They were evaluated based on the same clinical and laboratory tests and the same questionnaire about the variables related to lifestyle. Our study had several limitations. First, the diagnosis of CVD and kidney stones was based on self-report previously confirmed by a physician. Also, the type of kidney stone is not specified. Because this was a cross-sectional study, we could not conclude whether there was a potential causal relationship between kidney stones and CVD risk factors, which will require prospective studies and will be investigated in the follow-up phase of the cohort study.

Conclusion

In conclusion, in this study with over 9,990 urban and rural participants in Rafsanjan, a city in southern Iran, we found that the prevalence of CVD is high, and risk factors for cardiovascular diseases, such as kidney stones, gender, and age, increase the likelihood of developing cardiovascular diseases. Additional studies are necessary to understand the biological relationship between CVD and kidney stones.

Abbreviations

CVD	Cardiovascular diseases
USG	Urine specific gravity
CAD	Coronary artery disease
RCS	Rafsanjan cohort study
PERSIAN	Prospective epidemiological research studies in Iran
FBS	Fasting blood sugar
GFR	Glomerular filtration rate
Cr	Creatine
BUN	Blood urea nitrogen
TC	Total cholesterol
LDL	Low-density lipoprotein cholesterol
HDL	High-density lipoprotein cholesterol
TG	Triglycerides
BMI	Body Mass Index
WSI	Wealth score index
NHANES	National Health and Nutrition Examination Survey
PCA	Principal Component Analysis
IPAQ	International Physical Activity Questionnaire
MET. H/day	Metabolic equivalent hour per day
KDIGO	Kidney Disease: Improving Global Outcomes
SD	Standard deviation and interquartile ranges (IQR)

Supplementary Information

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Supplementary Material 1

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Author contributions
F.A., Z.J., and A.N. designed the study and supervised the project. N.S. collected the data. A.E. and M.K. prepared Tables 1 and 2, and 3. P.K. and R.V. performed the statistical analysis. F.A., Z.J., M.A., P.K., A.E., and A.N. wrote the main manuscript text. F.A. revised the paper. All authors reviewed the manuscript.

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Data availability
Sequence data that support the findings of this study have been deposited in the Persian Adult Cohort Study Center, Rafsanjan University of Medical Sciences, Iran. The data is not available publicly. However, the data can be obtained from the corresponding author upon a reasonable request by Email: ayoobi.fatemeh@gmail.com.

Declarations

Ethics approval and consent to participate
The Ethics Committee of Rafsanjan University of Medical Sciences approved this study (Code of Ethics: ID: IR.RUMETS.REC. 1402.033). Written informed consent was obtained from the participants. The data of participants was kept confidential and was only accessible to the study investigators. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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