



Relationship between renal calculi and the risk of myocardial infarction and stroke: results from the EPIC-Potsdam study

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Abstract

Background: Renal calculi are related to obesity and metabolic syndrome and may indicate an increased risk of cardiovascular disease, but data from prospective cohort studies are sparse. Therefore, the authors investigated the association between renal calculi and the risk of cardiovascular disease endpoints in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study.

Methods: The study population comprised 24,490 individuals aged mainly 35-65 years, who were free of cardiovascular diseases at recruitment (1994-1998). Information about the presence of renal calculi at baseline was ascertained via questionnaires. For all incident cases of myocardial infarction and stroke, confirmation was obtained from the attending physician. Hazard rate ratios (HR) were estimated using Cox proportional hazards regression.

Results: During a mean follow-up of 8.1 ± 1.6 years, 494 cases of cardiovascular disease were identified. Among persons with renal calculi ($n=2,645$), incidence rates were higher and selected cardiovascular risk factors were more common than among those without renal calculi. In multivariable adjusted models, no association between renal calculi and the risk of cardiovascular diseases (HR=1.05, 95% confidence interval (CI): 0.82-1.34) was observed. Endpoint specific analyses revealed similar results. In sub-analyses restricted to fatal endpoints, a more than twofold increased risk of fatal myocardial infarction was observed in persons with renal calculi, but this association did not reach statistical significance (HR=2.33, 95% CI: 0.88-6.13). The HR of fatal stroke was 1.24 (95% CI: 0.46-3.33) in persons with renal calculi compared to those without.

Conclusions: The authors observed a higher prevalence of cardiovascular risk factors in individuals with renal calculi but no independent relationship between the presence of renal calculi and the risk of myocardial infarction and stroke.

Keywords: Cardiovascular disease, nephrolithiasis, prospective, cohort study, kidney stone

Introduction

The prevalence of renal calculi is increasing worldwide [1], in particular in the Western World [2-5]. This increase is thought to relate to changes in lifestyle and diet [1,4]. Positive associations have been reported between renal calculi and several cardiovascular risk factors: obesity, diabetes, hypertension, metabolic syndrome, atherosclerosis, and chronic kidney disease have all been associated with the development of renal calculi [6-12]. These factors are also related to an increased risk of coronary heart disease (CHD) and/or stroke [13-18]. Thus, pathways that contribute to renal calculi formation, e.g., an increased urinary calcium excretion like in hypertension or obesity [19], may also play a role in the development of subclinical cardiovascular diseases (CVD) and the occurrence of myocardial infarction and stroke. Indeed, an increased risk of myocardial infarction has been observed in persons with renal calculi compared to matched controls [20]. Furthermore, in a recent investigation of three prospective

cohort studies [21], the authors reported an increased CHD risk in women but not men with renal calculi. These findings could have clinical implications as the occurrence of renal calculi may indicate an increased risk of future cardiovascular events and could prompt preventive measures. However, data on the association between renal calculi and myocardial infarction and stroke are sparse [20-23]. To shed more light on this issue the relationship between prevalent renal calculi and the risk of myocardial infarction and stroke was investigated in a large German population-based cohort.

Methods

Study population

The European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study is part of the large-scale Europe-wide cohort study EPIC and includes 27,548 individuals (16,644 women and 10,904 men). Participants were recruited between 1994 and 1998 from the general population with the preferred

ages 35 to 65 years in women and 40 to 65 years in men. The recruitment process was based on addresses from general population registries [24]. The baseline examination included standardized blood pressure measurements, anthropometric measurements, self-administered questionnaires on diet and lifestyle, computer-guided interviews including questions about prevalent diseases, and blood sampling. Blood was collected from 95% of participants at the Potsdam center. All participants gave their written informed consent and the Ethics Committee of the Federal State Brandenburg approved all study procedures. Information on incident diseases and changes in lifestyle was biennially assessed by self-administered questionnaires [25]. Response rates for all follow-up rounds so far have exceeded 90% at each occasion.

Since the question about prevalent renal calculi was first implemented in the questionnaire after recruitment has already started, the status of some participants was not provided. Consequently, together with individuals, who were not sure about the existence of renal calculi, 1,488 individuals were excluded from the analyses. Furthermore, 580 participants were not considered, because follow-up data was not available and 780 participants had prevalent CVD or verification of incident cases was not possible. Another 210 individuals were excluded as information on confounding factors was missing. Thereafter, 253 individuals with incident myocardial infarction and 249 individuals with incident stroke were identified. Of nine individuals, who suffered from both myocardial infarction and stroke, only the first event was considered, leaving altogether 494 incident CVD cases (251 myocardial infarctions, 196 ischemic strokes, 14 subarachnoid hemorrhagic strokes, 29 intracerebral strokes, and four undefined strokes).

For additional analyses including relevant biomarkers for inflammation and hyperlipidemia (high-sensitivity C-reactive protein (hsCRP), triglycerides and high density lipoprotein (HDL) cholesterol and total cholesterol), a prospective case-cohort design was used consisting of a random sub-cohort ($n=2,500$) of the EPIC-Potsdam study and all incident cases of myocardial infarction and stroke. After applying the same exclusion criteria as mentioned above, 2,414 participants remained for the case-cohort analysis. Of these, 2,068 individuals belonged to the sub-cohort (including 50 CVD cases and 2,018 non-cases).

Outcome ascertainment

In the present analysis only medically verified cases were considered for analyses. Potential cases of myocardial infarction or stroke were identified by self-report in one of the four follow-up questionnaires, by link to the hospital information system of the major hospital in the area and/or by death certificate. To increase sensitivity, the questionnaires included additional questions about typical stroke symptoms [26]. All potential cases were verified according to WHO MONICA criteria by contacting the patients' attending physician and by reviewing

medical records of the hospitals and the death certificates [27]. According to the International Statistical Classification of Disease and Related Health Problems 10th revision (ICD-10) cases were classified as incident myocardial infarction (ICD-10 I21), ischemic stroke (ICD-10 I63.0-I63.9), intracerebral (ICD-10 I61.0-I61.9) or subarachnoid hemorrhage (ICD-10 I60.0-I60.9), or undetermined stroke (ICD-10 I64.0-I64.9) by two physicians in the study center [28].

Assessment of exposure and covariates

Information about medical history, including the prevalence of renal calculi, was recorded by trained interviewers during a computer-guided interview. Participants were asked if they ever have been diagnosed with renal calculi and had the response options "yes", "no" or "don't know". Lifestyle characteristics including regular physical exercise and smoking history were documented at baseline by trained personnel during a computer-guided interview. Physical activity was defined as the mean time spent on leisure time physical activities during the summer and winter seasons (hours/week). Habitual alcohol intake during the last 12 months was assessed by a validated food frequency questionnaire [29] and categorized according to recommended upper intake limits (for women: one drink per day ($\triangleq 12g$ of alcohol) for men: two drinks per day ($\triangleq 24g$ of alcohol)) [30]. Anthropometric data and blood pressure were measured by trained and quality-monitored personnel [31]. Prevalent hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or self-reporting of a diagnosis or use of antihypertensive medication. The prevalence of diabetes at baseline was evaluated by a physician using information on self-reported medical diagnosis, medication records and dieting behavior. If any uncertainties occurred, the diagnosis was clarified by personal communication with the participant and/or treating physician. Dietary habits including alcohol consumption during the preceding year were assessed by a validated self-administered food frequency questionnaire [32]. Biomarker levels (hsCRP, total cholesterol, HDL cholesterol, uric acid, and triglycerides) were measured in all incident CVD cases and a random sub-cohort with the automatic ADVIA 1650 analyzer (Siemens Medical Solutions, Erlangen, Germany).

Statistical analysis

Statistical analysis was performed using SAS software package, release 9.2 (SAS Institute, Cary, NC). All tests were two-sided with $p < 0.05$ considered as statistically significant. Age and sex-adjusted baseline characteristics were compared between participants with and without renal calculi using analysis of covariance.

The association between the presence of renal calculi and the risk of CVD (including myocardial infarction and stroke) was examined by estimating sex-adjusted and multivariable-adjusted hazard rate ratios (HR) and 95% confidence intervals (CI) using Cox proportional hazards regression. Age was used as

the underlying time variable in the counting process with entry and exit time defined as the participants' age at recruitment and age at time of CVD diagnosis or censoring, respectively. The multivariable-adjusted models included age, sex, educational attainment (vocational school or less (reference), technical colleges, university as indicator variables), physical activity (<2 hour/week, ≥2hours/week), smoking status (never smoker (reference), past smoker, smoker <20 cigarettes/day, smoker ≥20 cigarettes/day as indicator variables), alcohol consumption (men: 0, >0 - ≤12 grams/day (reference), >12 - ≤24 grams/day, >24 grams/day, women: 0, >0 - ≤6 grams/day (reference), >6 - ≤12 grams/day, >12 grams/day as indicator variables), body mass index and waist circumference (continuously), prevalent diabetes, and hypertension (present/absent). A sub-analysis was performed restricted to fatal events.

In addition, analyses including hsCRP, uric acid, triglycerides, HDL and total cholesterol were performed in the case-cohort sample. HRs for myocardial infarction, stroke and overall CVD were calculated regarding the presence of renal calculi using a weighted Cox proportional hazards model, modified for the case-cohort design according to Prentice [33]. The validity of the proportional hazards assumption was explored by Kolmogorov-type supremum test and revealed no violation.

Results

Among 24,490 participants, 2,645 reported a previous diagnosis of renal calculi at baseline (Table 1). These persons were older and more likely to be male compared to individuals without calculi. After adjustment for age and sex, participants with renal calculi had a slightly higher body mass index and waist circumference, were less likely to be smokers and more often had a history of hypertension and diabetes than individuals without renal calculi. The presence of renal calculi was furthermore related to a lower intake of alcohol and a higher intake of water. Moreover, levels of uric acid were slightly higher in individuals with renal calculi (Table 1).

During a mean follow-up of 8.1±1.6 years, 494 CVD cases were identified among 24,490 participants (2,645 persons with and 21,845 without prevalent renal calculi). Table 2 depicts the estimated HRs of CVD according to the presence of renal calculi. Crude incidence rates of CVD were 2.34 per 1,000 person-years in non-exposed and 3.64 cases per 1,000 person-years in exposed participants. After adjustment for age, sex, smoking status, alcohol consumption, education, physical activity, and prevalent diseases, the status of renal calculi was not associated with developing CVD. This was true for both men and women (men: HR=1.12, 95% CI: 0.84-1.50, women: HR=0.91, 95% CI: 0.56-1.49). Further adjustment for dietary factors did not change the risk estimates (data not shown), and endpoint-specific analyses revealed similar results (Table 2). Furthermore, restricting stroke cases to ischemic ones did not alter the results (HR and 95% CI of ischemic strokes for persons with renal calculi compared to those without: 1.01 (0.68-1.50), p=0.97). An additional analysis based on the case-cohort study

Table 1. Baseline characteristics* of participants according to status of renal calculi in the EPIC-Potsdam Study.

Characteristics	Renal calculi		p value
	No (n=21,845)	Yes (n=2,645)	
Age [†] , yrs	49.8±9.0	53.8±8.4	<0.001
Sex [†] , % male	36.2	52.5	<0.001
Body mass index, kg/m ²	26.3±0.0	26.7±0.1	<0.001
Waist circumference, cm			
Men	94.7±0.1	95.4±0.3	0.01
Women	80.5±0.1	82.0±0.3	<0.001
Physical activity, h/wk	0.98±0.0	0.96±0.0	0.64
Smoking, %			
Never	47.7	49.2	--
Former	31.4	34.0	--
Current, <20 cig/day	15.1	12.5	--
Current, ≥20 cig/day	5.9	4.3	--
Educational attainment, %			
No or vocational training	38.4	37.1	--
Technical school	24.6	25.6	--
Technical college, university	37.0	37.3	--
Alcohol intake, g/day	16.0±0.1	14.3±0.3	<0.001
Medical History, %			
Prevalent hypertension	47.3	54.8	<0.001
Prevalent diabetes	4.8	5.9	0.01
Nutritional factors[‡]			
Water, ml/day	418±3.1	486±8.6	<0.001
Fruits and vegetables	191±0.8	195±2.3	0.07
Red meat, g/day	30.2±0.1	30.5±0.4	0.39
Processed meat, g/day	61.5±0.3	60.6±0.8	0.28
Fat, g/day	82.7±0.1	82.8±0.3	0.66
Cholesterol, mg/day	307±0.6	304±1.6	0.15
Biomarkers[§], mg/dl			
	No (n=1,852)	Yes (n=216)	p value
hsCRP	1.80±0.1	1.96±0.2	0.49
Triglycerides	130±2.1	134±5.8	0.59
Total cholesterol	191±1.0	197±2.8	0.04
HDL cholesterol	51.7±0.3	50.9±0.9	0.43
Uric acid	4.50±0.0	4.68±0.1	0.03

Abbreviations: cig.: cigarettes, EPIC: European Investigation into Cancer and Nutrition, HDL: high density lipoprotein, hsCRP: high-sensitivity C-reactive protein.

*Baseline characteristics of participants are expressed as age- and sex-adjusted means±standard error (SE) or percentages and were compared between participants with and without stones using analysis of covariance. Age and sex were not adjusted and are expressed as mean±standard deviation or percentage.

[†]Age and gender distribution were compared between participants with and without stones using Student's unpaired t test or the χ^2 test, respectively.

[‡]Nutritional intakes are expressed as means±SE, adjusted for age, sex and total energy intake.

[§]Based on a randomised subcohort of the EPIC-Potsdam study.

design, in which relevant biomarkers were included in the fully adjusted model, did not considerably change the risk estimates (HR=1.15, 95% CI: 0.85-1.57 for CVD, HR=1.18, 95% CI: 0.79-1.79 for myocardial infarction and HR=1.11, 95% CI: 0.73-1.67 for stroke). However, in sub-analyses restricted to fatal endpoints, a more than twofold increased risk for fatal myocardial infarction was observed in persons with renal calculi, although this association did not reach statistical significance (Table 2).

Table 2. Hazard rate ratios of cardiovascular diseases according to the presence of renal calculi in the EPIC-Potsdam study.

	Renal calculi			
	No (n=21,845)	Yes (n=2,645)		
Person-years	177,658	21,388	--	--
Cardiovascular diseases				
Cases n (%)	416 (1.90)	78 (2.95)	--	--
	HR	HR	95% CI	p value
Model 1 [†]	1	1.03	0.80, 1.31	0.83
Model 2 [†]	1	1.05	0.82, 1.34	0.73
Fatal CVD				
Cases n (%)	38 (0.18)	11 (0.43)	--	--
Model 1 [†]	1	1.70	0.86, 3.38	0.13
Model 2 [†]	1	1.66	0.83, 3.31	0.15
Myocardial infarction				
Cases n (%)	209 (0.96)	42 (1.59)	--	--
	HR	HR	95% CI	p value
Model 1 [†]	1	1.08	0.77, 1.51	0.66
Model 2 [†]	1	1.13	0.80, 1.58	0.49
Fatal myocardial infarction				
Cases n (%)	16 (0.07)	6 (0.23)	--	--
Model 1 [†]	1	2.32	0.89, 6.09	0.09
Model 2 [†]	1	2.33	0.88, 6.13	0.09
Stroke				
Cases n (%)	207 (0.95)	36 (1.36)	--	--
	HR	HR	95% CI	p value
Model 1 [†]	1	0.98	0.68, 1.40	0.90
Model 2 [†]	1	0.97	0.68, 1.39	0.86
Fatal stroke				
Cases n (%)	22 (0.10)	5 (0.19)	--	--
Model 1 [†]	1	1.28	0.47, 3.44	0.63
Model 2 [†]	1	1.24	0.46, 3.33	0.68

Abbreviations: CI: confidence interval, EPIC: European Investigation into Cancer and Nutrition, HR: hazard rate ratio
[†]Adjusted for age and sex.

[†]Like model 1, further adjusted for education (vocational training or less(reference), technical school, university degree), physical activity (continuous in hours/week), smoking (never (reference), past, current <20 cigarettes/d, current ≥20 cigarettes/d), alcohol intake (men: 0, ≤12g/d (reference), >12 - ≤24g/d, >24g/d, women: 0, ≤6g/d (reference), >6 - ≤12g/d, >12g/d), BMI (continuously), waist circumference (continuously), prevalent hypertension and prevalent diabetes (present/absent).

Discussion

In the present prospective cohort study, which was based on a German population of middle-aged men and women, no association was observed between prevalent renal calculi and the risk of incident CVD (myocardial infarction and stroke).

This finding is contrary to those from previous studies in which an increased risk of CVD was observed among participants with renal calculi. Stoller and colleagues [34] hypothesized a common mechanism behind the development of CVD and renal calculi which is characterized by atherosclerotic-like plaque development. Accordingly, the calcification may erode into the renal papillary interstitium and into the papillary ducts of Bellini and ultimately incite calculus formation. However, this hypothesis could not yet be clarified. Moreover, arterial wall (intima media) thickness was associated with renal calculi in young individuals aged between 15 and 30 years [10]. Thus, arterial wall calcification and the development of renal calculi may be the consequences of impaired or lacking calcification inhibitors.

Recently, in a study based on the US American population, Rule et al., [20] obtained an increased risk of myocardial infarction in persons with renal calculi after adjustment for important comorbidities. However, another explanation for the observed risk increase may be merely due to sharing similar risk factors [22], as these were only roughly captured. In another recent study in Taiwan [23], an increased risk of stroke during the first five years after a diagnosis of urinary calculi was reported compared to matched controls. However, the authors did not take into account lifestyle factors such as smoking, physical activity and alcohol consumption. More recently, Ferraro et al., [21] investigated the association between renal calculi and the risk of CHD in three prospective cohort studies (Nurses' Health Study I, Nurses' Health Study II, and the Health Professionals Follow-up Study) and observed an increased CHD risk in women, but not men, with renal calculi compared to those without.

Those sex differences were not observed in the present study, but important cardiovascular risk factors were more common among stone formers. Indeed, increasing evidence suggests that the development of renal calculi is associated with the presence of important cardiovascular risk factors like hypertension, smoking, obesity, metabolic syndrome, and type 2 diabetes [7-9,11,22,35]. However, in the present study a lower percentage of current smokers was observed among participants with renal calculi - when compared to those without - which, actually, may be the result of recommendations to modify their lifestyles because of a renal calculi diagnosis. Further, Domingos et al., [36] assumed that renal calculi are associated with an increased prevalence of chronic diseases including myocardial infarction and stroke using data from a large health survey in Portugal. Due to controversial findings further prospective studies are needed taking into account detailed confounding variables to clarify the relation between renal calculi and CVD, in particular with

regards to possible gender differences.

Some limitations of the study need to be discussed. The follow-up period is relatively short and the number of CVD cases is rather limited, thus limiting the power to draw strong conclusions in the stratified analyses on major endpoints and fatal cases. Further, the presence of renal calculi was assessed by self-report at baseline. In contrast to the present investigation, previous studies [20-23] used participants with newly diagnosed incident renal calculi, thereby minimizing the threat of exposure misclassification. Furthermore, data on calculi composition and severity of stone disease are missing. In addition, healthy and health-conscious individuals may be overrepresented in the present study population, potentially decreasing the power of detecting an independent association between renal calculi and CVD, particular with small numbers of CVD cases.

Strengths of the study include the prospective cohort design and the application of computer-guided interviews, which are valid assessment tools for the evaluation of medical history, including renal calculi [37]. Furthermore, detailed data on cardiovascular risk factors and measurements of relevant biomarkers were available for the studied cohort, underlining the validity of the observations.

Conclusions

The present findings do not indicate an independent association of prevalent renal calculi and CVD risk. However, the prevalence of unfavorable cardiovascular health conditions is higher among individuals with renal calculi. The occurrence of renal calculi may, therefore, suggest a targeted screening for cardiovascular risk factors in all patients concerned.

List of abbreviations

EPIC: European Prospective Investigation into Cancer and Nutrition
 CHD: coronary heart disease
 CI: confidence interval
 CVD: Cardiovascular disease
 HDL: high density lipoprotein
 HR: Hazard rate ratio
 hsCRP: high-sensitivity C-reactive protein
 ICD-10: International Statistical Classification of Disease and Related Health Problems 10th revision

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	JW	SW	RG	AF	HB	CW
Research concept and design	--	--	--	--	✓	✓
Collection and/or assembly of data	--	--	--	✓	✓	✓
Data analysis and interpretation	✓	✓	✓	✓	✓	✓
Writing the article	✓	✓	--	--	--	--
Critical revision of the article	✓	✓	✓	✓	✓	✓
Final approval of article	✓	✓	✓	✓	✓	✓
Statistical analysis	✓	--	✓	--	--	--

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