

# Association Between Kidney Stones and Risk of Stroke

## A Nationwide Population-Based Cohort Study

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**Abstract:** Nephrolithiasis is highly prevalent and has been associated with vascular diseases such as cardiovascular events. Few studies have comprehensively associated renal stones with stroke.

This study explored whether patients with renal stones were at a higher stroke risk than those without renal stones. A national insurance claim dataset of 22 million enrollees in Taiwan was used to identify 53,659 patients with renal stones, and 214,107 were selected as age-, sex-, and comorbidity-matched controls for a 13-year follow-up.

The relative stroke risk for the RS cohort was 1.06-fold higher than that for the non-RS group (95% confidence interval [CI] = 1.01–1.11). Age-specific analysis revealed that the adjusted stroke risk for the RS cohort increased as age decreased, with the highest risk of 1.47-fold (95% CI = 1.10–1.96) in patients aged 20 to 34 years, followed by a 1.12-fold risk (95% CI = 1.00–1.25) in patients aged 35 to 50 years.

Sex-specific analysis clarified that women in the RS group had a 1.12-fold stroke risk compared with women in the non-RS group (95% CI = 1.03–1.21). Patients who had undergone >4 surgeries had up to 42.5-fold higher risk of stroke (95% CI = 33.8–53.4).

The study utilized the national database and demonstrated that patients, particularly women and the younger population, with nephrolithiasis have an increased risk of ischemic stroke development. Patients treated with medication or through surgery for RSs showed steady and higher risks of stroke than those without surgical or medical intervention.

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**Abbreviations:** aHR = adjusted hazard ratio, BNHI = Bureau of National Health Insurance, CI = confidence interval, LHID 2000 = Longitudinal Health Insurance Database 2000, NHI = National Health Insurance, NHIA = National Health Insurance Administration, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, RSs = renal stones.

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## INTRODUCTION

The prevalence of nephrolithiasis is 5% to 20% and varies with age, sex, race, and area of residence.<sup>1,2</sup> Nephrolithiasis is usually asymptomatic but the attacks can be painful and morbid, requiring an emergency medical visit and surgery.<sup>3</sup> The focus on nephrolithiasis has shifted from these direct hazards to its effects, such as vascular events.<sup>4,5</sup>

Nephrolithiasis and systemic diseases have been linked in several epidemiological studies, including coronary heart disease (CHD),<sup>6–9</sup> hypertension,<sup>10,11</sup> diabetes,<sup>12,13</sup> atherosclerosis,<sup>14</sup> and metabolic syndrome.<sup>15</sup> Ferraro et al demonstrated an association between kidney stones and an up to 1.48-fold higher risk of CHD in prospective cohorts of women. Atherosclerosis is the risk factor for CHD and stroke, patients with nephrolithiasis might have a high stroke risk. Domingos et al reported that patients with nephrolithiasis did not have a higher incidence of stroke than those without nephrolithiasis did.<sup>7</sup> However, in their questionnaire-based study, adjustment for major confounders of stroke, such as hypertension, diabetes, and hyperlipidemia, was challenging in the absence of formal medical documentation. The association between nephrolithiasis and stroke is unclear. Thus, a nationwide population database was used to assess the association of nephrolithiasis with stroke risks in a cohort study with a 13-year follow-up.

## METHODS

### Data Source

The National Health Insurance (NHI) program was launched in Taiwan on March 1, 1995, and covered >99% of

Taiwan's residents and was contracted with 97% of clinics and hospitals by the end of 2010.<sup>16</sup> This study utilized the Longitudinal Health Insurance Database 2000 (LHID2000) claims data established by the National Health Research Institute (NHRI), Department of Health, Taiwan. LHID2000 contains the medical claims data of 1 million randomly sampled beneficiaries from among the enrollees of the NHI program between 1996 and 2010. No statistically significant differences in the distribution of sex, age, or healthcare costs between cohorts in the LHID2000 and the enrollees were reported by the NHRI. The *International Classification of Diseases Revision Ninth Clinical Modification* (ICD-9-CM) was used for the diagnoses. The study was approved by the Institutional Review Board of China Medical University and Hospital (CMUH104-REC2-115).

## Study Patients

A retrospective cohort study was conducted to determine the association between renal stone (RS) (ICD-9-CM 592.0: calculus of kidney, ICD-9-CM 592.1: calculus of ureter, ICD-9-CM 592.9: urinary calculus, ICD-9-CM 594.1: other calculus in bladder) and stroke (ICD-9-CM 430: subarachnoid hemorrhage, ICD-9-CM 431: intracerebral hemorrhage, ICD-9-CM 432: other and unspecified intracranial hemorrhage, ICD-9-CM 433: occlusion and stenosis of precerebral arteries, ICD-9-CM 434: occlusion of cerebral arteries, ICD-9-CM 435: transient cerebral ischemia, ICD-9-CM 436 acute, but ill-defined, cerebrovascular disease, ICD-9-CM 437 other and ill-defined cerebrovascular disease, ICD-9-CM 438: late effects of cerebrovascular disease). The claims data between 1998 and 2010 were used to identify patients aged  $\geq 20$  years with a first diagnosis of RS. The date of the initial diagnosis of RS was the index date. A comparison cohort was randomly selected from among the patients without RSs during the same period, frequency matched 1:4 for age (every 5 years), sex, comorbidities (diabetes, hyperlipidemia, hypertension, coronary artery disease [CAD], congestive heart failure [CHF], and atrial fibrillation), and index year. Patients with a stroke history and with missing information for age or sex were excluded from the data analysis.

## Outcome Measurements and Comorbidity

Diagnosis of stroke was the study endpoint. Stroke was confirmed on the basis of inpatient records in the NHI database. A follow-up for stroke occurrence was performed until the date of follow-up loss, withdrawal from the insurance system, or end of 2010, whichever occurred first. The baseline comorbidities were diabetes (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), hypertension (ICD-9-CM 401 to 405), CAD (ICD-9-CM 410 to 414), CHF (ICD-9-CM 398.91, 402, 404.01, 404.03, 404.10, 404.11, 404.13, and 404.9), and atrial fibrillation (ICD-9-CM 427.31). Surgical procedures for RS removal were based on ICD-9-OP codes (55.01: nephrotomy, 55.03: percutaneous nephrostomy without fragmentation, 55.04: percutaneous nephrostomy with fragmentation, 56.0: transurethral removal of obstruction from ureter and renal pelvis, 57.0: transurethral clearance of bladder, 59.95: ultrasonic fragmentation of urinary stones, 98.51: extracorporeal shockwave lithotripsy of the kidney, ureter, and/or bladder). Orthopedic surgeries of lower limbs were based on ICD-9 OP codes (ICD-9-CM 81.51: total hip replacement, 81.52: partial hip replacement, 81.53: revision of hip replacement, 81.54: total knee replacement).

## Statistical Analyses

The distribution of demographic status and comorbidities, including age, sex, diabetes, hyperlipidemia, hypertension, CAD, and CHF were compared between the RS and non-RS cohorts. The chi-square test was used for categorical variables. Student's *t* test was used for continuous variables. Incidence densities stratified by demographic variables were calculated for each cohort. Hazard ratios (HRs) and adjusted HRs (aHRs) were computed for stroke as a measure of the relative risk through the Cox proportional hazards regression model.

In addition, the Cox model was used to estimate stroke HRs associated with the frequency of medical visits for stone removal and was compared with the patients with RSs who received conservative medication. The stroke-free survival probability during the follow-up period was estimated using the Kaplan–Meier method, and the difference in frequency of stone removal among patients with RSs was examined using a log–rank test. Statistical analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC). Two-tailed  $P < 0.05$  was considered statistically significant.

## RESULTS

In total, 53,659 patients with newly diagnosed RSs and 236,107 patients without RSs (non-RS, comparison cohort) between 1998 and 2010 were identified (Table 1). The numbers of patients with follow-up loss were 1790 patients (3.34%) in RS cohort and 7048 patients (3.29%) in non-RS cohort. The median duration of follow-up was 6.78 years in the RS cohort (0.003–13.0 years) and 6.62 years in the non-RS cohort (0.003–13.0 years). Because the RS and non-RS groups were matched with respect to predefined conditions (age, sex, diabetes mellitus, hypertension, hyperlipidemia, CAD, CHF, and atrial fibrillation), no statistically significant difference between the 2 cohorts with regard to these variables was observed.

The mean ages of the RS and non-RS cohorts were  $47.7 \pm 14.9$  and  $48.1 \pm 14.1$  years, respectively. The 2 cohorts showed male predominance (65.9% in RS cohort; 65.8% in non-RS cohort). The overall incidence of stroke was higher in the RS cohort compared with the non-RS cohort (6.64 vs 6.27 per 1000 person-years, Table 2). The relative stroke risk for the RS cohort was 1.06-fold higher than that for the non-RS cohort (95% CI = 1.01–1.11). Because the incidence of stroke varied with age and sex, we examined the effects of these variables on stroke in the 2 cohorts. The sex-specific analysis showed that women with RS had a higher stroke incidence than women without RSs (IRR = 1.12, 95% CI = 1.03–1.21). The women in the RS cohort were 1.14-fold (95% CI = 1.05–1.23) more prone to stroke than were women in the non-RS group, after adjustment for confounders. The age-specific incidence analysis shows that the RS cohort had a higher HR than the non-RS cohort in the youngest age group did (20–34 years, HR = 1.47, 95% CI = 1.10–1.96), followed by the middle-aged adults group (35–49 years, HR = 1.12, 95% CI = 1.00–1.25). No statistically significant difference of stroke events between the 2 groups was observed for patients aged  $\geq 50$ .

We examined the association of nephrolithiasis and stroke type. Patients with RSs had a significantly higher risk of ischemic stroke (HR = 1.07, 95% CI = 1.03–1.23), particularly women (HR = 1.13, 95% CI = 1.03–1.23), and the younger age group (20–34 years, HR = 1.45, 95% CI = 1.01–2.10; 35–49 years, HR = 1.19, 95% CI = 1.04–1.35, Table 3).

In addition, we evaluated whether the risk of stroke increased with the severity of RSs. The RSs severity was

**TABLE 1.** Baseline Characteristics Between Renal Stone Group and Nonrenal Stone Group in 1998 to 2010

Variables	Renal Stone				P
	Yes N = 53,659		No N = 214,107		
	n	%	n	%	
Sex					0.78
Women	18294	34.1	73132	34.2	
Men	35365	65.9	140975	65.8	
Age, y					0.98
20–34	10837	20.2	43301	20.2	
35–49	20370	38.0	81393	38.0	
50–64	14784	27.6	58820	27.5	
≥65	7668	14.3	30593	14.3	
Comorbidity					
Diabetes	24829	11.6	6261	11.7	0.64
Hyperlipidemia	40363	18.9	10201	19.0	0.40
Hypertension	14743	27.5	58645	27.4	0.69
CAD	6952	13.0	27355	12.8	0.27
CHF	6249	11.7	24622	11.5	0.34
Atrial fibrillation	217	0.40	990	0.46	0.07

Chi-square test.  
CAD = coronary artery disease, CHF = congestive heart failure.

stratified using the data on medical visits for RSs and surgical procedures for stone removal. For surgical procedures, compared with the control group, a severity-dependent stroke risk was noted with RS severity stratifications: 1 to 2 surgical procedures, aHR = 0.94, 95% CI = 0.88–1.01; 3–4 medical visits, aHR = 8.29, 95% CI = 6.50–10.6; >4 surgical procedures, aHR = 42.5, 95% CI = 33.8–53.4; P for trend < 0.0001 (Table 4).

Further, in our study population, we analyzed incidences of deep venous thromboembolism and orthopedic surgeries of

lower limbs, which were also risk factors of stroke. Among 2343 stroke patients in the RS cohort, there were 25 patients (1.07%) who had deep venous thromboembolism, whereas among 8730 stroke patients in the non-RS cohort, 67 patients (0.77%) had deep venous thromboembolism (P = 0.16). Among 2343 stroke patients in the renal stone cohort, 44 patients (1.88 %) had received orthopedic surgery of lower limbs, whereas among 8730 stroke patients, 174 patients (1.99 %) had received orthopedic surgery of lower limbs (P = 0.72).

**TABLE 2.** Hazard Ratios and 95% Confidence Interval of Stroke Associated With Renal Stone in Cox’s Regression Analysis

Variables	Renal Stone			Nonrenal Stone			Crude HR <sup>‡</sup> (95% CI)
	Case	PY	Rate <sup>†</sup>	Case	PY	Rate <sup>†</sup>	
Overall	2347	353,597	6.64	8743	1,393,764	6.27	1.06 (1.01, 1.11)*
Sex							
Female	750	121,608	6.17	2679	484,850	5.53	1.12 (1.03, 1.21)**
Male	1597	231,989	6.88	6064	908,914	6.67	1.03 (0.98, 1.09)
Age, y							
20–34	64	75,237	0.85	169	292,547	0.58	1.47 (1.10, 1.96)**
35–49	398	143,255	2.78	1401	566,244	2.47	1.12 (1.00, 1.25)*
50–64	826	93,152	8.87	3168	369,869	8.57	1.04 (0.96, 1.12)
≥65	1059	41,952	25.2	4005	165,105	24.3	1.04 (0.97, 1.11)

HR = hazard ratio, PY = person-years.  
<sup>†</sup> Rate, incidence rate, per 1000 person-years.  
<sup>‡</sup> Crude HR: relative hazard ratio.  
 \* P < 0.05.  
 \*\* P < 0.01.

**TABLE 3.** Hazard Ratios and 95% Confidence Interval of Stroke Associated With Renal Stone in Cox’s Regression Analysis

Variables	Renal Stone		Nonrenal Stone		Crude HR <sup>‡</sup> (95% CI)
	Case	Rate <sup>†</sup>	Case	Rate <sup>†</sup>	
Hemorrhage stroke	385	1.09	1485	1.07	1.02 (0.91, 1.14)
Sex					
Female	105	0.86	393	0.81	1.07 (0.86, 1.32)
Male	280	1.21	1092	1.20	1.00 (0.88, 1.14)
Age, y					
20–34	25	0.33	65	0.22	1.49 (0.94, 2.37)
35–49	105	0.73	425	0.75	0.98 (0.79, 1.21)
50–64	141	1.51	516	1.40	1.08 (0.90, 1.31)
≥65	114	2.72	479	2.90	0.94 (0.76, 1.15)
Ischemia stroke	1962	5.55	7258	5.21	1.07 (1.01, 1.12)*
Sex					
Female	645	5.30	2286	4.71	1.13 (1.03, 1.23)**
Male	1317	5.68	4972	5.47	1.04 (0.98, 1.10)
Age, y					
20–34	39	0.52	104	0.36	1.45 (1.01, 2.10)*
35–49	299	2.09	976	1.72	1.19 (1.04, 1.35)*
50–64	685	7.35	2652	7.17	1.03 (0.94, 1.12)
≥65	945	22.5	3526	21.4	1.05 (0.98, 1.13)

<sup>†</sup> Rate, incidence rate, per 1,000 person-years.

<sup>‡</sup> Crude HR: relative hazard ratio.

\* *P* < 0.05.

\*\* *P* < 0.01.

A Kaplan–Meier analysis showed that, during the 13-year study period, the overall stroke rate was 54.2% higher for patients with RSs who have undergone >4 surgical procedures for stone removal than for those who did not undergo surgery (*P* < 0.0001, Figure 1).

**DISCUSSION**

Previous studies have shown an association between nephrolithiasis and systemic diseases, such as CHD, hypertension,<sup>10,11</sup> and diabetes.<sup>12,13</sup> The present population-based study enrolling a large number of patients with nephrolithiasis and

matched controls from the NHIRD revealed that nephrolithiasis is associated with an increased risk of ischemic stroke.

The patients with RSs were predominantly men, consistent with previous studies,<sup>2</sup> indicating that the NHIRD RS patient population is valid and representative. Despite the male predominance in the RS cohort, women with nephrolithiasis had a significantly increased stroke risk. Appelros et al reported that men have a higher stroke risk than women.<sup>17</sup> Because of the adjustment for the major comorbidities that increase stroke risk in the enrolled population, nephrolithiasis was a significant risk factor of stroke, particularly in women.

**TABLE 4.** The Risk of Stroke Among Stone Patients Frequency for Medical Visits of Stones Removal in Cox Proportional Hazard Regression

Frequency for Medical Visit, Per 1 Years	Event	PY	Rate <sup>†</sup>	Crude HR <sup>‡</sup> (95% CI)	Adjusted HR <sup>§</sup> (95% CI)
Stone removal <sup>  </sup>					
none	1343	201561	6.66	1 (Reference)	1 (Reference)
1–2	859	150715	5.70	0.85 (0.78, 0.92)***	0.94 (0.88, 1.01)
3–4	66	1114	59.25	9.59 (7.47, 12.3)***	8.29 (6.50, 10.6)***
>4	79	207	381.64	67.2 (52.5, 86.0)***	42.5 (33.8, 53.4)***
<i>P</i> for trend				<0.0001	<0.0001

<sup>†</sup> Rate, incidence rate, per 1,000 person-years.

<sup>‡</sup> Crude HR: relative hazard ratio.

<sup>§</sup> Adjusted HR: multivariable analysis including age, sex, and comorbidities.

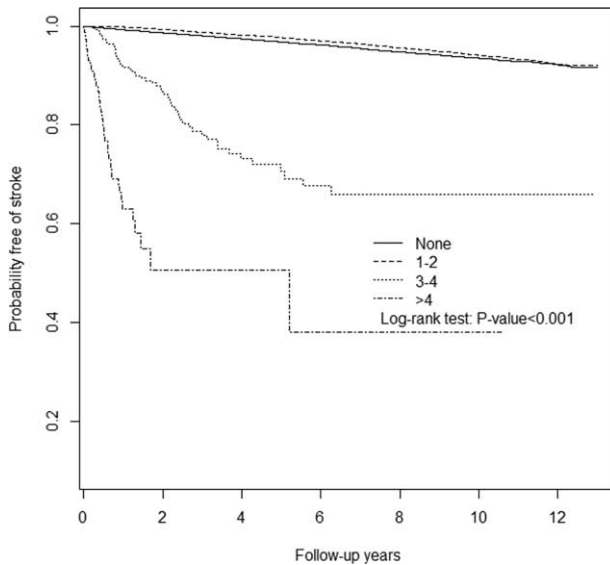
\* *P* < 0.05.

\*\* *P* < 0.01.

\*\*\* *P* < 0.001.

<sup>||</sup> Stone removal (ICD-9-OP): 55.01, 55.03, 56.0, 57.0, 55.04, 59.95, 57.19, 98.51.





**FIGURE 1.** Probability free of stroke for stone patients in difference frequency of stone removal.

The sex-specific difference that women with nephrolithiasis are prone to stroke is challenging to explain. However, several studies have reported the sex-specific difference that women with nephrolithiasis have an increased risk of adverse renal outcomes,<sup>18,19</sup> cardiovascular disease,<sup>6</sup> and hypertension. These observations, along with those of the present study emphasize the strong association of nephrolithiasis with vascular diseases and end organ damage (stroke, myocardial infarction, and kidney failure). Additional studies to understand the mechanism and validate the effects of nephrolithiasis on associated vascular diseases are warranted.

Old age has been recognized as a critical risk factor for stroke.<sup>20</sup> Several explanations account for the positive association of nephrolithiasis with stroke in patients >50 years. First, elderly patients have a high likelihood of being bedridden, immobile, or functionally weak because of traumatic fracture, dementia, or medical illness.<sup>21–23</sup> Thus, a stroke event may remain unrecognized without medical service. Second, elderly patients may have a high competing risk between death and stroke than do patients <50 years.<sup>24</sup> However, the high risk of stroke in the relatively low cardiovascular risk young population with nephrolithiasis emphasizes that the causality of nephrolithiasis is stroke development.

This is the first study that determined the association between the severities of nephrolithiasis and stroke. Stroke risks increased with the increasing numbers of medical visits and surgical procedures. Patients who received >4 surgeries had up to 42.5-fold risk of stroke compared with those treated through conservative medication. Thus, stroke risks are significantly apparent in patients with symptomatic nephrolithiasis, emphasizing that nephrolithiasis is linked causally to stroke development.

The study has several advantages. First, the patients with a history of stroke were excluded because a previous stroke is a major predictor for recurrent stroke.<sup>25</sup> Extensive matching with 8 confounding variables was defined in selecting the controls to ascertain the association of nephrolithiasis with stroke. Second, the follow-up period of 13 years enabled comprehensive evaluation of the time-dependent effects of nephrolithiasis on stroke

development. Third, an NHI monitoring and auditing system was implemented to supervise insurance claims to prevent over diagnosis and medical resource wastage. Based on the accurate diagnosis of the disease of interest and confounding variables, the association between nephrolithiasis and stroke was clearly demonstrated.

The limitations of our study include the lack of definite patient information on blood pressure, levels of serum glucose, CAD severity, and serum lipids levels. Moreover, NHIRD does not provide information on the lifestyle and personal health behaviors, including smoking, drinking, exercise habits, and obesity; these variables are known to be related to stroke.<sup>26</sup> However, because NHI covers >99% of Taiwan's residents, this study generalizes the trend that nephrolithiasis is associated with stroke.

In conclusion, a history of renal stones is associated with a significantly increased stroke risk, particularly in women and young patients. The 42.5-fold higher risk of stroke in patients with symptomatic nephrolithiasis requires surgical treatment. The findings can prompt clinical awareness and suggests lifestyle modification to facilitate early prevention of stroke in patients with nephrolithiasis, particularly in women, young population, and those with symptomatic nephrolithiasis patients.

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