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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040034
Article Type:	Original research
Date Submitted by the Author:	03-May-2020
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Keywords:	Adult neurology < NEUROLOGY, Stroke < NEUROLOGY, Coronary heart disease < CARDIOLOGY

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Nephrolithiasis increases the risk of cardiovascular diseases: A longitudinal follow-up study using a national health screening cohort

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Running title: Nephrolithiasis and cardiovascular diseases

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Abstract

Objectives: The aim of this study was to explore the risks of stroke and ischemic heart disease in nephrolithiasis patients.

Design: A longitudinal follow-up study

Setting: Data from the Korean National Health Insurance Service-Health Screening Cohort (2002 to 2013) were retrieved to identify the occurrence of nephrolithiasis.

Participants and Interventions: In total, 19,103 nephrolithiasis patients were matched at a 1:4 ratio with control participants for age, sex, income, and region of residence.

Primary and secondary outcome measures: In both the nephrolithiasis and control participants, the occurrence of stroke and ischemic heart disease was analyzed. The hazard ratios (HRs) of stroke and ischemic heart disease were analyzed using a stratified Cox proportional hazard model. Smoking, alcohol consumption, obesity, and the Charlson comorbidity index were adjusted as covariates. The subgroup analyses were conducted according to age and sex.

Results: Eight percent (1,615/19,103) of nephrolithiasis patients and 7.2% (5,476/76,412) of control participants experienced stroke. Nine percent (1,879/19,103) of nephrolithiasis patients and 7.7% (5,895/76,412) of control participants had ischemic heart disease. The nephrolithiasis patients demonstrated 1.18 times (95% confidence interval [95% CI] = 1.11–1.24) and 1.25 times (95% CI = 1.18–1.31) increased risks of stroke and ischemic heart disease, respectively. The age and sex subgroups showed consistent results.

Conclusions: Nephrolithiasis was associated with increased risks of stroke and ischemic heart disease.

Key words: Nephrolithiasis; Coronary Artery Disease; Stroke; Risk Factors; Cohort Studies

Strengths and limitations of this study

- This study added to previous findings by analyzing a large cohort. The large study population provided many control populations matched for age, sex, income, and region of residence.
- The lifestyle factors of obesity, smoking status, and alcohol consumption as well as past medical histories were adjusted to minimize the confounding of from these covariates.
- Because these data were based on medical claim codes, subclinical or untreated patients might have been missed in the present results.
-

Funding: The authors have no conflicts of interest to declare. This work was supported in part by a research grant (NRF-2018-R1D1A1A02085328) from the National Research Foundation (NRF) of Korea, and Hallym University Research Fund (HURF-2018-53).

Competing interest: None declared.

Introduction

Nephrolithiasis is a common urinary tract disease. Approximately 8.8% (95% confidence interval [95% CI] = 8.1–9.5) of the United States population and 3.5% of the Korean population suffer from nephrolithiasis [1,2]. The prevalence of nephrolithiasis is increasing worldwide [3]. The increasing prevalence of obesity has been suspected to promote the formation of nephrolithiasis [4]. Acute renal colic due to the blockage of the ureter is an acute urinary manifestation of nephrolithiasis. In addition, chronic manifestations of nephrolithiasis can result in systemic comorbidities, including metabolic syndrome [5]. For decades, a growing number of epidemiologic studies have suggested the association of nephrolithiasis with systemic comorbidities, such as diabetes and hypertension [6,7]. Because these comorbidities are predisposing conditions for cardiovascular disorders, researchers have also explored the associations between nephrolithiasis and cardiovascular disorders [8-10].

Previous studies have reported an association between nephrolithiasis and stroke [9]. Our previous study also demonstrated an increased risk of ischemic stroke in nephrolithiasis patients [8]. However, to our knowledge, our prior study and most other published literature have not considered lifestyle factors, including obesity, smoking and alcohol consumption. Because renal stone formation, as well as cardiovascular disease, has been suggested to be related to obesity and smoking, the possible confounding effects of these covariates should be controlled to delineate the association between nephrolithiasis and cardiovascular diseases [11,12]. In addition, because cerebrovascular disease (stroke) and cardiovascular disease (ischemic heart disease) are associated with each other, these vascular disorders need to be independently considered for their relationship with nephrolithiasis.

We hypothesized that nephrolithiasis might increase the risks of both stroke and ischemic heart disease, probably due to their shared pathophysiology. The present study has improved our previous study on the association between nephrolithiasis and stroke by

including ischemic heart disease. In addition, potential confounders including obesity, smoking, and alcohol consumption were considered. The risks of stroke and ischemic heart disease were analyzed by adjusting for past medical histories using the Charlson comorbidity index (CCI) and lifestyle factors including obesity, smoking, and alcohol consumption. Because prior studies suspected sex differences in the association between nephrolithiasis and cardiovascular disease [9], subgroup analyses were conducted for these associations.

Materials and Methods

Study population

The ethics committee of Hallym University (2017-I102) approved this study. Written informed consent was waived by the Institutional Review Board. All analyses adhered to the guidelines and regulations of the ethics committee of Hallym University. A detailed description of the Korean National Health Insurance Service-Health Screening Cohort data is described elsewhere [13].

Definition of nephrolithiasis

Nephrolithiasis was defined if the participants were diagnosed with the International Classification of Diseases 10th Revision (ICD-10) code N20 ≥ 2 times, following our previous studies [8,14].

2.3. Definition of stroke and ischemic heart disease

Stroke and ischemic heart disease were identified based on ICD-10 codes (I60-I69 for stroke and I20-I25 for ischemic heart disease), as in our previous study [8].

Participant selection

Nephrolithiasis patients were selected from 514,866 participants with 497,931,549 medical claim codes (n = 22,003). The control group included participants who were never treated for nephrolithiasis from 2002 through 2013 (n = 492,863). Nephrolithiasis patients were matched at a 1:4 ratio with the control participants for age, sex, income, and region of residence. To minimize selection bias, the control participants were selected with random number generation. The index date of each nephrolithiasis patient was considered the date of initiation of treatment of nephrolithiasis. The index date of the control participants was considered the index date of their matched nephrolithiasis patient. Therefore, each matched nephrolithiasis patient and their respective control participants had the same index date. Nine nephrolithiasis patients with previous stroke or ischemic heart disease before the index date were excluded. Control participants with previous stroke or ischemic heart disease before the index date were also excluded. Among the control participants, 404,887 were excluded during the matching procedure. Finally, 21,994 nephrolithiasis patients were 1:4 matched with 87,976 control participants (Fig. 2).

Covariates

Age groups were divided into 5-year intervals: 40-44, 45-49, 50-54…, and 85+ years old. A total of 10 age groups were specified. Income groups were classified into 5 classes (classes 1 [lowest income]-5 [highest income]). The region of residence was categorized as urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) or rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

Tobacco smoking was categorized based on the participant's current smoking status (nonsmoker, past smoker, or current smoker). Alcohol consumption was categorized on the basis of the frequency of alcohol consumption (< 1 time a week or ≥ 1 time a week). Obesity

was measured using body mass index (BMI, kg/m^2). Missing BMI variables were replaced by the mean BMI from the final selected participants. BMI was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), or ≥ 30 (obese II) based on the Asia-Pacific criteria following the Western Pacific Regional Office (WPRO) 2000 [15].

The CCI has been used widely to measure disease burden considering 17 comorbidities. A score was given to each participant depending on the severity and number of diseases. The CCI was measured as a continuous variable (0 [no comorbidities] through 29 [multiple comorbidities]) [16,17]. The scores were calculated excluding cerebrovascular disease. The CCI score was applied as a continuous variable.

Statistical analyses

The general characteristics between the nephrolithiasis and control groups were compared using chi-square tests.

To analyze the hazard ratios (HRs) and 95% confidence intervals (CIs) of stroke and ischemic heart disease in nephrolithiasis patients compared to control participants, a stratified Cox proportional hazard model was used. In this analysis, a crude model and a model adjusted for obesity, smoking status, alcohol consumption, and CCI score were calculated. The analysis was stratified by matching variables such as age, sex, income, and region of residence. Kaplan-Meier curves were constructed and log rank tests were performed.

For the subgroup analyses, we divided the participants by age and sex (< 60 years old and ≥ 60 years old; males and females) and analyzed the crude and adjusted models.

Two-tailed analyses were performed, and significance was defined as a P value less than 0.05. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

Patients and Public Involvement Statement

This national cohort study used data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The detailed description of these data was described in our previous studies[18,19]. No patients were involved in the development of the research question or the design of the study. We have no plan to disseminate the results to the cases. Because the NHIS-NSC data are based on national health claim codes, releasing the data by the researcher is not allowed legally. All data are available from the database of National Health Insurance Sharing Service (NHISS) (https://nhiss.nhis.or.kr/).

NHISS allows all of these data for any researcher who promises to follow the research ethics with some cost. If one wants to access the data described in this article, one could download it from the website after promising to follow the research ethics requirements.

Results

Age, sex, income, and region of residence were exactly matched between the nephrolithiasis and control groups (P =1.000). The rates of low CCI, overweight, obesity I, obesity II, nonsmoker status, and alcohol consumption < 1 time a week were higher in the nephrolithiasis group than in the control group (each P < 0.05). The prevalence of stroke and ischemic heart disease were lower in the nephrolithiasis group than in the control group (P < 0.001, Table 1).

The adjusted HR of stroke in the nephrolithiasis group was 1.18 (95% CIs = 1.11–1.24, P < 0.001) (Fig. 1a). In the subgroup analyses according to age and sex, the adjusted HRs of stroke were higher in the nephrolithiasis group than in the control group, except for the subgroup of males ≥ 60 years old (Table 2).

The adjusted HR of ischemic heart disease in the nephrolithiasis group was 1.25 (95% CIs = 1.18–1.31, P < 0.001) (Fig. 1b). In the subgroup analyses according to age and sex, the

adjusted HRs of ischemic heart disease were higher in the nephrolithiasis group than in the control group (Table 3).

Discussion

Nephrolithiasis patients demonstrated 1.18 and 1.25 times higher risks of stroke and ischemic heart disease, respectively. These increased risks of stroke and ischemic heart disease were consistent in all age and sex subgroups, except for males ≥ 60 years old, who did not show an association between nephrolithiasis and stroke. This study added to previous findings by analyzing a large cohort. The large study population provided many control populations matched for age, sex, income, and region of residence. Furthermore, the lifestyle factors of obesity, smoking status, and alcohol consumption as well as past medical histories were adjusted to minimize the confounding of from these covariates. This study was a longitudinal follow-up study that explored the causal relationship between nephrolithiasis and stroke or ischemic heart disease. Participants who had previous histories of stroke or ischemic heart disease before the index date were excluded. In addition, the participants who had histories of stroke or ischemic heart disease at 1 year and 2 years after the index date were excluded from the supplementary analyses; the increased risks of stroke and ischemic heart disease in the nephrolithiasis patients remained consistent (Table S1 and Table S2).

The metabolic perturbations in nephrolithiasis patients, which manifests as hypercalciuria, hyperuricemia, or hyperoxaluria, could mediate the increased risk of cardiovascular plaque formation and metabolic changes associated with cardiovascular disorders. It has been suggested that the abnormal calcification process is similar in the atherosclerosis of cerebral or coronary vasculature and the formation of nephrolithiasis [18]. Supporting these metabolic changes in nephrolithiasis patients, calcification inhibitors were decreased in the blood and urine of atherosclerosis and nephrolithiasis patients [18]. In addition

to the direct calcification process, other indirect metabolic changes in nephrolithiasis patients might impact the risk of cardiovascular disorders. Metabolic syndrome patients showed that the odds of nephrolithiasis were increased by 1.25 times (95% CI = 1.03–1.50) in a cross-sectional study [19]. In an experimental animal study, a metabolic syndrome rat model with insulin resistance demonstrated an increased risk of urinary calcium stone formation [20]. In a clinical study, the metabolic syndromic traits of obesity, hypertension, diabetes, and dyslipidemia were increased by 1.78 times (95% CI = 1.22–2.66) in nephrolithiasis patients with recurrent or multiple stones [21]. Therefore, it was presumed that nephrolithiasis should be considered a systemic metabolic disease rather than a local metabolic disease involving calcification. These systemic metabolic disturbances in nephrolithiasis patients might mediate the increased risk of cardiovascular disorders.

The risk of stroke was higher in the nephrolithiasis patients than in the control patients in the present study. Our previous study reported a 1.13 times (95% CI = 1.06–1.21) higher risk of ischemic stroke in nephrolithiasis patients than in the control group [8]. A recent meta-analysis reported that a history of nephrolithiasis was associated with a 1.23-fold (95% CI = 1.06–1.38) increased relative risk of stroke [10]. However, few previous studies considered smoking, obesity, and alcohol consumption, and only selected comorbidities were adjusted. After adjusting for both lifestyle factors and past medical histories, the risk of stroke was higher in the nephrolithiasis patients in the current study. Moreover, the risk of ischemic heart disease was higher in the nephrolithiasis patients in this study. A recent meta-analysis reported that the relative risk of coronary heart disease increased by 1.24 times (95% CI = 1.14–1.36) in nephrolithiasis patients [10]. This figure is similar to the present HR of 1.25 (95% CI = 1.18–1.31).

The age and sex subanalyses indicated increased risks of stroke and ischemic heart disease in nephrolithiasis patients, except for males ≥ 60 years old. A meta-analysis

demonstrated that the pooled HR for myocardial infarction was 1.49 (95% CI = 1.21–1.82) in the female group, while the male group did not show any association between nephrolithiasis and myocardial infarction [9]. This female-specific association between nephrolithiasis and myocardial infarction was explained by the higher rate of urinary tract infection in females than in males, which makes the female population vulnerable to systemic inflammation and atherosclerotic changes [22,23]. In the present study, the risk of ischemic heart disease was increased in both male and female nephrolithiasis patients. The large population cohort, in addition to the matched control group and considered covariates, permitted a sufficiently high number of male subgroups, thereby potentiating the statistical power of the present study. On the other hand, the ≥ 60 years old male group did not show an association between nephrolithiasis and stroke in this study. The relatively small size of this subgroup could have influenced the nonsignificant association in this group. In addition, the decreased rate of urinary tract infection and increased health-related quality of life in older males could attenuate the impact of nephrolithiasis on stroke [22,24].

A longitudinal follow-up study design with a control group matched for demographic and socioeconomic factors may elucidate the previously mixed results on the association between nephrolithiasis and cardiovascular diseases with causalities. Past medical histories and lifestyle factors were comprehensively adjusted using the CCI and a survey of obesity, smoking, and alcohol consumption. However, primarily because this was a medical claims data study, a few limitations should be considered when interpreting the present results. Because these data were based on medical claim codes, subclinical or untreated patients might have been missed in the present results. The severity and types of nephrolithiasis were not specified; thus, nephrolithiasis was heterogeneous in this study. In addition, this study used a Korean national cohort; therefore, there could be ethic difference in the association between nephrolithiasis and cardiovascular diseases [25].

Conclusion

Nephrolithiasis was associated with increased risks of stroke and ischemic heart disease. This relation was consistent after considering comorbidities and lifestyle factors including obesity, smoking, and alcohol consumption.

Author Contributions

HGC designed the study; WB, CM, and HGC analyzed the data; SYK and WB drafted and revised the paper; all authors approved the final version of the manuscript.

Data sharing statement

Release of the data by the researcher is not allowed legally. All data are available from the database of National Health Insurance Sharing Service (NHISS) (https://nhiss.nhis.or.kr/). NHISS allows all of these data for any researcher who promises to follow the research ethics with some cost. If one wants to access the data of this article, one can download it from the website after promising to follow the research ethics requirements.

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Table 1 General Characteristics of Participants

Characteristics	Total participants		
	Nephrolithiasis (n, %)	Control (n, %)	P-value
Age (years old)			1.000
40-44	1,593 (8.3)	6,372 (8.3)	
45-49	3,659 (19.2)	14,636 (19.2)	
50-54	4,570 (23.9)	18,280 (23.9)	
55-59	3,525 (18.5)	14,100 (18.5)	
60-64	2,570 (13.5)	10,280 (13.5)	
65-69	1,709 (9.0)	6,836 (9.0)	
70-74	955 (5.0)	3,820 (5.0)	
75-79	402 (2.1)	1,608 (2.1)	
80-84	102 (0.5)	408 (0.5)	
85+	18 (0.1)	72 (0.1)	
Sex			1.000
Male	12,303 (64.4)	49,212 (64.4)	
Female	6,800 (35.6)	27,200 (35.6)	
Income			1.000
1 (lowest)	2,576 (13.5)	10,304 (13.5)	
2	2,269 (11.9)	9,076 (11.9)	
3	2,893 (15.1)	11,572 (15.1)	
4	4,108 (21.5)	16,432 (21.5)	
5 (highest)	7,257 (38.0)	29,028 (38.0)	
Region of residence			1.000
Urban	8,667 (45.4)	34,668 (45.4)	

Rural	10,436 (54.6)	41,744 (54.6)	
CCI score			0.005*
0	18,735 (98.1)	74,671 (97.7)	
1	58 (0.3)	370 (0.5)	
2	72 (0.4)	336 (0.4)	
3	53 (0.3)	257 (0.3)	
≥ 4	185 (1.0)	778 (1.0)	
Obesity (BMI, kg/m^2)			<0.001*
< 18.5 (underweight)	267 (1.4)	1,642 (2.2)	
≥ 18.5 to < 23 (normal)	5,546 (29.0)	27,089 (35.5)	
≥ 23 to < 25 (overweight)	5,586 (29.2)	21,246 (27.8)	
≥ 25 to < 30 (obese I)	7,069 (37.0)	24,472 (32.0)	
≥ 30 (obese II)	635 (3.3)	1,963 (2.6)	
Smoking status			<0.001*
Nonsmoker	12,434 (65.1)	48,225 (63.1)	
Past smoker	2,490 (13.0)	9,512 (12.5)	
Current smoker	4,179 (21.9)	18,675 (24.4)	
Alcohol consumption			<0.001*
< 1 time a week	14,015 (73.4)	52,636 (68.9)	
≥ 1 time a week	5,088 (26.6)	23,776 (31.1)	
Stroke	1,615 (8.5)	5,476 (7.2)	<0.001*
Ischemic heart disease	1,879 (9.8)	5,895 (7.7)	<0.001*

Abbreviations: BMI, body mass index, kg/m^2, CCI, Charlson comorbidity index

* Chi-square test. Significance at $P < 0.05$

Table 2 Crude and adjusted hazard ratios (95% confidence interval) for stroke in nephrolithiasis and control groups

Characteristics	Hazard ratios for stroke			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 95,515)				
Nephrolithiasis	1.19 (1.12-1.25)	<0.001*	1.18 (1.11-1.24)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 44,595)				
Nephrolithiasis	1.23 (1.12-1.36)	<0.001*	1.23 (1.11-1.36)	<0.001*
Control	1.00		1.00	
Age < 60 years old, women (n = 22,140)				
Nephrolithiasis	1.32 (1.16-1.51)	<0.001*	1.30 (1.14-1.48)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 16,920)				
Nephrolithiasis	1.03 (0.93-1.15)	0.543	1.02 (0.92-1.14)	0.675
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 11,860)				
Nephrolithiasis	1.23 (1.09-1.38)	0.001*	1.22 (1.09-1.37)	0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

† Models stratified by age, sex, income, and region of residence.

‡ Models adjusted for obesity, smoking, alcohol consumption, and CCI scores.

Table 3 Crude and adjusted hazard ratios (95% confidence interval) for ischemic heart disease in nephrolithiasis and control groups

Characteristics	Hazard ratios for ischemic heart disease			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 95,515)				
Nephrolithiasis	1.29 (1.23-1.36)	<0.001*	1.25 (1.18-1.31)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 44,595)				
Nephrolithiasis	1.29 (1.19-1.39)	<0.001*	1.24 (1.15-1.35)	<0.001*
Control	1.00		1.00	
Age < 60 years old, women (n = 22,140)				
Nephrolithiasis	1.51 (1.34-1.70)	<0.001*	1.45 (1.29-1.64)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 16,920)				
Nephrolithiasis	1.23 (1.10-1.37)	<0.001*	1.18 (1.05-1.32)	0.004*
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 11,860)				
Nephrolithiasis	1.18 (1.04-1.35)	0.009*	1.16 (1.02-1.32)	0.023*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

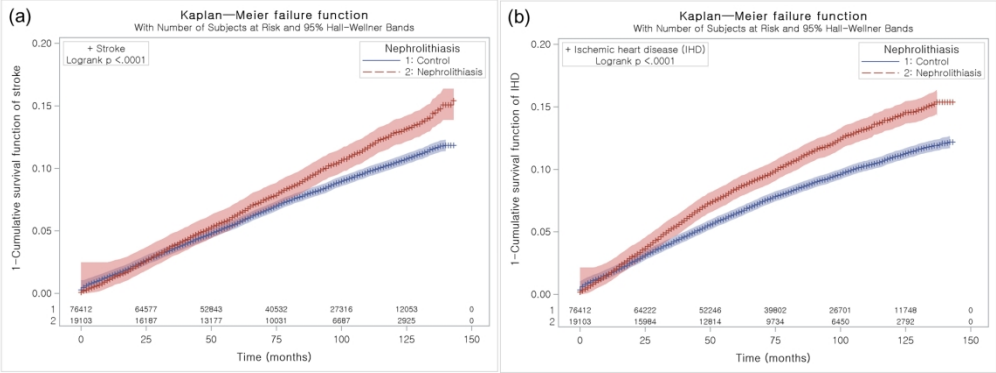
† Models stratified by age, sex, income, and region of residence.

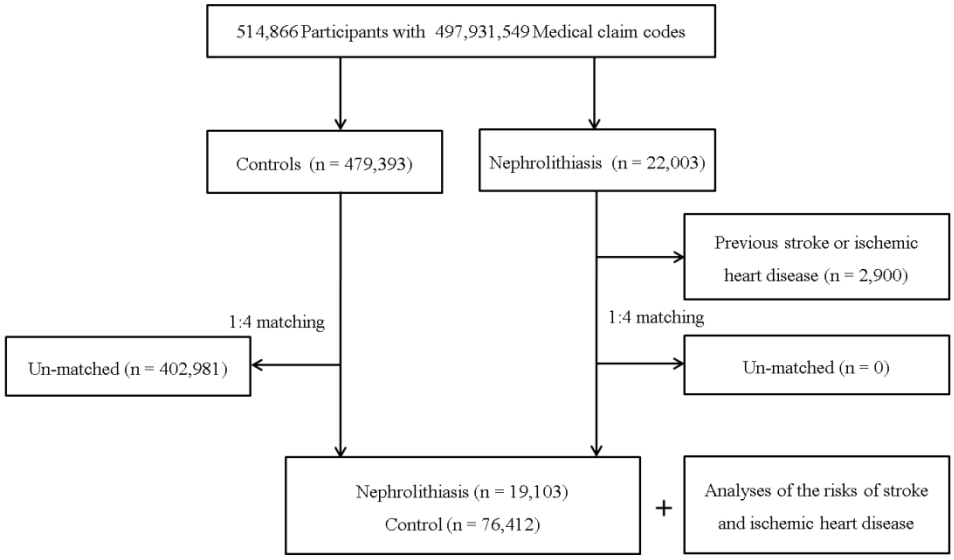
‡ Models adjusted for obesity, smoking, alcohol consumption, and CCI scores.

Figure legend

Figure 1 Kaplan-Meier survival analysis. (a) The cumulative rate of stroke was higher in the nephrolithiasis group than in the control group. (b) The cumulative rate of ischemic heart disease was higher in the nephrolithiasis group than in the control group.

Figure 2 A schematic illustration of the participant selection process that was used in the present study. Of a total of 514,866 participants, 21,994 nephrolithiasis participants were matched with 87,976 control participants for age, sex, income, and region of residence.


(a)
Kaplan—Meier failure function
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Stroke
Logrank p <.0001
Nephrolithiasis
1: Control
2: Nephrolithiasis
1−Cumulative survival function of stroke
0.20
0.15
0.10
0.05
0.00
1 76412 64577 52843 40532 27316 12053 0
2 19103 16187 13177 10031 6687 2925 0
0 25 50 75 100 125 150
Time (months)
(b)
Kaplan—Meier failure function
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Ischemic heart disease (IHD)
Logrank p <.0001
Nephrolithiasis
1: Control
2: Nephrolithiasis
1−Cumulative survival function of IHD
0.20
0.15
0.10
0.05
0.00
1 76412 64222 52246 39802 26701 11748 0
2 19103 15984 12814 9734 6450 2792 0
0 25 50 75 100 125 150
Time (months)


514,866 Participants with 497,931,549 Medical claim codes
Controls (n = 479,393)
Nephrolithiasis (n = 22,003)
Previous stroke or ischemic heart disease (n = 2,900)
1:4 matching
1:4 matching
Un-matched (n = 402,981)
Un-matched (n = 0)
Nephrolithiasis (n = 19,103)
Control (n = 76,412)
+
Analyses of the risks of stroke and ischemic heart disease

Nephrolithiasis increases the risk of cardiovascular diseases: A longitudinal follow-up study using a national health screening cohort

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Key words: Nephrolithiasis; Coronary Artery Disease; Stroke; Risk Factors; Cohort Studies

S1 Table Crude and adjusted hazard ratios (95% confidence interval) for stroke and ischemic heart disease in nephrolithiasis and control groups considering 1-year washout period (n = 84,605)

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
Stroke				
Nephrolithiasis	1.15 (1.08-1.22)	<0.001*	1.14 (1.07-1.21)	<0.001*
Control	1.00		1.00	
Ischemic heart disease				
Nephrolithiasis	1.28 (1.21-1.36)	<0.001*	1.24 (1.17-1.32)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Models adjusted for obesity, smoking, alcohol consumption, and CCI scores.

S2 Table Crude and adjusted hazard ratios (95% confidence interval) for stroke and ischemic heart disease in nephrolithiasis and control groups considering 2-year washout period (n = 74,400)

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
Stroke				
Nephrolithiasis	1.14 (1.07-1.23)	<0.001*	1.14 (1.06-1.22)	<0.001*
Control	1.00		1.00	
Ischemic heart disease				
Nephrolithiasis	1.25 (1.17-1.34)	<0.001*	1.21 (1.13-1.30)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Models adjusted for obesity, smoking, alcohol consumption, and CCI scores.

S2 Table Crude and adjusted hazard ratios (95% confidence interval) for stroke and ischemic heart disease in nephrolithiasis and control groups considering 2-year washout period (n = 74,400)

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
Stroke				
Nephrolithiasis	1.14 (1.07-1.23)	<0.001*	1.14 (1.06-1.22)	<0.001*
Control	1.00		1.00	
Ischemic heart disease				
Nephrolithiasis	1.25 (1.17-1.34)	<0.001*	1.21 (1.13-1.30)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Models adjusted for obesity, smoking, alcohol consumption, and CCI scores.

BMJ Open

Association of nephrolithiasis with the risk of cardiovascular diseases: A longitudinal follow-up study using a national health screening cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040034.R1
Article Type:	Original research
Date Submitted by the Author:	15-Jul-2020
Complete List of Authors:	Kim, So Young; CHA University, Otorhinolaryngology-Head & Neck Surgery Bang, Woo Jin; Hallym University College of Medicine, Department of Urology Min, Chanyang; Hallym University College of Medicine, Hallym Data Science Laboratory Choi, Hyo Geun; Hallym University, Otorhinolaryngology-Head & Neck Surgery
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Adult neurology < NEUROLOGY, Stroke < NEUROLOGY, Coronary heart disease < CARDIOLOGY

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Association of nephrolithiasis with the risk of cardiovascular diseases: A longitudinal follow-up study using a national health screening cohort

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Running title: Nephrolithiasis and cardiovascular diseases

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Abstract

Objectives: The aim of this study was to explore the associations of stroke and ischemic heart disease in nephrolithiasis patients.

Design: A longitudinal follow-up study

Setting: Data from the Korean National Health Insurance Service-Health Screening Cohort (2002 to 2013) were retrieved to identify the occurrence of nephrolithiasis.

Participants and Interventions: In total, 19,103 nephrolithiasis patients were matched at a 1:4 ratio with control participants for age, sex, income, and region of residence.

Primary and secondary outcome measures: In both the nephrolithiasis and control participants, the occurrence of stroke and ischemic heart disease was analyzed. The primary outcome was the hazard ratios (HRs) of stroke and ischemic heart disease in a stratified Cox proportional hazard model. Smoking, alcohol consumption, obesity, and the Charlson comorbidity index were adjusted as covariates. The secondary outcome was the subgroup analyses according to age and sex.

Results: The 8.5% (1,615/19,103) of nephrolithiasis patients and 7.2% (5,476/76,412) of control participants experienced stroke. The 9.8% (1,879/19,103) of nephrolithiasis patients and 7.7% (5,895/76,412) of control participants had ischemic heart disease. The nephrolithiasis patients demonstrated 1.18 times (95% confidence interval [95% CI] = 1.11–1.24) and 1.24 times (95% CI = 1.18–1.31) increased risks of stroke and ischemic heart disease, respectively. The age and sex subgroups showed consistent results.

Conclusions: Nephrolithiasis was associated with increased risks of stroke and ischemic heart disease.

Key words: Nephrolithiasis; Myocardial Ischemia; Stroke; Risk Factors; Cohort Studies

Strengths and limitations of this study

- This study adds to previous findings by analyzing a large cohort. The large study population provided many control patients matched for age, sex, income, and region of residence.
- The lifestyle factors of obesity, smoking status, and alcohol consumption as well as Charlson comorbidity index, total cholesterol, and fasting blood glucose were adjusted to minimize the confounding of from these covariates.
- Because these data were based on medical claim codes, subclinical or untreated patients might have been missed in the present results.
-

Funding: The authors have no conflicts of interest to declare. This work was supported in part by a research grant (NRF-2018-R1D1A1A02085328) from the National Research Foundation (NRF) of Korea, and Hallym University Research Fund (HURF-2018-53).

Competing interest: None declared.

Introduction

Nephrolithiasis is a common urinary tract disease. Approximately 4.2% - 10.1% of the worldwide population and 3.5% of the Korean population suffer from nephrolithiasis [1-3]. The prevalence of nephrolithiasis is increasing worldwide [4]. The increasing prevalence of obesity has been suspected to promote the formation of nephrolithiasis [5]. Acute renal colic due to the blockage of the ureter is an acute urinary manifestation of nephrolithiasis. In addition, nephrolithiasis can be associated with systemic comorbidities, including metabolic syndrome [6]. For decades, a growing number of epidemiologic studies have suggested the association of nephrolithiasis with systemic comorbidities, such as diabetes and hypertension [7,8]. Because these comorbidities are predisposing conditions for cardiovascular disorders, researchers have also explored the associations between nephrolithiasis and cardiovascular disorders [9-11].

Previous studies have reported an association between nephrolithiasis and stroke [9,10]. However, to our knowledge, our prior study and most other published literature have not considered the impacts of lifestyle factors, including obesity, smoking and alcohol consumption on the association between nephrolithiasis and stroke. Because renal stone formation, as well as cardiovascular disease, has been suggested to be related to obesity and smoking, the possible confounding effects of these covariates should be controlled to delineate the association between nephrolithiasis and cardiovascular diseases [12,13]. In addition, because cerebrovascular disease (stroke) and cardiovascular disease (ischemic heart disease) are associated with each other, these vascular disorders need to be independently considered for their relationship with nephrolithiasis.

We hypothesized that nephrolithiasis might increase the risks of both stroke and ischemic heart disease, probably due to their shared pathophysiology. The present study has improved our previous study on the association between nephrolithiasis and stroke by including ischemic heart disease. In addition, potential confounders including obesity,

smoking, and alcohol consumption were considered. The risks of stroke and ischemic heart disease were analyzed by adjusting for past medical histories using the Charlson comorbidity index (CCI) and lifestyle factors including obesity, smoking, and alcohol consumption. Because prior studies suspected sex differences in the association between nephrolithiasis and cardiovascular disease [10], subgroup analyses were conducted for these associations.

Materials and Methods

Study population

The ethics committee of Hallym University (2017-I102) approved this study. Written informed consent was waived by the Institutional Review Board. All analyses adhered to the guidelines and regulations of the ethics committee of Hallym University. A detailed description of the Korean National Health Insurance Service-Health Screening Cohort data is described elsewhere [14].

Definition of nephrolithiasis

Nephrolithiasis was defined if the participants were diagnosed with the International Classification of Diseases 10th Revision (ICD-10) code N20 $\geq$ 2 times, following our previous studies [9,15].

2.3. Definition of stroke and ischemic heart disease

Stroke and ischemic heart disease were identified based on ICD-10 codes (I60-I69 for stroke and I20-I25 for ischemic heart disease), as in our previous study [9].

Participant selection

Nephrolithiasis patients (n = 22,003) were selected from 514,866 participants with 497,931,549 medical claim codes. The control group included participants who were never diagnosed for nephrolithiasis from 2002 through 2013 (n = 492,863). Nephrolithiasis patients were matched at a 1:4 ratio with the control participants for age, sex, income, and region of residence. To minimize selection bias, the control participants were selected with random number generation. The index date of each nephrolithiasis patient was considered the date of initiation of diagnosis of nephrolithiasis. The index date of the control participants was considered the index date of their matched nephrolithiasis patient. Therefore, each matched nephrolithiasis patient and their respective control participants had the same index date. Nine nephrolithiasis patients with previous stroke or ischemic heart disease before the index date were excluded. Control participants with previous stroke or ischemic heart disease before the index date were also excluded. Among the control participants, 404,887 were excluded during the matching procedure. Finally, 19,103 nephrolithiasis patients were 1:4 matched with 76,412 control participants (Fig. 1). The nephrolithiasis patients who visited emergency department or hospitalization were classified as severe nephrolithiasis patients and others were classified as mild to moderate nephrolithiasis patients in subgroup analysis according to severity of nephrolithiaisis.

Covariates

Age groups were divided into 5-year intervals: 40-44, 45-49, 50-54…, and 85+ years old. A total of 10 age groups were specified. Income groups were classified into 5 classes (classes 1 [lowest income]-5 [highest income]). The region of residence was categorized as urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) or rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

Tobacco smoking was categorized based on the participant's current smoking status (nonsmoker, past smoker, or current smoker). Alcohol consumption was categorized on the basis of the frequency of alcohol consumption (nondrinker, 1 – 3 times a month, and ≥ 1 time a week), because previous studies indicated positive association of nephrolithiasis with binge drinking [16], while negative association with moderate alcohol consumption [17]. Obesity was measured using body mass index (BMI, kg/m^2). Missing BMI variables were replaced by the mean BMI from the final selected participants. BMI was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), or ≥ 30 (obese II) based on the Asia-Pacific criteria following the Western Pacific Regional Office (WPRO) 2000 [18]. Serum levels of total cholesterol (mg/dL) and fasting glucose (mg/dL) were included as continuous variables.

The CCI has been used widely to measure disease burden considering 17 comorbidities. A score was given to each participant depending on the severity and number of diseases. The CCI was measured as a continuous variable (0 [no comorbidities] through 29 [multiple comorbidities]) [19,20]. The scores were calculated excluding cerebrovascular disease. The CCI score was applied as a continuous variable.

Statistical analyses

The general characteristics between the nephrolithiasis and control groups were compared using chi-square tests.

To analyze the hazard ratios (HRs) and 95% confidence intervals (CIs) of stroke and ischemic heart disease in nephrolithiasis patients compared to control participants, a stratified Cox proportional hazard model was used. In this analysis, a crude model and a model adjusted for obesity, smoking status, alcohol consumption, and CCI score were calculated.

The analysis was stratified by matching variables such as age, sex, income, and region of residence. Kaplan-Meier curves were constructed and log rank tests were performed.

For the subgroup analyses, we divided the participants by age and sex (< 60 years old and ≥ 60 years old; males and females), severity of nephrolithiasis (mild to moderated and severe), and analyzed the crude and adjusted models.

Two-tailed analyses were performed, and significance was defined as a P value less than 0.05. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

Patients and Public Involvement Statement

This national cohort study used data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The detailed description of these data was described in our previous studies[21,22]. No patients were involved in the development of the research question or the design of the study. We have no plan to disseminate the results to the cases. Because the NHIS-NSC data are based on national health claim codes, releasing the data by the researcher is not allowed legally. All data are available from the database of National Health Insurance Sharing Service (NHISS) (https://nhiss.nhis.or.kr/).

NHISS allows all of these data for any researcher who promises to follow the research ethics with some cost. If one wants to access the data described in this article, one could download it from the website after promising to follow the research ethics requirements.

Results

Age, sex, income, and region of residence were exactly matched between the nephrolithiasis and control groups (P =1.000). The rates of low CCI, overweight, obesity I, obesity II, and nonsmoker status were higher in the nephrolithiasis group than in the control group (each P < 0.05). The distribution of alcohol consumption and the serum level of total cholesterol were

different between the nephrolithiasis group and the control group (each P < 0.001). The prevalence of stroke and ischemic heart disease were lower in the nephrolithiasis group than in the control group (P < 0.001, Table 1).

The adjusted HR of stroke in the nephrolithiasis group was 1.18 (95% CIs = 1.11–1.24, P < 0.001) (Fig. 2a). In the subgroup analyses according to age and sex, the adjusted HRs of stroke were higher in the nephrolithiasis group than in the control group, except for the subgroup of males ≥ 60 years old (Table 2).

The adjusted HR of ischemic heart disease in the nephrolithiasis group was 1.24 (95% CIs = 1.18–1.31, P < 0.001) (Fig. 2b). In the subgroup analyses according to age and sex, the adjusted HRs of ischemic heart disease were higher in the nephrolithiasis group than in the control group (Table 3). The associations of stroke and ischemic heart disease with nephrolithiasis were remained consistent when considering 1-year washout period (Table S1 and Table S2). According to severity of nephrolithiasis, both mild to moderate and severe nephrolithiasis patients demonstrated higher odds for stroke and ischemic heart disease, respectively (Table S3 and Table S4). According to smoking, alcohol consumption, and obesity, the association of nephrolithiasis with stroke were consistent in all subgroups, except for past smoker, underweight, and obese II subgroups (Table S5 and Table S6).

Discussion

Nephrolithiasis patients demonstrated 1.18 and 1.25 times higher risks of stroke and ischemic heart disease, respectively. These increased risks of stroke and ischemic heart disease were consistent in all age and sex subgroups, except for males ≥ 60 years old, who did not show an association between nephrolithiasis and stroke. This study added to previous findings by analyzing a large cohort. The large study population provided many control populations matched for age, sex, income, and region of residence. Furthermore, the lifestyle factors of

obesity, smoking status, and alcohol consumption as well as past medical histories were adjusted to minimize the confounding of from these covariates. This study was a longitudinal follow-up study that explored the causal relationship between nephrolithiasis and stroke or ischemic heart disease. Participants who had previous histories of stroke or ischemic heart disease before the index date were excluded. In addition, the participants who had histories of stroke or ischemic heart disease at 1 year and 2 years after the index date were excluded from the supplementary analyses.

The metabolic perturbations in nephrolithiasis patients, which manifests as hypercalciuria, hyperuricemia, or hyperoxaluria, could mediate the increased risk of cardiovascular plaque formation and metabolic changes associated with cardiovascular disorders. It has been suggested that the abnormal calcification process is similar in the atherosclerosis of cerebral or coronary vasculature and the formation of nephrolithiasis [23]. Supporting these metabolic changes in nephrolithiasis patients, calcification inhibitors were decreased in the blood and urine of atherosclerosis and nephrolithiasis patients [23]. In addition to the direct calcification process, other indirect metabolic changes in nephrolithiasis patients might impact the risk of cardiovascular disorders. Metabolic syndrome patients showed that the odds of nephrolithiasis were increased by 1.25 times (95% CI = 1.03–1.50) in a cross-sectional study [24]. In an experimental animal study, a metabolic syndrome rat model with insulin resistance demonstrated an increased risk of urinary calcium stone formation [25]. In a clinical study, the metabolic syndromic traits of obesity, hypertension, diabetes, and dyslipidemia were increased by 1.78 times (95% CI = 1.22–2.66) in nephrolithiasis patients with recurrent or multiple stones [26]. Therefore, it was presumed that nephrolithiasis should be considered a systemic metabolic disease rather than a local metabolic disease involving calcification. These systemic metabolic disturbances in nephrolithiasis patients might mediate the increased risk of cardiovascular disorders.

The risk of stroke was higher in the nephrolithiasis patients than in the control patients in the present study. Our previous study reported a 1.13 times (95% CI = 1.06–1.21) higher risk of ischemic stroke in nephrolithiasis patients than in the control group [9]. A recent meta-analysis reported that a history of nephrolithiasis was associated with a 1.23-fold (95% CI = 1.06–1.38) increased relative risk of stroke [11]. However, few previous studies considered smoking, obesity, and alcohol consumption, and only selected comorbidities were adjusted. After adjusting for both lifestyle factors and past medical histories, the risk of stroke was higher in the nephrolithiasis patients in the current study. Moreover, the risk of ischemic heart disease was higher in the nephrolithiasis patients in this study. A recent meta-analysis reported that the relative risk of coronary heart disease increased by 1.24 times (95% CI = 1.14–1.36) in nephrolithiasis patients [11]. This figure is similar to the present HR of 1.25 (95% CI = 1.18–1.31).

The age and sex subanalyses indicated increased risks of stroke and ischemic heart disease in nephrolithiasis patients, except for males ≥ 60 years old. A meta-analysis demonstrated that the pooled HR for myocardial infarction was 1.49 (95% CI = 1.21–1.82) in the female group, while the male group did not show any association between nephrolithiasis and myocardial infarction [10]. This female-specific association between nephrolithiasis and myocardial infarction was explained by the higher rate of urinary tract infection in females than in males, which makes the female population vulnerable to systemic inflammation and atherosclerotic changes [27,28]. In the present study, the risk of ischemic heart disease was increased in both male and female nephrolithiasis patients. The large population cohort, in addition to the matched control group and considered covariates, permitted a sufficiently high number of male subgroups, thereby potentiating the statistical power of the present study. On the other hand, the ≥ 60 years old male group did not show an association between nephrolithiasis and stroke in this study. The relatively small size of this subgroup could have

influenced the nonsignificant association in this group. In addition, the decreased rate of urinary tract infection and increased health-related quality of life in older males could attenuate the impact of nephrolithiasis on stroke [27,29].

A longitudinal follow-up study design with a control group matched for demographic and socioeconomic factors may elucidate the previously mixed results on the association between nephrolithiasis and cardiovascular diseases with causalities. Past medical histories and lifestyle factors were comprehensively adjusted using the CCI and a survey of obesity, smoking, and alcohol consumption. In addition, subgroup analyses were performed according to obesity, smoking, and alcohol consumption. However, primarily because this was a medical claims data study, a few limitations should be considered when interpreting the present results. Because these data were based on medical claim codes, subclinical or untreated patients might have been missed in the present results. The types of nephrolithiasis were not specified; thus, nephrolithiasis was heterogeneous in this study. To estimate the differences according to the severity of nephrolithiasis, subgroup analyses were conducted according to mild to moderate or severe nephrolithiasis. In addition, this study used a Korean national cohort; therefore, there could be ethic difference in the association between nephrolithiasis and cardiovascular diseases [30].

Conclusion

Nephrolithiasis was associated with increased risks of stroke and ischemic heart disease. This relation was consistent after considering comorbidities and lifestyle factors including obesity, smoking, and alcohol consumption.

Author Contributions

HGC designed the study; WB, CM, and HGC analyzed the data; SYK and WB drafted and revised the paper; all authors approved the final version of the manuscript.

Data sharing statement

Release of the data by the researcher is not allowed legally. All data are available from the database of National Health Insurance Sharing Service (NHISS) (https://nhiss.nhis.or.kr/). NHISS allows all of these data for any researcher who promises to follow the research ethics with some cost. If one wants to access the data of this article, one can download it from the website after promising to follow the research ethics requirements.

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Table 1 General Characteristics of Participants

Characteristics	Total participants		
	Nephrolithiasis	Control	P-value
Age (years old, n, %)			1.000
40-44	1,593 (8.3)	6,372 (8.3)	
45-49	3,659 (19.2)	14,636 (19.2)	
50-54	4,570 (23.9)	18,280 (23.9)	
55-59	3,525 (18.5)	14,100 (18.5)	
60-64	2,570 (13.5)	10,280 (13.5)	
65-69	1,709 (9.0)	6,836 (9.0)	
70-74	955 (5.0)	3,820 (5.0)	
75-79	402 (2.1)	1,608 (2.1)	
80-84	102 (0.5)	408 (0.5)	
85+	18 (0.1)	72 (0.1)	
Sex (n, %)			1.000
Male	12,303 (64.4)	49,212 (64.4)	
Female	6,800 (35.6)	27,200 (35.6)	
Income (n, %)			1.000
1 (lowest)	2,576 (13.5)	10,304 (13.5)	
2	2,269 (11.9)	9,076 (11.9)	
3	2,893 (15.1)	11,572 (15.1)	
4	4,108 (21.5)	16,432 (21.5)	
5 (highest)	7,257 (38.0)	29,028 (38.0)	
Region of residence (n, %)			1.000
Urban	8,667 (45.4)	34,668 (45.4)	

Rural	10,436 (54.6)	41,744 (54.6)	
CCI score (scores, n, %)			0.005*
0	18,735 (98.1)	74,671 (97.7)	
1	58 (0.3)	370 (0.5)	
2	72 (0.4)	336 (0.4)	
3	53 (0.3)	257 (0.3)	
≥ 4	185 (1.0)	778 (1.0)	
Obesity (BMI, kg/m^2, n, %)			<0.001*
< 18.5 (underweight)	267 (1.4)	1,642 (2.2)	
≥ 18.5 to < 23 (normal)	5,546 (29.0)	27,089 (35.5)	
≥ 23 to < 25 (overweight)	5,586 (29.2)	21,246 (27.8)	
≥ 25 to < 30 (obese I)	7,069 (37.0)	24,472 (32.0)	
≥ 30 (obese II)	635 (3.3)	1,963 (2.6)	
Smoking status (n, %)			<0.001*
Nonsmoker	12,434 (65.1)	48,225 (63.1)	
Past smoker	2,490 (13.0)	9,512 (12.5)	
Current smoker	4,179 (21.9)	18,675 (24.4)	
Alcohol consumption (n, %)			<0.001*
Nondrinker	11,030 (57.7)	40,219 (52.6)	
1-3 times a month	2,985 (15.6)	12,417 (16.3)	
≥ 1 time a week	5,088 (26.6)	23,776 (31.1)	
Total cholesterol (mg/dL, mean, SD)	201.8 (37.2)	199.4 (37.3)	<0.001†
Fasting blood glucose (mg/dL, mean, SD)	99.8 (28.8)	99.5 (29.9)	0.186

Stroke (n, %)	1,615 (8.5)	5,476 (7.2)	<0.001*
Ischemic heart disease (n, %)	1,879 (9.8)	5,895 (7.7)	<0.001*

Abbreviations: BMI, body mass index, kg/m^2, CCI, Charlson comorbidity index

* Chi-square test. Significance at $P < 0.05$

† Independent *t* test. Significance at $P < 0.05$

Table 2 Crude and adjusted hazard ratios (95% confidence interval) for stroke in nephrolithiasis and control groups

Characteristics	Hazard ratios for stroke			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 95,515)				
Nephrolithiasis	1.19 (1.12-1.25)	<0.001*	1.18 (1.11-1.24)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 44,595)				
Nephrolithiasis	1.23 (1.12-1.36)	<0.001*	1.22 (1.11-1.35)	<0.001*
Control	1.00		1.00	
Age < 60 years old, women (n = 22,140)				
Nephrolithiasis	1.32 (1.16-1.51)	<0.001*	1.27 (1.11-1.44)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 16,920)				
Nephrolithiasis	1.03 (0.93-1.15)	0.543	1.03 (0.92-1.14)	0.614
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 11,860)				
Nephrolithiasis	1.23 (1.09-1.38)	0.001*	1.22 (1.08-1.37)	0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

Table 3 Crude and adjusted hazard ratios (95% confidence interval) for ischemic heart disease in nephrolithiasis and control groups

Characteristics	Hazard ratios for ischemic heart disease			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 95,515)				
Nephrolithiasis	1.29 (1.23-1.36)	<0.001*	1.24 (1.18-1.31)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 44,595)				
Nephrolithiasis	1.29 (1.19-1.39)	<0.001*	1.24 (1.14-1.34)	<0.001*
Control	1.00		1.00	
Age < 60 years old, women (n = 22,140)				
Nephrolithiasis	1.51 (1.34-1.70)	<0.001*	1.43 (1.27-1.62)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 16,920)				
Nephrolithiasis	1.23 (1.10-1.37)	<0.001*	1.18 (1.05-1.32)	0.004*
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 11,860)				
Nephrolithiasis	1.18 (1.04-1.35)	0.009*	1.16 (1.02-1.32)	0.024*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

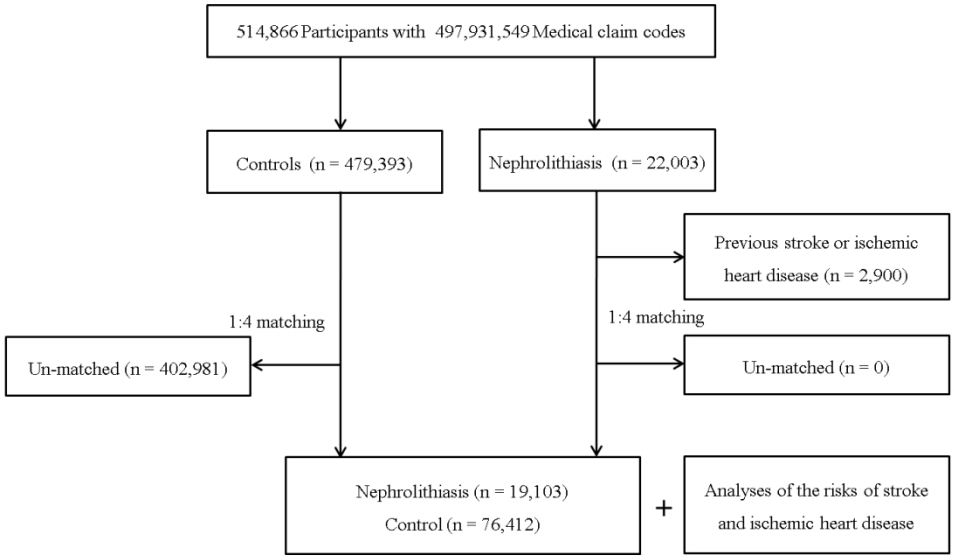
† Models stratified by age, sex, income, and region of residence.

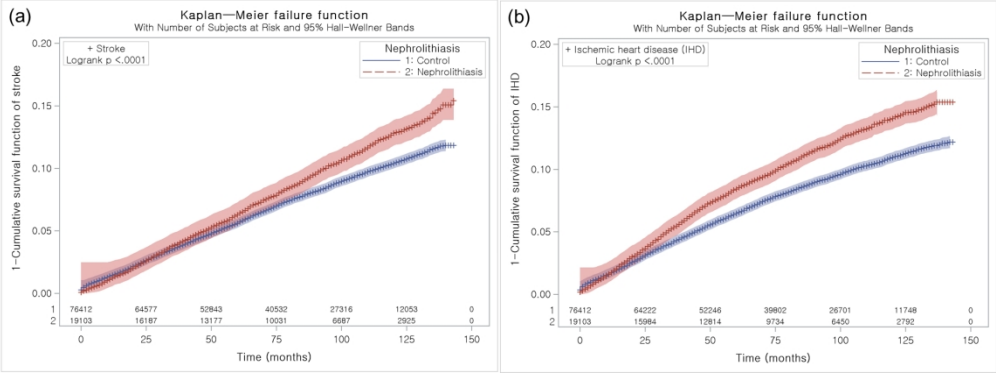
‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

Figure legend

Figure 1 A schematic illustration of the participant selection process that was used in the present study. Of a total of 514,866 participants, 21,994 nephrolithiasis participants were matched with 87,976 control participants for age, sex, income, and region of residence.

Figure 2 Kaplan-Meier survival analysis. (a) The cumulative rate of stroke was higher in the nephrolithiasis group than in the control group. (b) The cumulative rate of ischemic heart disease was higher in the nephrolithiasis group than in the control group.


514,866 Participants with 497,931,549 Medical claim codes
Controls (n = 479,393)
Nephrolithiasis (n = 22,003)
Previous stroke or ischemic heart disease (n = 2,900)
1:4 matching
1:4 matching
Un-matched (n = 402,981)
Un-matched (n = 0)
Nephrolithiasis (n = 19,103)
Control (n = 76,412)
+
Analyses of the risks of stroke and ischemic heart disease


(a)
Kaplan—Meier failure function
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Stroke
Logrank p <.0001
Nephrolithiasis
1: Control
2: Nephrolithiasis
1−Cumulative survival function of stroke
0.20
0.15
0.10
0.05
0.00
1 76412 64577 52843 40532 27316 12053 0
2 19103 16187 13177 10031 6687 2925 0
0 25 50 75 100 125 150
Time (months)
(b)
Kaplan—Meier failure function
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Ischemic heart disease (IHD)
Logrank p <.0001
Nephrolithiasis
1: Control
2: Nephrolithiasis
1−Cumulative survival function of IHD
0.20
0.15
0.10
0.05
0.00
1 76412 64222 52246 39802 26701 11748 0
2 19103 15984 12814 9734 6450 2792 0
0 25 50 75 100 125 150
Time (months)

S1 Table Crude and adjusted hazard ratios (95% confidence interval) for stroke and ischemic heart disease in nephrolithiasis and control groups considering 1-year washout period (n = 84,605)

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
Stroke				
Nephrolithiasis	1.15 (1.08-1.22)	<0.001*	1.14 (1.07-1.21)	<0.001*
Control	1.00		1.00	
Ischemic heart disease				
Nephrolithiasis	1.28 (1.21-1.36)	<0.001*	1.23 (1.16-1.31)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

S2 Table Crude and adjusted hazard ratios (95% confidence interval) for stroke and ischemic heart disease in nephrolithiasis and control groups considering 2-year washout period (n = 74,400)

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
Stroke				
Nephrolithiasis	1.19 (1.12-1.25)	<0.001*	1.18 (1.11-1.24)	<0.001*
Control	1.00		1.00	
Ischemic heart disease				
Nephrolithiasis	1.29 (1.23-1.36)	<0.001*	1.24 (1.18-1.31)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

S3 Table Crude and adjusted hazard ratios (95% confidence interval) for stroke in nephrolithiasis and control groups according to the severity of nephrolithiasis

Characteristics	Hazard ratios for stroke			
	Crude†	P-value	Adjusted†‡	P-value
Mild to moderate nephrolithiasis and matched control groups (n = 55,740)				
Nephrolithiasis	1.15 (1.07-1.24)	<0.001*	1.14 (1.06-1.23)	<0.001*
Control	1.00		1.00	
Severe nephrolithiasis and matched control groups (n = 39,775)				
Nephrolithiasis	1.24 (1.14-1.35)	<0.001*	1.23 (1.12-1.34)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

S4 Table Crude and adjusted hazard ratios (95% confidence interval) for ischemic heart disease in nephrolithiasis and control groups according to the severity of nephrolithiasis

Characteristics	Hazard ratios for ischemic heart disease			
	Crude†	P-value	Adjusted†‡	P-value
Mild to moderate nephrolithiasis and matched control groups (n = 55,740)				
Nephrolithiasis	1.29 (1.20-1.37)	<0.001*	1.25 (1.17-1.34)	<0.001*
Control	1.00		1.00	
Severe nephrolithiasis and matched control groups (n = 39,775)				
Nephrolithiasis	1.30 (1.20-1.42)	<0.001*	1.23 (1.14-1.34)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

S5 Table Subgroup of crude and adjusted hazard ratios (95% confidence interval) for stroke in nephrolithiasis and control groups according to smoking status, alcohol consumption, and obesity

Characteristics	Hazard ratios for stroke			
	Crude	P-value	Adjusted†	P-value
Smoking status				
Nonsmoker (n = 60,659)				
Nephrolithiasis	1.20 (1.12-1.28)	<0.001*	1.32 (1.24-1.41)	<0.001*
Control	1.00		1.00	
Past smoker (n = 12,002)				
Nephrolithiasis	1.18 (0.99-1.42)	0.069	1.17 (1.00-1.38)	0.055
Control	1.00		1.00	
Current smoker (n = 22,854)				
Nephrolithiasis	1.13 (1.00-1.28)	0.050	1.26 (1.13-1.41)	<0.001*
Control	1.00		1.00	
Alcohol consumption				
Nondrinker (n = 51,249)				
Nephrolithiasis	1.14 (1.06-1.23)	<0.001*	1.15 (1.07-1.24)	<0.001*
Control	1.00		1.00	
2-3 time a month (n = 15,402)				
Nephrolithiasis	1.14 (1.06-1.23)	<0.001*	1.20 (1.02-1.40)	0.025*
Control	1.00		1.00	
≥ 1 time a week (n = 28,864)				
Nephrolithiasis	1.22 (1.10-1.37)	<0.001*	1.23 (1.10-1.37)	<0.001*
Control	1.00		1.00	

Obesity				
Underweight (n = 1,909)				
Nephrolithiasis	1.34 (0.90-2.01)	0.149	1.41 (0.94-2.11)	0.098
Control	1.00		1.00	
Normal weight (n = 32,635)				
Nephrolithiasis	1.18 (1.06-1.31)	0.002*	1.16 (1.04-1.29)	0.007*
Control	1.00		1.00	
Overweight (n = 26,832)				
Nephrolithiasis	1.16 (1.04-1.29)	0.007*	1.17 (1.05-1.30)	0.004*
Control	1.00		1.00	
Obese I (n = 31,541)				
Nephrolithiasis	1.17 (1.07-1.28)	0.001*	1.17 (1.07-1.28)	0.001*
Control	1.00		1.00	
Obese II (n = 2,598)				
Nephrolithiasis	1.31 (0.98-1.76)	0.068	1.30 (0.97-1.74)	0.085
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Adjusted for age, sex, income, region, obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

S6 Table Subgroup of crude and adjusted hazard ratios (95% confidence interval) for ischemic heart disease in nephrolithiasis and control groups according to smoking status, alcohol consumption, and obesity

Characteristics	Hazard ratios for ischemic heart disease			
	Crude	P-value	Adjusted†	P-value
Smoking status				
Nonsmoker (n = 60,659)				
Nephrolithiasis	1.19 (1.11-1.27)	<0.001*	1.27 (1.19-1.35)	<0.001*
Control	1.00		1.00	
Past smoker (n = 12,002)				
Nephrolithiasis	1.16 (0.96-1.39)	0.120	1.13 (0.96-1.33)	0.139
Control	1.00		1.00	
Current smoker (n = 22,854)				
Nephrolithiasis	1.14 (1.01-1.29)	0.033*	1.21 (1.08-1.35)	0.001*
Control	1.00		1.00	
Alcohol consumption				
Nondrinker (n = 51,249)				
Nephrolithiasis	1.29 (1.21-1.38)	<0.001*	1.25 (1.17-1.34)	<0.001*
Control	1.00		1.00	

2-3 time a month (n = 15,402)				
Nephrolithiasis	1.43 (1.25-1.64)	<0.001*	1.39 (1.21-1.59)	<0.001*
Control	1.00		1.00	
≥ 1 time a week (n = 28,864)				
Nephrolithiasis	1.18 (1.06-1.31)	0.002*	1.14 (1.03-1.26)	0.015*
Control	1.00		1.00	
Obesity				
Underweight (n = 1,909)				
Nephrolithiasis	0.54 (0.25-1.17)	0.120	0.58 (0.27-1.26)	0.167
Control	1.00		1.00	
Normal weight (n = 32,635)				
Nephrolithiasis	1.26 (1.13-1.41)	<0.001*	1.24 (1.12-1.39)	<0.001*
Control	1.00		1.00	
Overweight (n = 26,832)				
Nephrolithiasis	1.35 (1.22-1.48)	<0.001*	1.33 (1.21-1.47)	<0.001*
Control	1.00		1.00	
Obese I (n = 31,541)				
Nephrolithiasis	1.19 (1.10-1.29)	<0.001*	1.19 (1.10-1.29)	<0.001*

Control	1.00		1.00	
Obese II (n = 2,598)				
Nephrolithiasis	1.28 (1.00-1.64)	0.048*	1.26 (0.98-1.61)	0.072
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Adjusted for age, sex, income, region, obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	p5
Methods			
Study design	4	Present key elements of study design early in the paper	p5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	p5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	p7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p5-7
Bias	9	Describe any efforts to address potential sources of bias	p5-8
Study size	10	Explain how the study size was arrived at	p7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p7-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P7-8
		(*b*) Describe any methods used to examine subgroups and interactions	P7-8
		(*c*) Explain how missing data were addressed	p6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	p6
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			**Pages**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p8
		(b) Give reasons for non-participation at each stage	p6
		(c) Consider use of a flow diagram	p6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p8
		(b) Indicate number of participants with missing data for each variable of interest	p6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	p8-9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p8-9
		(*b*) Report category boundaries when continuous variables were categorized	p8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	P8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	p9-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association of nephrolithiasis with the risk of cardiovascular diseases: A longitudinal follow-up study using a national health screening cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040034.R2
Article Type:	Original research
Date Submitted by the Author:	15-Sep-2020
Complete List of Authors:	Kim, So Young; CHA University, Otorhinolaryngology-Head & Neck Surgery Bang, Woo Jin; Hallym University College of Medicine, Department of Urology Min, Chanyang; Hallym University College of Medicine, Hallym Data Science Laboratory Choi, Hyo Geun; Hallym University, Otorhinolaryngology-Head & Neck Surgery
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Adult neurology < NEUROLOGY, Stroke < NEUROLOGY, Coronary heart disease < CARDIOLOGY

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Association of nephrolithiasis with the risk of cardiovascular diseases: A longitudinal follow-up study using a national health screening cohort

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Running title: Nephrolithiasis and cardiovascular diseases

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Abstract

Objectives: The aim of this study was to explore the associations of stroke and ischemic heart disease in nephrolithiasis patients.

Design: A longitudinal follow-up study

Setting: Data from the Korean National Health Insurance Service-Health Screening Cohort (2002 to 2013) were retrieved to identify the occurrence of nephrolithiasis.

Participants and Interventions: In total, 19,103 nephrolithiasis patients were matched at a 1:4 ratio with control participants for age, sex, income, and region of residence.

Primary and secondary outcome measures: The occurrence of stroke and ischemic heart disease was analyzed in both the nephrolithiasis and control participants. The primary outcome was the hazard ratios (HRs) of stroke and ischemic heart disease in a stratified Cox proportional hazard model. Smoking, alcohol consumption, obesity, and the Charlson comorbidity index were adjusted for as covariates. Subgroup analyses according to age and sex were also performed.

Results: Eight percent (1,615/19,103) of the nephrolithiasis patients and 7.2% (5,476/76,412) of the control participants experienced stroke. Nine percent (1,879/19,103) of the nephrolithiasis patients and 7.7% (5,895/76,412) of the control participants had ischemic heart disease. The nephrolithiasis patients had risks of stroke and ischemic heart disease that were 1.18 times (95% confidence interval [95% CI] = 1.11–1.24) and 1.24 times (95% CI = 1.18–1.31) those of the control participants, respectively. The age and sex subgroups showed consistent results.

Conclusions: Nephrolithiasis was associated with increased risks of stroke and ischemic heart disease.

Key words: Nephrolithiasis; Myocardial Ischemia; Stroke; Risk Factors; Cohort Studies

Strengths and limitations of this study

- This study adds to previous findings by analyzing a large cohort. The large study population provided many control patients matched for age, sex, income, and region of residence.
- The lifestyle factors of obesity, smoking status, and alcohol consumption and the additional factors of the Charlson comorbidity index, total cholesterol, and fasting blood glucose were adjusted for to minimize confounding by these covariates.
- Because these data were based on medical claim codes, subclinical or untreated patients might have been missed in this study.

Funding: The authors have no conflicts of interest to declare. This work was supported in part by a research grant (NRF-2018-R1D1A1A02085328) from the National Research Foundation (NRF) of Korea and the Hallym University Research Fund (HURF-2018-53).

Competing interest: None declared.

Introduction

Nephrolithiasis is a common urinary tract disease. Approximately 4.2% - 10.1% of the worldwide population and 3.5% of the Korean population suffer from nephrolithiasis [1-3]. The prevalence of nephrolithiasis is increasing worldwide [4]. The increasing prevalence of obesity has been suspected to promote the formation of nephrolithiasis [5]. Acute renal colic due to the blockage of the ureter is an acute urinary manifestation of nephrolithiasis. In addition, nephrolithiasis can be associated with systemic comorbidities, including metabolic syndrome [6]. For decades, a growing number of epidemiologic studies have suggested the association of nephrolithiasis with systemic comorbidities, such as diabetes and hypertension [7,8]. Because these comorbidities are predisposing conditions for cardiovascular disorders, researchers have also explored the associations between nephrolithiasis and cardiovascular disorders [9-11].

Previous studies have reported an association between nephrolithiasis and stroke [9,10]. However, to our knowledge, neither our prior study nor most other published studies have considered the impacts of lifestyle factors, including obesity, smoking and alcohol consumption, on the association between nephrolithiasis and stroke. Because renal stone formation, as well as cardiovascular disease, has been suggested to be related to obesity and smoking, the possible confounding effects of these covariates should be controlled to elucidate the true association between nephrolithiasis and cardiovascular diseases [12,13]. In addition, because cerebrovascular disease (stroke) and cardiovascular disease (ischemic heart disease) are associated with each other, these vascular disorders need to be independently considered with regard to their relationship with nephrolithiasis.

We hypothesized that nephrolithiasis might increase the risks of both stroke and ischemic heart disease, probably due to their shared pathophysiology. The present study is an improvement on our previous study on the association between nephrolithiasis and stroke due to the inclusion of ischemic heart disease. In addition, potential confounders, including

obesity, smoking, and alcohol consumption, were considered. The risks of stroke and ischemic heart disease were analyzed by adjusting for past medical histories using the Charlson comorbidity index (CCI) and lifestyle factors, including obesity, smoking, and alcohol consumption. Because prior studies indicated that there might be sex-based differences in the association between nephrolithiasis and cardiovascular disease [10], subgroup analyses were conducted.

Materials and Methods

Study population

The ethics committee of Hallym University (2017-I102) approved this study. The need to obtain written informed consent was waived by the Institutional Review Board. All analyses adhered to the guidelines and regulations of the ethics committee of Hallym University. A detailed description of the Korean National Health Insurance Service-Health Screening Cohort data is available elsewhere [14].

Definition of nephrolithiasis

Nephrolithiasis was defined if the participants were diagnosed with the International Classification of Diseases 10th Revision (ICD-10) code N20 $\geq$ 2 times, as in our previous studies [9,15].

2.3. Definition of stroke and ischemic heart disease

Stroke and ischemic heart disease were identified based on ICD-10 codes (I60-I69 for stroke and I20-I25 for ischemic heart disease), as in our previous study [9].

Participant selection

Nephrolithiasis patients (n = 22,003) were selected from 514,866 participants with 497,931,549 medical claim codes. The control group included participants who were never diagnosed with nephrolithiasis from 2002 through 2013 (n = 492,863). Nephrolithiasis patients were matched at a 1:4 ratio with the control participants for age, sex, income, and region of residence. To minimize selection bias, the control participants were selected with random number generation. The index date of each nephrolithiasis patient was considered the date of the first diagnosis of nephrolithiasis. The index date of the control participants was considered the index date of their matched nephrolithiasis patient. Therefore, each matched nephrolithiasis patient and their respective control participants had the same index date. Nine nephrolithiasis patients with previous stroke or ischemic heart disease before the index date were excluded. Control participants with previous stroke or ischemic heart disease before the index date were also excluded. Among the control participants, 404,887 were excluded during the matching procedure. Finally, 19,103 nephrolithiasis patients were 1:4 matched with 76,412 control participants (Fig. 1). The nephrolithiasis patients who visited the emergency department or were hospitalized were classified as having severe nephrolithiasis, while the others were classified as having mild to moderate nephrolithiasis.

Covariates

Patients were divided into age groups with 5-year intervals: 40-44, 45-49, 50-54…, and 85+ years old. A total of 10 age groups were specified. There were 5 income classes (classes 1 [lowest income]-5 [highest income]). The region of residence was categorized as urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) or rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

Tobacco smoking was categorized based on the participant's current smoking status (nonsmoker, past smoker, or current smoker). Alcohol consumption was categorized on the basis of the frequency of alcohol consumption (nondrinker, 1 – 3 times a month, and ≥ 1 time a week) because previous studies indicated a positive association of nephrolithiasis with binge drinking [16] and a negative association with moderate alcohol consumption [17]. Obesity was determined according to the body mass index (BMI, kg/m^2). Missing BMI variables were replaced by the mean BMI of the final selected participants. BMI was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), or ≥ 30 (obese II) based on the Asia-Pacific criteria produced by the Western Pacific Regional Office (WPRO) 2000 [18]. Serum levels of total cholesterol (mg/dL) and fasting glucose (mg/dL) were included as continuous variables.

The CCI has been used widely to measure the disease burden based on 17 comorbidities. A score was calculated for each participant depending on the number and severity of diseases. The CCI was measured as a continuous variable (0 [no comorbidities] through 29 [multiple comorbidities]) [19,20]. The scores excluding cerebrovascular disease were calculated. The CCI score was evaluated as a continuous variable.

Statistical analyses

The general characteristics were compared between the nephrolithiasis and control groups with chi-square tests.

To analyze the hazard ratios (HRs) and 95% confidence intervals (CIs) of stroke and ischemic heart disease in nephrolithiasis patients compared to control participants, a stratified Cox proportional hazard model was used. In this analysis, a crude model and a model adjusted for obesity, smoking status, alcohol consumption, and CCI score were generated.

The analysis was stratified by matching variables such as age, sex, income, and region of residence. Kaplan-Meier curves were constructed, and log-rank tests were performed.

For the subgroup analyses, we stratified the participants by age and sex (< 60 years old and ≥ 60 years old; males and females), severity of nephrolithiasis (mild to moderate and severe), and analyzed the crude and adjusted models.

Two-tailed analyses were performed, and significance was defined as a P value less than 0.05. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

Patients and public involvement statement

This national cohort study used data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). Detailed descriptions of these data are available in our previous studies[21,22]. No patients were involved in the development of the research question or the design of the study. We have no plan to disseminate the results to the patients. Because the NHIS-NSC data are based on national health claim codes, release of the data by the researcher is illegal. All data are available from the National Health Insurance Sharing Service (NHISS) database (https://nhiss.nhis.or.kr/).

The NHISS allows all of these data to be used by any researcher who promises to follow the research ethics guidelines, with some associated costs. If one wants to access the data described in this article, one could download them from the website after promising to adhere to the research ethics requirements.

Results

Age, sex, income, and region of residence were exactly matched between the nephrolithiasis and control groups (P =1.000). The rates of low CCI, overweight, obesity I, obesity II, and nonsmoker status were higher in the nephrolithiasis group than in the control group (each P <

0.05). The distribution of alcohol consumption and the serum level of total cholesterol were different between the nephrolithiasis group and the control group (each $P < 0.001$). The prevalence of stroke and ischemic heart disease was lower in the nephrolithiasis group than in the control group ($P < 0.001$, Table 1).

The adjusted HR of stroke in the nephrolithiasis group was 1.18 (95% CIs = 1.11–1.24, $P < 0.001$) (Fig. 2a). In the subgroup analyses according to age and sex, the adjusted HRs of stroke were higher in the nephrolithiasis group than in the control group, except for in the subgroup of males ≥ 60 years old (Table 2).

The adjusted HR of ischemic heart disease in the nephrolithiasis group was 1.24 (95% CIs = 1.18–1.31, $P < 0.001$) (Fig. 2b). In the subgroup analyses according to age and sex, the adjusted HRs of ischemic heart disease were higher in the nephrolithiasis group than in the control group (Table 3). The associations of stroke and ischemic heart disease with nephrolithiasis remained consistent when considering a 1-year washout period (Table S1 and Table S2). Patients with both mild to moderate and severe nephrolithiasis had higher odds of stroke and ischemic heart disease (Table S3 and Table S4). When the participants were stratified by smoking, alcohol consumption, and obesity, the association of nephrolithiasis with stroke was consistent in all subgroups, except for in the past smoker, underweight, and obese II subgroups (Table S5 and Table S6).

Discussion

Nephrolithiasis patients had 1.18 and 1.25 times higher risks of stroke and ischemic heart disease, respectively. These increased risks of stroke and ischemic heart disease were consistent in all age and sex subgroups, except for in males ≥ 60 years old, in whom there was not an association between nephrolithiasis and stroke. This study added to previous findings by analyzing a large cohort. The large study population provided many control

participants matched for age, sex, income, and region of residence. Furthermore, the lifestyle factors of obesity, smoking status, and alcohol consumption and past medical histories were adjusted for to minimize confounding by these covariates. This study was a longitudinal follow-up study that explored the causal relationship between nephrolithiasis and stroke or ischemic heart disease. Participants who had previous histories of stroke or ischemic heart disease before the index date were excluded. In addition, the participants who had histories of stroke or ischemic heart disease at 1 year and 2 years after the index date were excluded from the supplementary analyses.

The metabolic perturbations in nephrolithiasis patients, which manifest as hypercalciuria, hyperuricemia, or hyperoxaluria, could mediate the increased risk of cardiovascular plaque formation and metabolic changes associated with cardiovascular disorders. It has been suggested that the abnormal calcification process is similar in the atherosclerosis of cerebral or coronary vasculature and the formation of nephrolithiasis [23]. There is evidence of the presence of these metabolic changes in nephrolithiasis patients; the levels of calcification inhibitors were found to be decreased in the blood and urine of atherosclerosis and nephrolithiasis patients [23]. In addition to the direct calcification process, other indirect metabolic changes in nephrolithiasis patients might impact the risk of cardiovascular disorders. Metabolic syndrome patients had 1.25 times (95% CI = 1.03–1.50) higher odds of nephrolithiasis in a cross-sectional study [24]. In an experimental animal study, a metabolic syndrome rat model with insulin resistance had an increased risk of urinary calcium stone formation [25]. In a clinical study, the metabolic syndromic traits of obesity, hypertension, diabetes, and dyslipidemia were 1.78 times (95% CI = 1.22–2.66) more common in nephrolithiasis patients with recurrent or multiple stones [26]. Therefore, nephrolithiasis should be considered a systemic metabolic disease rather than a local metabolic disease involving

calcification. These systemic metabolic disturbances in nephrolithiasis patients might mediate the increased risk of cardiovascular disorders.

The risk of stroke was greater in the nephrolithiasis patients than in the control patients in the present study. Our previous study reported a 1.13 times (95% CI = 1.06–1.21) greater risk of ischemic stroke in nephrolithiasis patients than in the control group [9]. A recent meta-analysis reported that a history of nephrolithiasis was associated with a 1.23-fold (95% CI = 1.06–1.38) increased relative risk of stroke [11]. However, few previous studies considered smoking, obesity, and alcohol consumption, and only selected comorbidities were used for adjustment. After adjusting for both lifestyle factors and past medical histories, the risk of stroke was greater in the nephrolithiasis patients than in the controls in the current study. Moreover, the risk of ischemic heart disease was greater in the nephrolithiasis patients than in the controls in this study. A recent meta-analysis reported that the relative risk of coronary heart disease was 1.24 times (95% CI = 1.14–1.36) higher in nephrolithiasis patients [11]. This figure is similar to the present HR of 1.25 (95% CI = 1.18–1.31).

The age and sex subgroup analyses indicated increased risks of stroke and ischemic heart disease in nephrolithiasis patients, except for in males ≥ 60 years old. A meta-analysis showed that the pooled HR for myocardial infarction was 1.49 (95% CI = 1.21–1.82) in the female group, while there was no association between nephrolithiasis and myocardial infarction in the male group [10]. This female-specific association between nephrolithiasis and myocardial infarction can be explained by the higher rate of urinary tract infection in females than in males, which makes the female population vulnerable to systemic inflammation and atherosclerotic changes [27,28]. In the present study, the risk of ischemic heart disease was increased in both male and female nephrolithiasis patients. Further analyses adjusting for urinary tract infection (ICD-10: N30, 300,301, 302, 303, 304, 308, 309, 340, 341, and 342) were conducted, which showed the consistent association of nephrolithiasis with stroke and

ischemic heart disease, except for in the subgroup of women ≥ 60 years old, in whom there was no significant association between nephrolithiasis and ischemic heart disease (Table S7-S9). The large sample population, matched control group and adjusted covariates meant that there were sufficient participants in the male subgroups, increasing the statistical power of the present study. On the other hand, there was no association between nephrolithiasis and stroke in the ≥ 60-year-old male group in this study. The relatively small size of this subgroup could have led to the nonsignificant association in this group. In addition, the decreased rate of urinary tract infection and increased health-related quality of life in older males could attenuate the impact of nephrolithiasis on stroke [27,29].

The longitudinal follow-up study design with a control group matched for demographic and socioeconomic factors enabled the elucidation of the previously mixed results on the causal association between nephrolithiasis and cardiovascular diseases. Past medical histories and lifestyle factors were comprehensively adjusted for using the CCI and a survey of obesity, smoking, and alcohol consumption. In addition, subgroup analyses were performed stratified by obesity, smoking, and alcohol consumption. However, primarily because this study used medical claims data, a few limitations should be considered when interpreting the present results. Because these data were based on medical claim codes, laboratory findings, such as serum creatinine, bicarbonate, HbA1C, and serum calcium levels, could not be obtained. In addition, subclinical or untreated patients might have been missed in the present results. The types of nephrolithiasis were not specified; thus, nephrolithiasis was heterogeneous in this study. To estimate the differences according to the severity of nephrolithiasis, subgroup analyses were conducted comparing patients with mild to moderate and severe nephrolithiasis. In addition, this study used a Korean national cohort; therefore, there could be ethnic differences in the association between nephrolithiasis and cardiovascular diseases [30].

Conclusion

Nephrolithiasis was associated with increased risks of stroke and ischemic heart disease in men and women ≥ 40 years old. Mild to moderate and severe nephrolithiasis were related to elevated risks of stroke and ischemic heart disease. This relationship was consistent after considering comorbidities and lifestyle factors, including obesity, smoking, and alcohol consumption.

Author contributions

HGC designed the study; WB, CM, and HGC analyzed the data; SYK and WB drafted and revised the paper; all authors approved the final version of the manuscript.

Data sharing statement

Release of the data by the researcher is illegal. All data are available from the National Health Insurance Sharing Service (NHISS) database (https://nhiss.nhis.or.kr/).

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Table 1 General characteristics of participants

Characteristics	Total participants		
	Nephrolithiasis	Control	P-value
Age (years old, n, %)			1.000
40-44	1,593 (8.3)	6,372 (8.3)	
45-49	3,659 (19.2)	14,636 (19.2)	
50-54	4,570 (23.9)	18,280 (23.9)	
55-59	3,525 (18.5)	14,100 (18.5)	
60-64	2,570 (13.5)	10,280 (13.5)	
65-69	1,709 (9.0)	6,836 (9.0)	
70-74	955 (5.0)	3,820 (5.0)	
75-79	402 (2.1)	1,608 (2.1)	
80-84	102 (0.5)	408 (0.5)	
85+	18 (0.1)	72 (0.1)	
Sex (n, %)			1.000
Male	12,303 (64.4)	49,212 (64.4)	
Female	6,800 (35.6)	27,200 (35.6)	
Income (n, %)			1.000
1 (lowest)	2,576 (13.5)	10,304 (13.5)	
2	2,269 (11.9)	9,076 (11.9)	
3	2,893 (15.1)	11,572 (15.1)	
4	4,108 (21.5)	16,432 (21.5)	
5 (highest)	7,257 (38.0)	29,028 (38.0)	
Region of residence (n, %)			1.000
Urban	8,667 (45.4)	34,668 (45.4)	

Rural	10,436 (54.6)	41,744 (54.6)	
CCI score (scores, n, %)			0.005*
0	18,735 (98.1)	74,671 (97.7)	
1	58 (0.3)	370 (0.5)	
2	72 (0.4)	336 (0.4)	
3	53 (0.3)	257 (0.3)	
≥ 4	185 (1.0)	778 (1.0)	
Obesity (BMI, kg/m^2, n, %)			<0.001*
< 18.5 (underweight)	267 (1.4)	1,642 (2.2)	
≥ 18.5 to < 23 (normal)	5,546 (29.0)	27,089 (35.5)	
≥ 23 to < 25 (overweight)	5,586 (29.2)	21,246 (27.8)	
≥ 25 to < 30 (obese I)	7,069 (37.0)	24,472 (32.0)	
≥ 30 (obese II)	635 (3.3)	1,963 (2.6)	
Smoking status (n, %)			<0.001*
Nonsmoker	12,434 (65.1)	48,225 (63.1)	
Past smoker	2,490 (13.0)	9,512 (12.5)	
Current smoker	4,179 (21.9)	18,675 (24.4)	
Alcohol consumption (n, %)			<0.001*
Nondrinker	11,030 (57.7)	40,219 (52.6)	
1-3 times per month	2,985 (15.6)	12,417 (16.3)	
≥ 1 time per week	5,088 (26.6)	23,776 (31.1)	
Total cholesterol (mg/dL, mean, SD)	201.8 (37.2)	199.4 (37.3)	<0.001†
Fasting blood glucose (mg/dL, mean, SD)	99.8 (28.8)	99.5 (29.9)	0.186

Stroke (n, %)	1,615 (8.5)	5,476 (7.2)	<0.001*
Ischemic heart disease (n, %)	1,879 (9.8)	5,895 (7.7)	<0.001*

Abbreviations: BMI, body mass index, kg/m^2, CCI, Charlson comorbidity index

* Chi-square test. Significance at $P < 0.05$

† Independent *t* test. Significance at $P < 0.05$

Table 2 Crude and adjusted hazard ratios (95% confidence interval) for stroke in the nephrolithiasis and control groups

Characteristics	Hazard ratios for stroke			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 95,515)				
Nephrolithiasis	1.19 (1.12-1.25)	<0.001*	1.18 (1.11-1.24)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 44,595)				
Nephrolithiasis	1.23 (1.12-1.36)	<0.001*	1.22 (1.11-1.35)	<0.001*
Control	1.00		1.00	
Age < 60 years old, women (n = 22,140)				
Nephrolithiasis	1.32 (1.16-1.51)	<0.001*	1.27 (1.11-1.44)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 16,920)				
Nephrolithiasis	1.03 (0.93-1.15)	0.543	1.03 (0.92-1.14)	0.614
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 11,860)				
Nephrolithiasis	1.23 (1.09-1.38)	0.001*	1.22 (1.08-1.37)	0.001*
Control	1.00		1.00	

* Cox proportional hazard regression model, significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

Table 3 Crude and adjusted hazard ratios (95% confidence interval) for ischemic heart disease in the nephrolithiasis and control groups

Characteristics	Hazard ratios for ischemic heart disease			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 95,515)				
Nephrolithiasis	1.29 (1.23-1.36)	<0.001*	1.24 (1.18-1.31)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 44,595)				
Nephrolithiasis	1.29 (1.19-1.39)	<0.001*	1.24 (1.14-1.34)	<0.001*
Control	1.00		1.00	
Age < 60 years old, women (n = 22,140)				
Nephrolithiasis	1.51 (1.34-1.70)	<0.001*	1.43 (1.27-1.62)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 16,920)				
Nephrolithiasis	1.23 (1.10-1.37)	<0.001*	1.18 (1.05-1.32)	0.004*
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 11,860)				
Nephrolithiasis	1.18 (1.04-1.35)	0.009*	1.16 (1.02-1.32)	0.024*
Control	1.00		1.00	

* Cox proportional hazard regression model, significance at $P < 0.05$

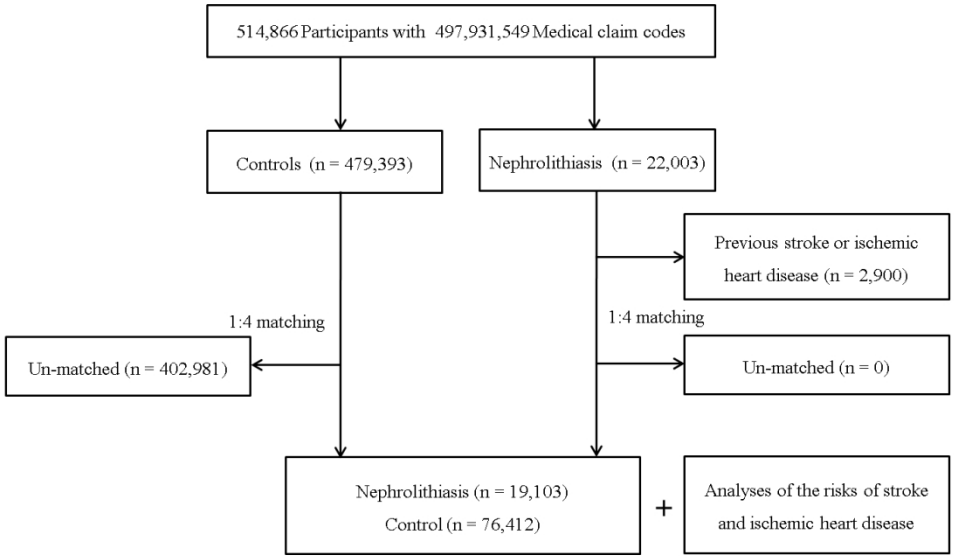
† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

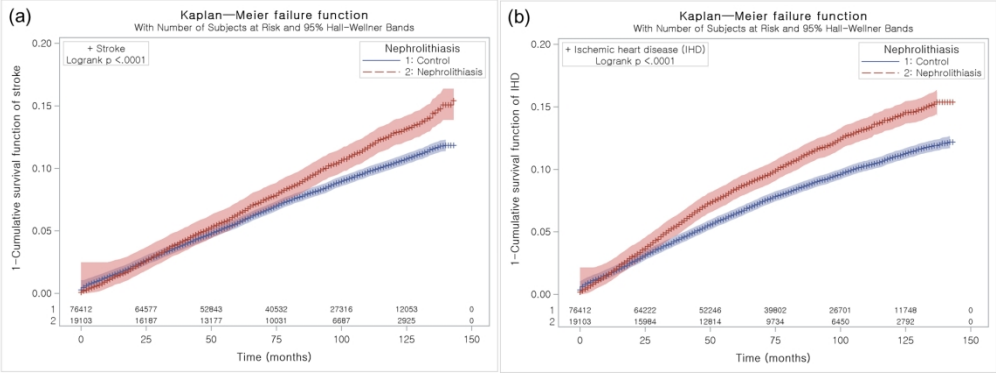
Figure legends

Figure 1 A schematic illustration of the participant selection process that was used in the present study. Of a total of 514,866 participants, 21,994 nephrolithiasis participants were matched with 87,976 control participants for age, sex, income, and region of residence.

Figure 2 Kaplan-Meier survival analysis. (a) The cumulative rate of stroke was higher in the nephrolithiasis group than in the control group. (b) The cumulative rate of ischemic heart disease was higher in the nephrolithiasis group than in the control group.



A schematic illustration of the participant selection process that was used in the present study. Of a total of 514,866 participants, 21,994 nephrolithiasis participants were matched with 87,976 control participants for age, sex, income, and region of residence.



Kaplan-Meier survival analysis. (a) The cumulative rate of stroke was higher in the nephrolithiasis group than in the control group. (b) The cumulative rate of ischemic heart disease was higher in the nephrolithiasis group than in the control group.

Table S1 Crude and adjusted hazard ratios (95% confidence interval) for stroke and ischemic heart disease in the nephrolithiasis and control groups considering a 1-year washout period (n = 84,605)

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
Stroke				
Nephrolithiasis	1.15 (1.08-1.22)	<0.001*	1.14 (1.07-1.21)	<0.001*
Control	1.00		1.00	
Ischemic heart disease				
Nephrolithiasis	1.28 (1.21-1.36)	<0.001*	1.23 (1.16-1.31)	<0.001*
Control	1.00		1.00	

* Cox proportional hazard regression model, significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

Table S2 Crude and adjusted hazard ratios (95% confidence interval) for stroke and ischemic heart disease in the nephrolithiasis and control groups considering a 2-year washout period (n = 74,400)

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
Stroke				
Nephrolithiasis	1.19 (1.12-1.25)	<0.001*	1.18 (1.11-1.24)	<0.001*
Control	1.00		1.00	
Ischemic heart disease				
Nephrolithiasis	1.29 (1.23-1.36)	<0.001*	1.24 (1.18-1.31)	<0.001*
Control	1.00		1.00	

* Cox proportional hazard regression model, significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

Table S3 Crude and adjusted hazard ratios (95% confidence interval) for stroke in the nephrolithiasis and control groups according to the severity of nephrolithiasis

Characteristics	Hazard ratios for stroke			
	Crude†	P-value	Adjusted†‡	P-value
Mild to moderate nephrolithiasis and matched control groups (n = 55,740)				
Nephrolithiasis	1.15 (1.07-1.24)	<0.001*	1.14 (1.06-1.23)	<0.001*
Control	1.00		1.00	
Severe nephrolithiasis and matched control groups (n = 39,775)				
Nephrolithiasis	1.24 (1.14-1.35)	<0.001*	1.23 (1.12-1.34)	<0.001*
Control	1.00		1.00	

* Cox proportional hazard regression model, significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

Table S4 Crude and adjusted hazard ratios (95% confidence interval) for ischemic heart disease in the nephrolithiasis and control groups according to the severity of nephrolithiasis

Characteristics	Hazard ratios for ischemic heart disease			
	Crude†	P-value	Adjusted†‡	P-value
Mild to moderate nephrolithiasis and matched control groups (n = 55,740)				
Nephrolithiasis	1.29 (1.20-1.37)	<0.001*	1.25 (1.17-1.34)	<0.001*
Control	1.00		1.00	
Severe nephrolithiasis and matched control groups (n = 39,775)				
Nephrolithiasis	1.30 (1.20-1.42)	<0.001*	1.23 (1.14-1.34)	<0.001*
Control	1.00		1.00	

* Cox proportional hazard regression model, significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

Table S5 Crude and adjusted hazard ratios (95% confidence interval) for stroke in the nephrolithiasis and control subgroups stratified by smoking status, alcohol consumption, and obesity

Characteristics	Hazard ratios for stroke			
	Crude	P-value	Adjusted†	P-value
Smoking status				
Nonsmoker (n = 60,659)				
Nephrolithiasis	1.20 (1.12-1.28)	<0.001*	1.32 (1.24-1.41)	<0.001*
Control	1.00		1.00	
Past smoker (n = 12,002)				
Nephrolithiasis	1.18 (0.99-1.42)	0.069	1.17 (1.00-1.38)	0.055
Control	1.00		1.00	
Current smoker (n = 22,854)				
Nephrolithiasis	1.13 (1.00-1.28)	0.050	1.26 (1.13-1.41)	<0.001*
Control	1.00		1.00	
Alcohol consumption				
Nondrinker (n = 51,249)				
Nephrolithiasis	1.14 (1.06-1.23)	<0.001*	1.15 (1.07-1.24)	<0.001*
Control	1.00		1.00	
2-3 times per month (n = 15,402)				
Nephrolithiasis	1.14 (1.06-1.23)	<0.001*	1.20 (1.02-1.40)	0.025*
Control	1.00		1.00	
≥ 1 time per week (n = 28,864)				
Nephrolithiasis	1.22 (1.10-1.37)	<0.001*	1.23 (1.10-1.37)	<0.001*
Control	1.00		1.00	

Obesity				
Underweight (n = 1,909)				
Nephrolithiasis	1.34 (0.90-2.01)	0.149	1.41 (0.94-2.11)	0.098
Control	1.00		1.00	
Normal weight (n = 32,635)				
Nephrolithiasis	1.18 (1.06-1.31)	0.002*	1.16 (1.04-1.29)	0.007*
Control	1.00		1.00	
Overweight (n = 26,832)				
Nephrolithiasis	1.16 (1.04-1.29)	0.007*	1.17 (1.05-1.30)	0.004*
Control	1.00		1.00	
Obese I (n = 31,541)				
Nephrolithiasis	1.17 (1.07-1.28)	0.001*	1.17 (1.07-1.28)	0.001*
Control	1.00		1.00	
Obese II (n = 2,598)				
Nephrolithiasis	1.31 (0.98-1.76)	0.068	1.30 (0.97-1.74)	0.085
Control	1.00		1.00	

* Cox proportional hazard regression model, significance at $P < 0.05$

† Adjusted for age, sex, income, region, obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

S6 Table Crude and adjusted hazard ratios (95% confidence interval) for ischemic heart disease in the nephrolithiasis and control subgroups stratified by smoking status, alcohol consumption, and obesity

Characteristics	Hazard ratios for ischemic heart disease			
	Crude	P-value	Adjusted†	P-value
Smoking status				
Nonsmoker (n = 60,659)				
Nephrolithiasis	1.19 (1.11-1.27)	<0.001*	1.27 (1.19-1.35)	<0.001*
Control	1.00		1.00	
Past smoker (n = 12,002)				
Nephrolithiasis	1.16 (0.96-1.39)	0.120	1.13 (0.96-1.33)	0.139
Control	1.00		1.00	
Current smoker (n = 22,854)				
Nephrolithiasis	1.14 (1.01-1.29)	0.033*	1.21 (1.08-1.35)	0.001*
Control	1.00		1.00	
Alcohol consumption				
Nondrinker (n = 51,249)				
Nephrolithiasis	1.29 (1.21-1.38)	<0.001*	1.25 (1.17-1.34)	<0.001*
Control	1.00		1.00	

2-3 times per month (n = 15,402)				
Nephrolithiasis	1.43 (1.25-1.64)	<0.001*	1.39 (1.21-1.59)	<0.001*
Control	1.00		1.00	
≥ 1 time per week (n = 28,864)				
Nephrolithiasis	1.18 (1.06-1.31)	0.002*	1.14 (1.03-1.26)	0.015*
Control	1.00		1.00	
Obesity				
Underweight (n = 1,909)				
Nephrolithiasis	0.54 (0.25-1.17)	0.120	0.58 (0.27-1.26)	0.167
Control	1.00		1.00	
Normal weight (n = 32,635)				
Nephrolithiasis	1.26 (1.13-1.41)	<0.001*	1.24 (1.12-1.39)	<0.001*
Control	1.00		1.00	
Overweight (n = 26,832)				
Nephrolithiasis	1.35 (1.22-1.48)	<0.001*	1.33 (1.21-1.47)	<0.001*
Control	1.00		1.00	
Obese I (n = 31,541)				
Nephrolithiasis	1.19 (1.10-1.29)	<0.001*	1.19 (1.10-1.29)	<0.001*

Control	1.00		1.00	
Obese II (n = 2,598)				
Nephrolithiasis	1.28 (1.00-1.64)	0.048*	1.26 (0.98-1.61)	0.072
Control	1.00		1.00	

* Cox proportional hazard regression model, significance at $P < 0.05$

† Adjusted for age, sex, income, region, obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, and CCI scores.

Table S7 General characteristics of participants

Characteristics	Total participants		
	Nephrolithiasis	Control	P-value
Age (years old, n, %)			1.000
40-44	1,593 (8.3)	6,372 (8.3)	
45-49	3,659 (19.2)	14,636 (19.2)	
50-54	4,570 (23.9)	18,280 (23.9)	
55-59	3,525 (18.5)	14,100 (18.5)	
60-64	2,570 (13.5)	10,280 (13.5)	
65-69	1,709 (9.0)	6,836 (9.0)	
70-74	955 (5.0)	3,820 (5.0)	
75-79	402 (2.1)	1,608 (2.1)	
80-84	102 (0.5)	408 (0.5)	
85+	18 (0.1)	72 (0.1)	
Sex (n, %)			1.000
Male	12,303 (64.4)	49,212 (64.4)	
Female	6,800 (35.6)	27,200 (35.6)	
Income (n, %)			1.000
1 (lowest)	2,576 (13.5)	10,304 (13.5)	
2	2,269 (11.9)	9,076 (11.9)	
3	2,893 (15.1)	11,572 (15.1)	
4	4,108 (21.5)	16,432 (21.5)	
5 (highest)	7,257 (38.0)	29,028 (38.0)	
Region of residence (n, %)			1.000

Urban	8,667 (45.4)	34,668 (45.4)	
Rural	10,436 (54.6)	41,744 (54.6)	
CCI score (scores, n, %)			0.005*
0	18,735 (98.1)	74,671 (97.7)	
1	58 (0.3)	370 (0.5)	
2	72 (0.4)	336 (0.4)	
3	53 (0.3)	257 (0.3)	
≥ 4	185 (1.0)	778 (1.0)	
Obesity (BMI, kg/m^2, n, %)			<0.001*
< 18.5 (underweight)	267 (1.4)	1,642 (2.2)	
≥ 18.5 to < 23 (normal)	5,546 (29.0)	27,089 (35.5)	
≥ 23 to < 25 (overweight)	5,586 (29.2)	21,246 (27.8)	
≥ 25 to < 30 (obese I)	7,069 (37.0)	24,472 (32.0)	
≥ 30 (obese II)	635 (3.3)	1,963 (2.6)	
Smoking status (n, %)			<0.001*
Nonsmoker	12,434 (65.1)	48,225 (63.1)	
Past smoker	2,490 (13.0)	9,512 (12.5)	
Current smoker	4,179 (21.9)	18,675 (24.4)	
Alcohol consumption (n, %)			<0.001*
Nondrinker	11,030 (57.7)	40,219 (52.6)	
1-3 times per month	2,985 (15.6)	12,417 (16.3)	
≥ 1 time per week	5,088 (26.6)	23,776 (31.1)	
Total cholesterol (mg/dL, mean, SD)	201.8 (37.2)	199.4 (37.3)	<0.001†

Fasting blood glucose (mg/dL, mean, SD)	99.8 (28.8)	99.5 (29.9)	0.186
Cystitis or urethritis (n, %)	8,355 (43.7)	20,272 (26.5)	<0.001*
Stroke (n, %)	1,615 (8.5)	5,476 (7.2)	<0.001*
Ischemic heart disease (n, %)	1,879 (9.8)	5,895 (7.7)	<0.001*

Abbreviations: BMI, body mass index, kg/m^2, CCI, Charlson comorbidity index

* Chi-square test. Significance at $P < 0.05$

† Independent *t* test. Significance at $P < 0.05$

Table S8 Crude and adjusted hazard ratios (95% confidence interval) for stroke in the nephrolithiasis and control groups

Characteristics	Hazard ratios for stroke			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 95,515)				
Nephrolithiasis	1.19 (1.12-1.25)	<0.001*	1.13 (1.07-1.20)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 44,595)				
Nephrolithiasis	1.23 (1.12-1.36)	<0.001*	1.20 (1.08-1.32)	0.001*
Control	1.00		1.00	
Age < 60 years old, women (n = 22,140)				
Nephrolithiasis	1.32 (1.16-1.51)	<0.001*	1.19 (1.04-1.36)	0.012*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 16,920)				
Nephrolithiasis	1.03 (0.93-1.15)	0.543	0.99 (0.89-1.11)	0.888
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 11,860)				
Nephrolithiasis	1.23 (1.09-1.38)	0.001*	1.18 (1.05-1.32)	0.007*
Control	1.00		1.00	

* Cox proportional hazard regression model, significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, cystitis or urethritis, and CCI scores.

Table S9 Crude and adjusted hazard ratios (95% confidence interval) for ischemic heart disease in the nephrolithiasis and control groups

Characteristics	Hazard ratios for ischemic heart disease			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 95,515)				
Nephrolithiasis	1.29 (1.23-1.36)	<0.001*	1.19 (1.12-1.25)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 44,595)				
Nephrolithiasis	1.29 (1.19-1.39)	<0.001*	1.18 (1.09-1.28)	<0.001*
Control	1.00		1.00	
Age < 60 years old, women (n = 22,140)				
Nephrolithiasis	1.51 (1.34-1.70)	<0.001*	1.35 (1.20-1.53)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 16,920)				
Nephrolithiasis	1.23 (1.10-1.37)	<0.001*	1.13 (1.01-1.27)	0.031*
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 11,860)				
Nephrolithiasis	1.18 (1.04-1.35)	0.009*	1.11 (0.97-1.26)	0.130
Control	1.00		1.00	

* Cox proportional hazard regression model, significance at $P < 0.05$

† Models stratified by age, sex, income, and region of residence.

‡ Adjusted for obesity, smoking, alcohol consumption, fasting blood glucose, total cholesterol, cystitis or urethritis, and CCI scores.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	p5
Methods			
Study design	4	Present key elements of study design early in the paper	p5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	p5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	p7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p5-7
Bias	9	Describe any efforts to address potential sources of bias	p5-8
Study size	10	Explain how the study size was arrived at	p7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p7-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P7-8
		(*b*) Describe any methods used to examine subgroups and interactions	P7-8
		(*c*) Explain how missing data were addressed	p6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	p6
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			**Pages**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p8
		(b) Give reasons for non-participation at each stage	p6
		(c) Consider use of a flow diagram	p6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p8
		(b) Indicate number of participants with missing data for each variable of interest	p6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	p8-9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p8-9
		(*b*) Report category boundaries when continuous variables were categorized	p8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	P8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	p9-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.