

# Urinary Stones and Risk of Coronary Heart Disease and Stroke: the Japan Public Health Center-Based Prospective Study

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**Aim:** Evidence is lacking about whether urinary stones are associated with the subsequent risk of cardiovascular diseases. Herein, we investigated the association between history of urinary stones and the risk of coronary heart disease (CHD) and stroke among middle-aged Japanese.

**Methods:** This cohort study included 89,037 Japanese men and women (45–74 years) registered in the Japan Public Health Center-based prospective study. Cox proportional hazard models were used to calculate the hazard ratios (HRs) and their 95% confidence intervals (CIs) for incident CHD and stroke among Japanese adults with a self-reported history of urinary stones compared with those without it. The following covariates were included in the regression models: age, sex, area, body mass index, and histories of hypertension, diabetes, hyperlipidemia, smoking habit, alcohol intake, and physical activity.

**Results:** In total, 1.31% of Japanese adults reported a positive history of urinary stones. Throughout a median follow-up period of 12 years, 1.16% of Japanese adults developed CHD, and 4.96% developed stroke. No associations were detected between history of urinary stones and the risk of CHD (HR 1.04; 95% CI: 0.64–1.67), stroke (HR 0.92; 95% CI: 0.71–1.20), or total CVD (HR 0.95; 95% CI: 0.75–1.19). Younger urinary stone formers (45–59 years) tended to have a higher, though statistically insignificant, risk of CHD than older urinary stone formers (60–74 years): [(HR 1.15; 95% CI: 0.61–2.15) versus (HR 0.83; 95% CI: 0.40–1.76)], respectively.

**Conclusion:** The history of urinary stones was shown to be not associated with the risk of CVD among Japanese adults.

**Key words:** Cardiovascular diseases, Cohort study, Coronary heart disease, Stroke, Urinary stones

## Introduction

The prevalence of urinary stones has been increasing in Asia and worldwide<sup>1</sup>. In Japan, the age-standardized prevalence of urinary stones jumped throughout the period between 1965 and 2005, from 81.3/100,000 to 165.1/100,000 in men and 29.5/100,000 to 65.1/100,000 in women<sup>2</sup>. On the

other hand, coronary heart disease (CHD) and stroke are among the leading causes of health loss worldwide<sup>3</sup>. In Japan, the incidence and mortality of CHD and stroke have substantially declined, yet they remain the chief cause of mortality among middle-aged Japanese<sup>4</sup>. Urinary stones share several risk factors with cardiovascular diseases (CVD) such as hypertension, diabetes, dyslipidemia, and metabolic syndrome<sup>5-8</sup>;

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however, evidence on whether urinary stones can be independently associated with the subsequent risk of CVD is still inconclusive.

A few cohort studies investigated the association between urinary stones and the risk of CVD and reached inconsistent findings<sup>9-15</sup>. On the one hand, a study using data from the Taiwan National Health Insurance Research Database showed an increased risk of CHD and stroke among urinary stone formers compared with non-formers<sup>9</sup>. Another study using the Alberta Kidney Disease Network database detected a higher incidence of CHD and stroke among Canadian adults with urinary stones than among those without urinary stones<sup>10</sup>. On the other hand, the Health Professionals Follow-up Study (HPFS) revealed that the history of urinary stones among US men was not associated with the risk of CHD<sup>11</sup>. A follow-up study using the data of the US National Health and Nutrition Examination Survey (NHANES) showed no association between urinary stones and the risk of atherosclerotic CVD<sup>12</sup>.

The underlying mechanisms of the association between urinary stones and CVD are still obscure, but theories have suggested that both disorders pose familiar risk factors or similar pathogenesis<sup>16</sup>. While metabolic syndrome traits are considered potential risk factors for urinary stone formation and CVD incidence<sup>5-8</sup>, atherosclerosis can be involved in the pathogenesis of both disorders<sup>17, 18</sup>.

Since urinary stones and CVD are potentially preventable, determining the epidemiological evidence of their association should be studied. Based on our hypothesis that a history of urinary stones might increase the risk of CVD and the previous findings of possible sex and age interactions<sup>10, 11</sup>, we used the data of the Japan Public Health Center (JPHC)-based prospective study to investigate the urinary stone/CVD association in overall and stratified analyses by sex and age groups.

## Methods

### Study Population

The JPHC protocols and baseline questionnaire survey were described elsewhere<sup>19</sup>. Briefly, the JPHC was initiated in 1990 (Cohort I), and then another cohort was initiated in 1993 (Cohort II) within 11 public health centers across the country. The study population was defined as Japanese adults aged between 45 and 74 years. We excluded subjects with a positive history of CVD or cancer, leaving a total of 89,037 subjects for analyses.

### Exposures and Outcomes

The primary exposure was determined using a self-report question in the 5 year-follow-up-questionnaire (1995 for Cohort I and 1998 for Cohort II) about the history of ureter or kidney stones, as diagnosed by health care providers. It should be noted that bias would usually accompany a self-report in epidemiologic evidence<sup>20</sup> and could have led to either under- or over-reporting on the history of urinary stones in our studied population.

Surveillance of CHD and stroke was previously described<sup>21, 22</sup>. In brief, the major hospitals within the areas of the JPHC cohort reviewed the medical records and detected acute coronary events. CHD included myocardial infarction and sudden cardiac deaths. Myocardial infarction was confirmed according to the Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) criteria, while deaths that occurred within one hour from the onset of myocardial infarction symptoms were regarded as sudden cardiac deaths<sup>23</sup>. Stroke diagnosis was primarily based on computed tomography and/or magnetic resonance imaging per the criteria of the National Survey of Stroke<sup>24</sup>. Total CVD included all CHD and stroke incidents.

### Statistical Analyses

The differences in age-adjusted mean values and proportions of individual characteristics and CVD risk factors among participants with and without urinary stones, as assessed by the 5 year-follow-up-questionnaire that was considered as the baseline, were calculated using the linear and logistic regression tests. Cox proportional hazards analysis models were used to compute the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Person-years of follow-up were censored at the first incidence of CHD or stroke, the date of death or emigration from Japan, or the end of the study (December 31, 2009 for Cohort I and December 31, 2012 for Cohort II), whichever came first. For persons who did not continue follow-up, the last confirmed date of their presence in the study area was used as the date of censoring. The HRs were adjusted for the following variables: age, sex, area, body mass index (BMI), smoking habit, alcohol intake, physical activity, and histories of hypertension, diabetes, and hyperlipidemia. These covariates were named by several Japanese scientific societies as potential risk factors for CHD and stroke<sup>25</sup>. We further stratified the results by sex and age groups (45–59 years versus 60–74 years) to investigate differences that could be present between sexes or age groups. Kaplan–Meier curves for the exposure and the outcomes were also conducted (**Supplemen-**

**Table 1.** Age-adjusted mean values and proportions of risk factors at baseline according to the history of urinary stones

Variables	No urinary stones	Urinary stones	P-value*
Number of subjects	87,870	1,167	---
Age, y**	56.56 ± 7.86	55.59 ± 7.47	< 0.001
Men, %	45.78	70.52	< 0.001
BMI, kg/m <sup>2</sup> **	23.59 ± 3.39	24.12 ± 3.32	< 0.001
Current smoker, %	22.60	29.22	0.618
Alcohol intake, g/w**	21.94 ± 38.37	29.11 ± 37.77	< 0.001
Hypertension, %	19.13	23.74	< 0.001
Diabetes, %	5.10	4.54	0.613
Hyperlipidemia, %	5.00	5.14	0.475
Physical activity ≥ 3 d/w, %	10.10	12.85	0.008

BMI: Body mass index

\*Age-adjusted linear regression for continuous variables and logistic regression for categorical variables.

\*\*Mean ± standard deviation for all such variables.

tary Fig. 1 and 2). SAS version 9.4 software (SAS Institute Inc, Cary, NC) was used for the statistical analyses.

## Results

A positive history of urinary stones was reported in 1.31% of Japanese adults and was identified to be associated with a higher BMI ( $24.1 \pm 3.3$  versus  $23.6 \pm 3.4$  kg/m<sup>2</sup>), more alcohol intake ( $29.1 \pm 37.8$  versus  $21.9 \pm 38.4$  g/w), and a higher prevalence of hypertension (23.7% versus 19.1%) compared with Japanese adults without a history of urinary stones (Table 1).

Within 12 years of median follow-up, 1.16% of Japanese adults developed CHD, and 4.96% developed stroke. Having a positive history of urinary stones was not associated with the risk of CHD, stroke, or total CVD in both the age-, sex-, and area-adjusted model (HRs [95% CIs] were 1.03 [0.64–1.66] for CHD, 0.92 [0.71–1.20] for stroke, and 0.94 [0.75–1.19] for total CVD) and the multivariable-adjusted model (HRs [95% CIs] were 1.04 [0.64–1.67] for CHD, 0.92 [0.71–1.20] for stroke, and 0.95 [0.75–1.19] for total CVD) (Table 2).

No effect modifications by sex (CHD;  $P$ -value = 0.929 and stroke;  $P$ -value = 0.738) or age groups (45–59 years versus 60–74 years) (CHD;  $P$ -value = 0.405 and stroke;  $P$ -value = 0.277) were detected. Stratifying the results by sex did not change the findings, however, a statistically insignificant increased risk of CHD was observed in younger urinary stone formers (45–59 years) (HR 1.15; 95% CI: 0.61–2.15) compared with older urinary stone formers (60–74 years) (HR 0.83; 95% CI: 0.40–1.76) (Table 2).

## Discussion

This study indicated that, contrary to our prior hypothesis, having a positive history of urinary stones was not associated with the risk of CHD or stroke among Japanese adults during a median follow-up period of 12 years. Adjusting for potential confounders such as hypertension, diabetes, hyperlipidemia, BMI, physical activity, smoking, and alcohol intake had no impact on the results. Sex and age did not significantly influence the risk estimates.

In line with our findings, the results of the HPFS (follow-up period 9.8 years) showed no association between urinary stones and the risk of CHD among US men (HR 1.06; 95% CI: 0.99–1.13)<sup>11</sup>. Also, the Pooled Cohort Equations in all ethnic groups within the NHANES study revealed that having urinary stones was not associated with increased odds of atherosclerotic CVD within the next 10 years (Odds Ratio 1.03; 95% CI: 0.58–1.82)<sup>12</sup>.

On the other hand, Alexander et al. detected a significant association between a history of urinary stones and the risk of CHD (HR 1.63; 95% CI: 1.51–1.76) and stroke (HR 1.26; 95% CI: 1.12–1.42) among Canadian adults<sup>10</sup>. Two women cohorts; the Nurses' Health Study (NHS) I (follow-up period 8.2 years) and the NHS II (follow-up period 8.9 years), showed that a history of urinary stones led to an excess risk of CHD by 41% (95% CI: 30–54) and 119% (95% CI: 83–163) in the age-adjusted model before decreasing to 18% (95% CI: 8–28) and 48% (95% CI: 23–78), respectively, after adjusting for lifestyle factors and chronic diseases<sup>11</sup>. An Asian study from Taiwan showed that compared with a matched control group without urinary stones, adults with urinary

**Table 2.** Hazard ratios and 95% confidence intervals of coronary heart disease, stroke, and ischemic cardiovascular diseases incidence according to the history of urinary stones

Variables	Overall		Men		Women		45-59 Years		60-74 Years	
	No urinary stones	Urinary stones	No urinary stones	Urinary stones	No urinary stones	Urinary stones	No urinary stones	Urinary stones	No urinary stones	Urinary stones
Person-years	1,061,228	14,026	473,231	9,702	587,997	4,324	697,322	9,857	363,906	4,169
CHD, <i>n</i>	1012	17	717	15	295	2	405	10	607	7
Model I	1	1.03 (0.64–1.66)	1	1.03 (0.61–1.71)	1	1.03 (0.26–4.14)	1	1.21 (0.65, 2.28)	1	0.78 (0.37–1.65)
Model II	1	1.04 (0.64–1.67)	1	1.04 (0.62–1.73)	1	1.03 (0.26–4.15)	1	1.15 (0.61–2.15)	1	0.83 (0.40–1.76)
Stroke, <i>n</i>	4359	56	2482	45	1877	11	1824	23	2535	33
Model I	1	0.92 (0.71–1.20)	1	0.93 (0.69–1.24)	1	0.87 (0.48–1.57)	1	0.75 (0.50–1.14)	1	1.00 (0.71–1.42)
Model II	1	0.92 (0.71–1.20)	1	0.94 (0.70–1.26)	1	0.86 (0.48–1.56)	1	0.73 (0.48–1.10)	1	1.03 (0.73–1.45)
Total CVD, <i>n</i>	5371	73	3199	60	2172	13	2229	33	3142	40
Model I	1	0.94 (0.75–1.19)	1	0.95 (0.74–1.23)	1	0.89 (0.52–1.53)	1	0.85 (0.60–1.20)	1	0.96 (0.70–1.31)
Model II	1	0.95 (0.75–1.19)	1	0.96 (0.74–1.24)	1	0.88 (0.51–1.52)	1	0.82 (0.58–1.16)	1	0.98 (0.72–1.35)

CHD: Coronary heart diseases, CVD: Cardiovascular diseases,

Total CVD refers to CHD + stroke,

Model I: adjusted for age, sex, and area,

Model II: further adjusted for BMI, smoking, alcohol intake, physical activity, hypertension, diabetes, and hyperlipidemia.

The values of P-interaction with sex were 0.929 for CHD and 0.738 for stroke, and those for age groups were 0.405 for CHD and 0.277 for stroke.

stones were more likely to develop myocardial infarction (HR 1.31; 95% CI: 1.09–1.56) and stroke (HR 1.39; 95% CI: 1.24–1.55) during a 10-year follow-up period<sup>9</sup>. A meta-analysis of cohort studies showed that a history of urinary stones may be modestly associated with the risk of CHD (HR 1.19; 95% CI: 1.05–1.35; *n*=6 cohorts) and stroke (HR 1.40; 95% CI: 1.20–1.64; *n*=3 cohorts), yet the meta-analysis was limited by the few numbers of studies, the likelihood of residual confounding, and the substantial heterogeneity between studies<sup>26</sup>.

The discrepancy between our findings and previous positive results can be partially explained by the wide variations in the individual characteristics and medical histories of the included subjects across studies. For example, the mean age of urinary stone formers in our study (55.5 years) was significantly higher than that in the Taiwanese (46.5 years), Canadian (46.0 years), and NHS II studies (37.5 years), which concluded a significant association between urinary stones and the risk of CVD, but close to that in the

HPFS (56.0 years) and NHANES (53.5 years) studies, which showed insignificant findings<sup>9-12</sup>. Also, when we stratified our results by age, persons aged 45–59 years had a higher, though statistically insignificant, HR of CHD than persons aged 60–74 years: 1.15 (95% CI: 0.61–2.15) versus 0.83 (95% CI: 0.40–1.76), respectively. Furthermore, Alexander *et al.* concluded that the magnitude of excess myocardial infarction risk associated with urinary stones was more evident for younger persons than older persons with HRs (95% CIs): 2.43 (2.08–2.83) for 18–49 years, 1.28 (1.14–1.44) for 50–69 years, and 1.10 (0.95–1.28) for ≥ 70 years<sup>10</sup>.

Another explanation for the discrepancy could be the differences in CHD definitions across studies. CHD in the current study included fatal and non-fatal myocardial infarctions and sudden cardiac deaths. In the HPFS and NHS I and II studies, CHD included fatal and non-fatal myocardial infarctions in addition to revascularization<sup>11</sup>. Alexander *et al.* differentiated between the mortality rates of CHD and the



incidence rates of revascularization and concluded heterogeneous results: HR (95% CI) 0.97 (0.90–1.05) for CHD death compared with 1.63 (1.51–1.76) for revascularization and 1.40 (1.30–1.51) for hospitalized acute myocardial infarction<sup>10</sup>). Therefore, it could be suggested that different CHD events might have different relationships with urinary stones. Unfortunately, the limited number of CHD cases among patients with urinary stones in our study did not allow us to stratify the analysis by CHD type.

Currently, no conclusive theory can explain the possible relationship between urinary stones and the risk of CVD; however, it could be postulated that urinary stones and CVD have common risk factors or shared pathogenesis<sup>16</sup>). For instance, several metabolic syndrome traits, including hypertension, diabetes, and obesity, in addition to lifestyle factors such as smoking and alcohol consumption, were previously found to be associated with both urinary stone formation and CVD development<sup>5–8, 25</sup>). These factors may cast the relationship between urinary stones and CVD. In the current study, people with a positive history of urinary stones were shown to have a higher prevalence of hypertension at baseline than those with a negative history of urinary stones. Hypertension, the single most important contributor to several CVD events, is closely associated with osteoporosis and hypercalciuria that can increase the risk of urinary stones<sup>27</sup>). Also, the Canadian study and the NHS I and II studies showed a higher prevalence of diabetes, a known risk factor for various CVD events, among urinary stone formers than among non-formers<sup>10, 11</sup>). Insulin resistance inhibits ammonia synthesis and transport leading to lowered urinary pH and decreased urinary citrate excretion, which enhance urinary stone formation<sup>28, 29</sup>); however, the low prevalence of diabetes in previous studies, as well as in this study, makes it unlikely for diabetes to solely configure the relationship between urinary stones and CVD. Besides, for the urinary stones to be formed, a supersaturation status to allow crystal precipitation and an anchoring site to allow crystal aggregation are needed<sup>16</sup>). While hyperoxaluria offers a supersaturation status, the crystal aggregation step can be started by the atherosclerotic plaques in the renal papillae vascular system before they pass through the nephrons, obliterate the tubular lumen, and create urinary stones<sup>17, 18</sup>). Further, alteration of calcium metabolism associated with low calcium intake and osteoporosis can also contribute to urinary stone formation and the pathological cascade of ischemic CVD<sup>30, 31</sup>). Also, oxalates, essential components of most urinary stones, inhibit the proliferation and migration of endothelial cells<sup>32</sup>). Endothelial cells orchestrate vascular tone and regulate angiogenesis,

and their dysfunction may lead to several CVDs<sup>33</sup>). Other genetic and dietary mechanisms were also suggested but not confirmed<sup>16</sup>).

This study encompassed several strengths such as the large cohort, the long follow-up period, the standardized approaches of CVD diagnosis, the exclusion of individuals with previous CVD or cancers, the control for several potential confounders, and being the first prospective cohort study to investigate the association between history of urinary stones and the risk of CVD in Japanese adults. Still, some limitations should be considered. First, the history of urinary stones was collected by self-reporting, making it vulnerable to misclassification bias. Since a proportion of urinary stone formers can be asymptomatic, there is a possibility that the unexposed group might have been contaminated by undiagnosed cases; however, the possibility of over-reporting should not be excluded as well. Consequently, the prevalence of urinary stones in our study should be read cautiously. Second, the number, size, and type of urinary stones were not identified, as well as the factors that can affect their medical consequences<sup>34</sup>). Third, data on urinary stone treatment was not available. It could be speculated that those who were aware of their urinary stones sought medical or surgical treatments and became free of urinary stones that might have biased the results toward the null if urinary stones, *per se*, cause CVD. Fourth, the limited number of incident CHD and stroke cases among patients with urinary stones did not allow us to examine the outcomes by their subtypes.

In conclusion, our study indicated that the history of urinary stones was not associated with the risk of CHD or stroke. Future studies assessing the types and metrics of urinary stones with the subsequent risk of developing CVD events should be considered.

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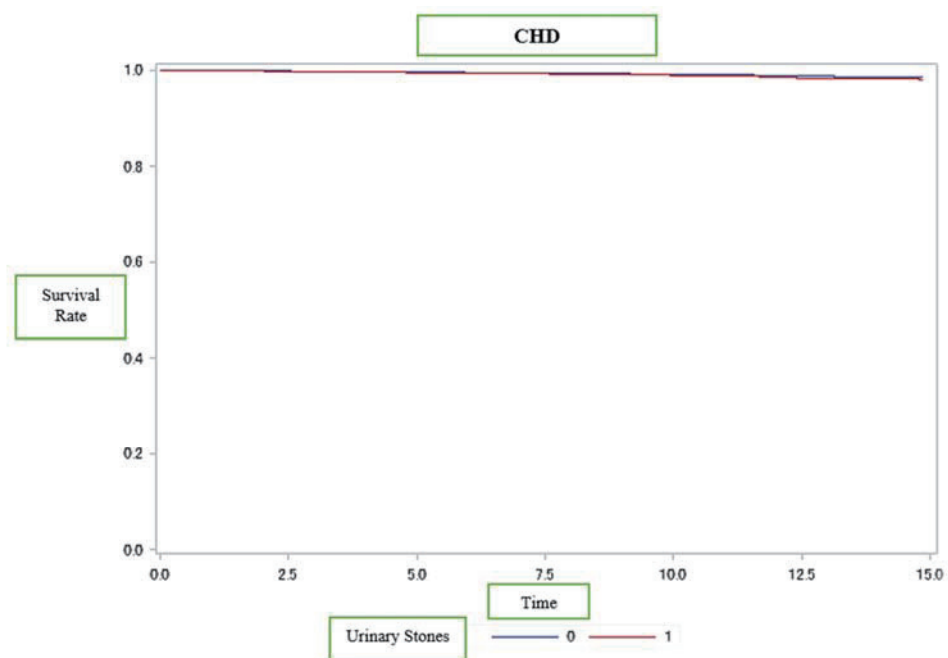
## Disclosures

None.

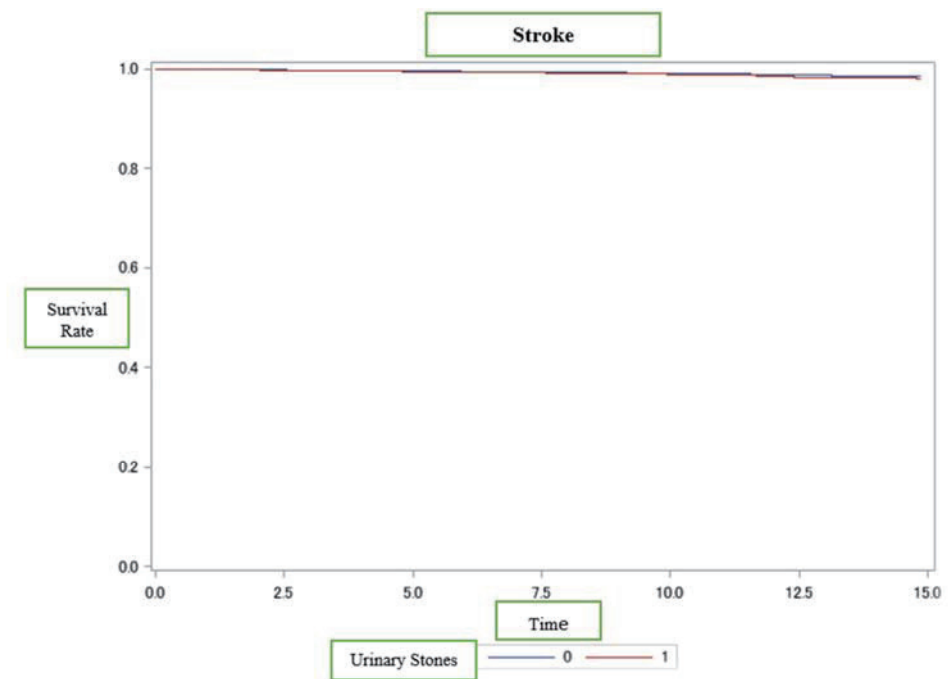
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**Supplementary Fig. 1.** Survival curve for the association between history of urinary stones (0=No, 1=Yes) and the risk of CHD



**Supplementary Fig. 2.** Survival curve for the association between history of urinary stones (0=No, 1=Yes) and the risk of stroke