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Kidney stones may increase the risk of coronary heart disease and stroke
A PRISMA-Compliant meta-analysis

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Abstract

Background: We aimed to quantitatively assess the potential relationship between kidney stones and coronary heart disease or stroke.

Methods: A meta-analysis was conducted on eligibly studies published before 31 May 2016 in PubMed or Embase. The data were pooled, and the relationship was assessed by the random-effect model with inverse variance-weighted procedure. The results were expressed as relative risk (RR) with 95% confidence intervals (95%CI).

Results: Eight studies of 11 cohorts (n = 11) were included in our analysis with 3,658,360 participants and 157,037 cases. We found that a history of kidney stones was associated with increased risk of coronary heart disease (CHD) (RR = 1.24; 95%CI: 1.14–1.36; $I^2 = 79.0\%$, n = 11); similar effect on myocardial infarction, a serious condition of CHD, was observed (RR = 1.24; 95%CI: 1.10–1.40; $I^2 = 80.4\%$, n = 8). We also found that a history of kidney stones may increase the risk of stroke (RR = 1.21, 95%CI: 1.06–1.38; $I^2 = 54.7\%$, n = 4). In subgroup analysis, the risk of coronary heart disease was higher in men (RR = 1.23, 95%CI: 1.02–1.49) while the risk for stroke was higher in women (RR = 1.12; 95%CI: 1.03–1.21). No obvious publications bias was detected (Egger test: $P = .47$).

Conclusion: Kidney stones are associated with increased risk of coronary heart disease and stroke, and the effect may differ by sex.

Abbreviations: 95%CI = 95% confidence intervals, CHD = coronary heart disease, MI = myocardial infarction, RR = relative risk.

Keywords: coronary heart disease, kidney stones, meta-analysis, risk, stroke

1. Introduction

Kidney stone is a common disease affecting about 1% to 20% of the population worldwide.[1,2] In the United States, it is estimated that 1 in 11 individuals will suffer stones, and the prevalence is likely to increase over the next decades.[3] Small stones typically pass from the kidney into the ureter and leave the body, while bigger stones may block the ureter and cause intermittent pain and metabolic changes, which can lead to long-term comorbidities.[4]

Increasing evidence suggests that kidney stones may be associated with cardiovascular disease. In 2014, Cheungpasitporn et al[5] published their meta-analysis of 4 cohort studies, and indicated that kidney stones are associated with increased risk for coronary heart disease (CHD) or stroke incidents, especially in women. Another meta-analysis published in the same year by Liu et al[6] was based on 4 cohort studies and 1 cross-section study, and also found that kidney stones are associated with a significantly increased risk of CHD in women. While both reports provided valuable information regarding the association between kidney stones and cardiovascular disease, the number of studies included in each analysis was small, and several important studies were overlooked in these meta-analyses. These aspects suggest that there may be considerable bias in the conclusion regarding the association between kidney stones and cardiovascular disease.[7]

Therefore, the present study represents an up-to-date meta-analysis of available data, and is reported according to the guidelines put forward in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8] We aimed to assess the potential association between kidney stones and risk of CHD or stroke.

2. Methods

2.1. Literature search

Two reviewers conducted the literature search independently. Eligible studies published before 31 May 2016 were identified by searching PubMed and Embase, without any restrictions regarding the language of publication. The following terms were used during the search process: "kidney stone," "kidney calculi," "kidney calculus," "renal stone," "renal calculi," "renal calculus," "nephrolithiasis," "coronary heart disease," "myocardial infarction," "angina," "stroke," "apoplexy," "brain

vascular accident," and "cerebrovascular accident." We also screened the reference lists of relevant reviews and meta-analyses. The term "Humans" was used to limit the search results to studies involving human subjects. Further details regarding the literature search are given in the appendix file (Table S1, http://links.lww.com/MD/B842).

2.2. Inclusion criteria

The inclusion criteria were predefined as follows: Population: general population without CHD and stroke at entry; Exposure: kidney stone and ureteral stone; Comparison: no kidney stone and ureteral stone exposure; Outcome: the primary outcomes were coronary heart disease and stroke, and the secondary outcome was myocardial infarction (serious condition of CHD); Study design: cohort-based, case-cohort, or nested case-control. Cross-sectional studies and case-control studies were excluded, it was expected they might bring significant bias. Grey literature and conference proceedings were also excluded. An ethical approval was not necessary since meta-analysis was based on secondary data.

2.3. Data extraction and quality assessment

Two reviewers extracted the data independently. A preproduced data-collection sheet was used to record the following information: first author's name, publication year, geographical region, follow-up of the study, population characteristics, number of cases with exposure, total number of study participants, relative risk (RR) with confidence intervals (CI) for measured outcomes, and adjusted variables. When adjusted RRs were given for several models, only the model adjusted for the largest number of variables was extracted. Unadjusted RRs were only used when no other results were available. If the same analysis (i.e., same study population, similar outcome measures) was published as part of several studies, only the study with the longest follow-up or with the highest amount of available information was included in the analysis. Any divergences were resolved by discussion between the 2 reviewers.

The Newcastle-Ottawa Scale was used to assess the quality of each study.[9] Within this quality-assessment tool, each of the 9 items accounts for 1 point. A given study was considered to have a high risk of bias if it had a quality score of ≤ 5.

2.4. Statistical analysis

RR was used to measure the association between kidney stones and measured outcomes, since our study only included cohorts. Stata/SE12.0 (Stata Corp, College Station, TX) was used to perform the analyses. The Cochrane Q test (P value) and I^2 (varied from 0% to 100%) were used to test heterogeneity. When mild heterogeneity ($I^2 < 25\%$) was detected, a fixed-effects model was selected; otherwise, a random-effect model was applied.[10] Each RR was weighted by the inverse variance.

Subgroup analyses were also performed, to see if specific characteristics including sex, follow-up duration (<10 years vs ≥ 10 years), and geographical region are relevant to the potential relationship between kidney stones and incidence of CHD or stroke. Egger regression test was used to detect potential publication bias.[11] All P values were 2-sided, and $P < .05$ was considered to represent statistical significance.

3. Results

Figure 1 provides an overview of the process by which we identified relevant studies to be included in our analysis.
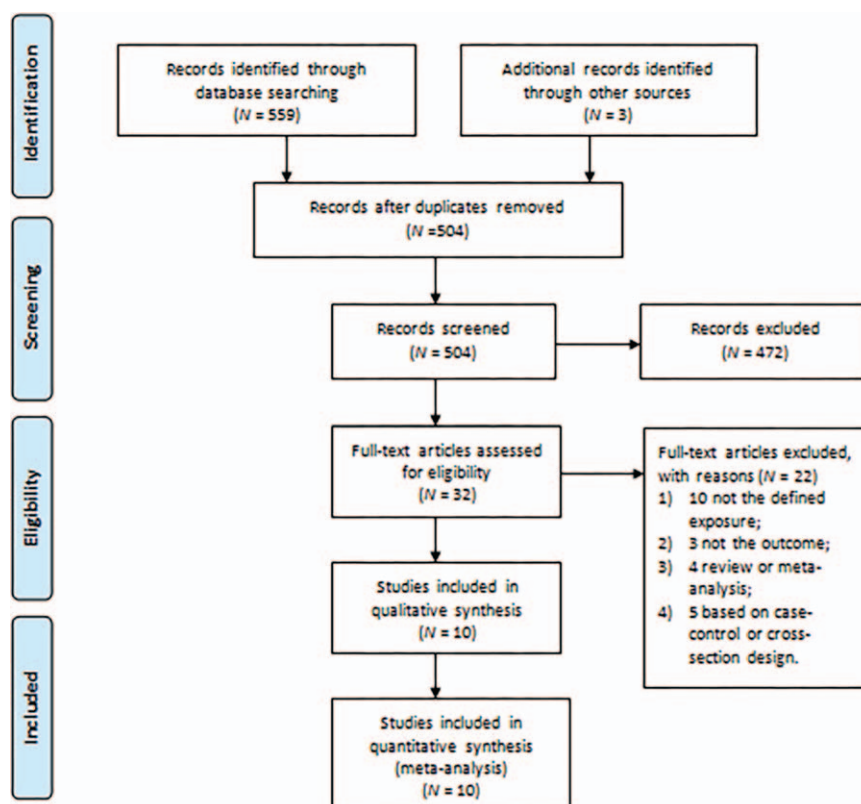

Figure 1. Process of literature screen.

Table 1

Main characteristics of included cohorts.

Author	Description	Variable controlled	NOS score
Glover, 2016	National Health and Nutrition Examination Survey, general adults, 40 to 79 years	Poverty-to-income ratio, age, sex, physical activity, education, self-reported smoking status, total dietary energy intake, protein intake, calcium intake, sodium intake, and alcohol consumption.	8
Hsu, 2016	LHID2010, 1995 to 2010, general population, age >18	Age, sex, CCI score, site of stone, and procedure for stone.	7
Alexander, 2014	Alberta kidney disease network database, general population, age >18	Age, sex, aboriginal status, social assistance, residence location, and comorbid conditions	8
Ferraro, 2013	The Health Professionals Follow-up Study, only male aged 40 to 75; The Nurses 'Health Study, female nurses aged 25 to 55	Age, race, region, family history of heart disease, diabetes, hypertension, gout, elevated cholesterol, aspirin, thiazide diuretics, loop diuretics, oral steroids, lipid-lowering drugs, antihypertensive drugs, menopausal status, postmenopausal, smoking, BMI, PA, intake of calcium, potassium, magnesium, animal protein, total fat, vitamin D, caffeine, dietary approaches to stop hypertension score, and alcohol.	7
Rule, 2010	Rochester Epidemiology Project	Age, sex, CKD, hypertension, diabetes, obesity, dyslipidemia, gout, smoke, alcohol.	9
Eisner, 2009	Study of Osteoporotic Fractures, only old female	Age, history of diabetes mellitus, history of hypertension, waist circumference, smoking history, and aspirin use.	5
Li, 2005	Malmo Diet and Cancer (MDC) study, general population, 45 to 73 years old	Age, education, smoking, BMI, WHR, systolic BP, Diastolic BP, CD.	6
Westlund, 1973	Study in Oslo City Hospitals, male patients	Sex and age.	5

BMI = body mass index, BP = blood pressure, CCI = chronic constriction injury, CD = chronic disease, CKD = chronic kidney diseases, NOS = newcastle-ottawa scale, PA = physical activity, WHR = waist hip rate.

Following the initial search, we obtained 562 records. After scanning the titles and abstracts, we removed 58 duplicates and 472 unrelated studies. The remaining 32 studies underwent full-text assessment. We further excluded 10 studies for not meeting the defined exposure criterion, 3 for not describing the outcomes of interest, and 9 for not meeting the study design criteria (4 reviews or meta-analyses, and 5 case-control or cross-section studies, i.e., not cohort-based). We further evaluated a total of 10 studies,[12–21] which described results regarding 13 cohorts. Among these 10 studies, 3 were based on the same data set,[12–14] and thus we only included one of them in the meta-analysis.[13]

Finally, 8 studies were included in our meta-analysis.[13,15–21] These 8 studies described the results regarding 11 cohorts, totaling 3,658,360 participants and 157,037 cases (CHD and stroke). All participants were aged >18 years, and the mean follow-up duration was 9.71 years (range, 5.7–13.7 years). Information regarding the geographic region was available for 7 out of the 8 studies included in our meta-analysis; specifically, 3 studies were conducted in the United States, 1 in China, 1 in Canada, 1 in Sweden, and 1 in Norway.[16,21] The mean quality score was 6.88 and 2 studies fulfilled the criterion for high risk of bias. The main characteristics of the studies included in the meta-analysis are shown in Table 1 (Description).

3.1. Kidney stones and risk of CHD

Eight studies reported the relationship between kidney stones and incidence of CHD based on the results regarding 11 cohorts.[13,15–21] The pooled results (Fig. 2) indicated a slightly higher incidence of CHD in individuals with kidney stones (RR = 1.24; 95%CI: 1.14–1.36). However, substantial heterogeneity ($P < .01$, $I^2 = 79.0\%$) among the studies was detected.

Five studies reported the relationship between kidney stones and incidence of myocardial infarction (MI, as serious condition of CHD) based on the results regarding 8 cohorts.[13,15–17,20] The pooled results (Fig. 2) also indicated increased risk of MI in individuals with kidney stones (RR = 1.24; 95%CI: 1.10–1.40), which fitted well to the earlier results of CHD. Nevertheless,

substantial heterogeneity ($P < .01$, $I^2 = 80.4\%$) among the studies was also noted.

3.2. Kidney stones and risk of stroke

Three studies reported the relationship between kidney stones and stroke based on the results regarding 4 cohorts.[13,15,19] The pooled results (Fig. 2) indicated increased risk of stroke in individuals with kidney stones (RR = 1.21; 95%CI: 1.06–1.38). As we noted only moderate heterogeneity ($P = .09$; $I^2 = 54.7\%$) among the studies, these results suggest that kidney stones may associated with increased risk of stroke.

3.3. Subgroup analysis

We also conducted analyses on subgroups defined in terms of sex, follow-up duration (<10 years vs ≥10 years), and geographic region. The pooled results (Fig. 3) indicated that men (RR = 1.23; 95%CI: 1.02–1.49), populations with shorter follow-up (RR = 1.30; 95%CI: 1.04–1.62), and populations in the United States (RR = 1.19; 95%CI: 1.04–1.36) had higher risk of CHD. On the other hand, women (RR = 1.37; 95%CI: 1.13–1.67) and Asian populations (RR = 1.30; 95%CI: 1.08–1.56) had higher risk for MI, while women (RR = 1.12; 95%CI: 1.03–1.21) and populations in the United States (RR = 1.26; 95%CI: 1.11–1.43) had higher risk for stroke.

3.4. Publication bias

Based on the results of the Egger test, we detected no obvious publication bias among the 11 cohorts evaluated ($P = .47$), suggesting little evidence of small study effects (Fig. 4).

4. Discussion

In this meta-analysis, we summarized the data regarding 11 cohorts, and found that kidney stones are associated with increased risk of CHD and stroke, and this effect depends on sex,
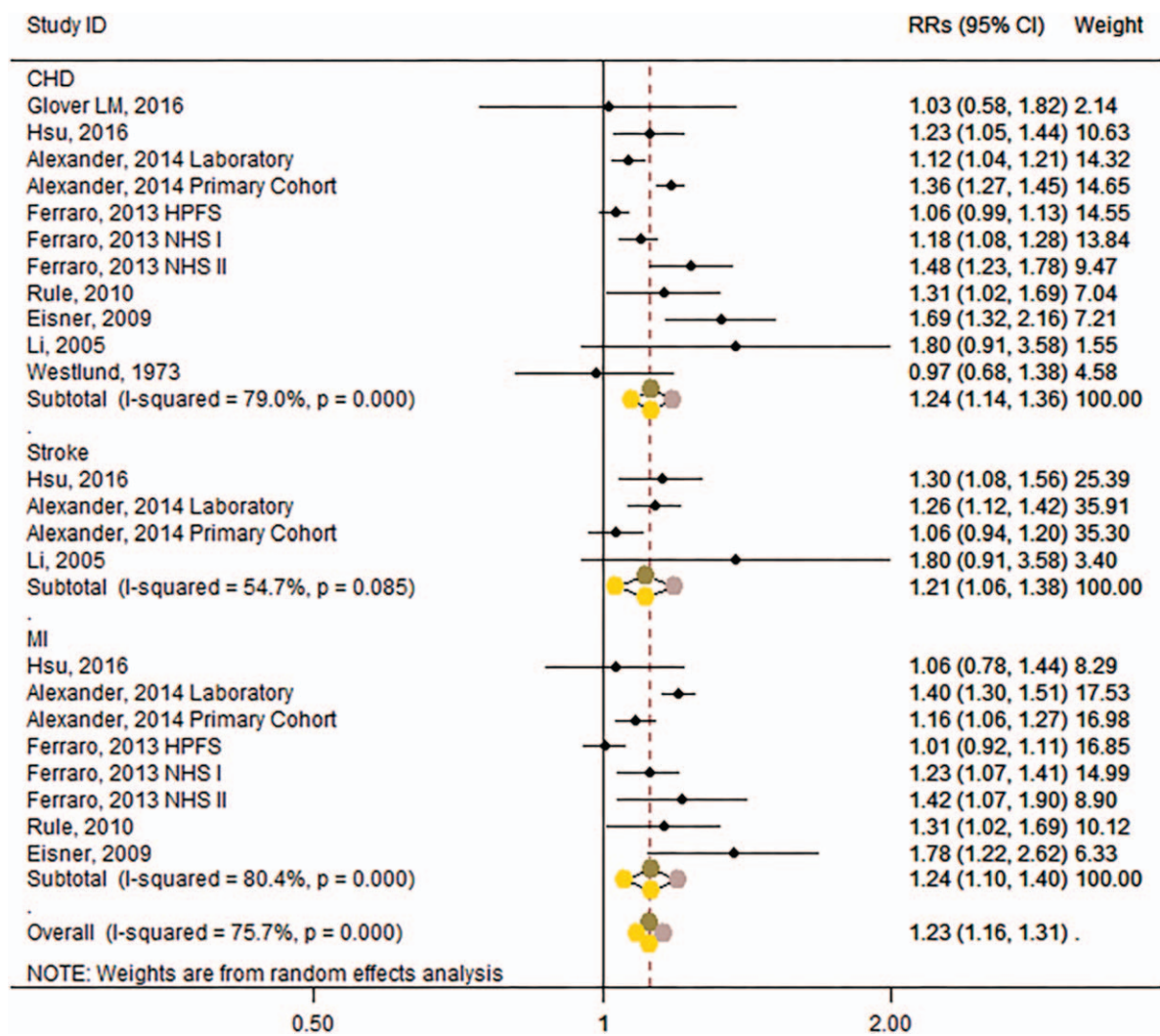
Figure 2. Pooled relative risks (RR) of total coronary heart disease, myocardial infarction, and stroke by kidney stone.

follow-up duration, and geographical region. Men with kidney stones may have higher risk of CHD, while women with kidney stones may have higher risk for stroke. Furthermore, individuals from Asian and the United States may be more susceptible to CHD and stroke if they have a history of kidney stones. The results of the Egger test and quality assessment suggest that publication bias is unlikely for the studies included in our analysis.

A previous meta-analysis included 4 studies describing 6 cohorts,[5] and found that a history of kidney stones was associated with increased risk of CHD and stroke, especially in women in agreement with another meta-analysis,[6] which pooled evidence from 6 cohort studies and 1 cross-sectional study. While our results support the finding that women with a history of kidney stones may have higher risk of stroke, we found that the risk for CHD is higher in men. This discrepancy may be due to the fact that our meta-analysis included more studies. On the other hand, the extent of heterogeneity among the studies included in our analysis is similar to that reported in the previous meta-analyses.[5,6] We found that sex, follow-up duration, and geographical region may account for part of the heterogeneity, though other variables such a mean age, type of stone, and other

population characters may also be relevant in this respect. We could not assess the effect of these other variables due to lack of data.

Several mechanisms may explain the association between kidney stones and CHD or stroke. For example, smoking and caffeine consumption are considered potential risk factors for kidney stones,[22,23] as well as for CHD and stroke,[24,25] suggesting that the underlying mechanisms for these conditions may be related. Some variables, such as urinary protein, overweight, and excessive flesh protein intake, may partly contribute to the results due to the potential confounding effects.[26] Another possible explanation may be related to the impact of kidney stones on kidney function, the deterioration of which is known to be associated with increased risk of cardiovascular disease.[27] Ageing may also serve as a framework for interconnecting the underlying mechanisms of kidney stone formation and CHD or stroke. For example, men aged 60 to 69 years are more likely to develop a kidney stone as well as to have cardiovascular disease.[28,29]

In this meta-analysis, we confirmed that a history of kidney stones is associated with increased risk of CHD and stroke. We believe that our conclusions represent reliable evidence of this
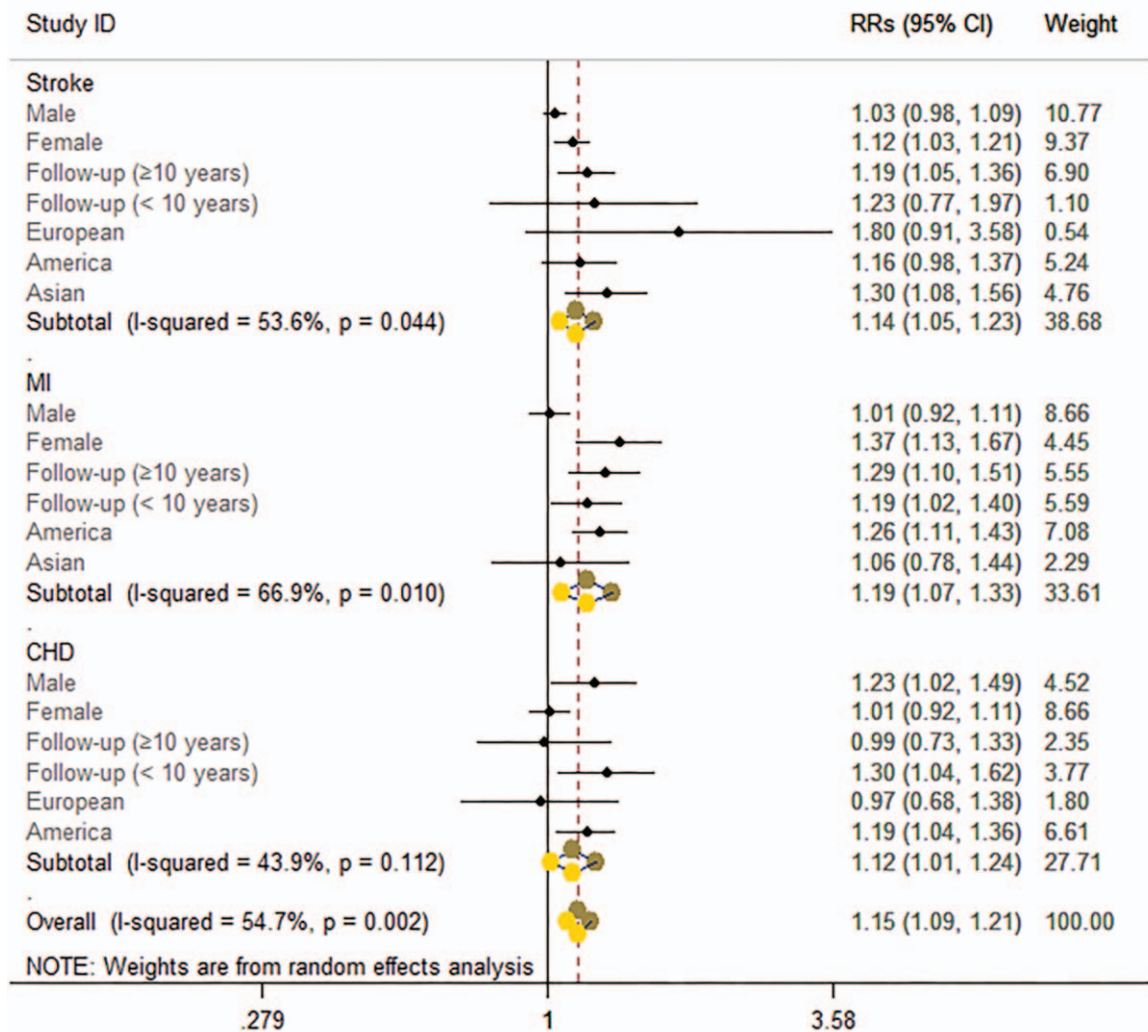
Figure 3. Subgroup analysis by sex, follow-up, and region.

relationship. First, while we performed a comprehensive literature search, we only included in our meta-analysis cohort-based studies with a considerable sample size, and used the adjusted RRs. Furthermore, we found that most studies

Figure 4. Egger test that with the circle weighted by standard error.

included in the analysis had low risk of bias, and the data did not exhibit a significant small-study effect. Thus, our results are more reliable than those of previous meta-analyses. However, there were also several limitations. First, although the sample size was sufficient for assessing the relationship between kidney stones and CHD, outcomes in terms of stroke were provided only for 4 cohorts, which may lead to low power of our result regarding stroke. Second, for each subgroup, we pooled the data from a small number of studies, which may imply that the results of the subgroup analysis have low power and should be interpreted with caution. Third, we detected moderate to substantial heterogeneity among the studies. The results of our subgroup analysis suggest that sex, geographic region, and follow-up duration may explain at least part of the heterogeneity. However, this aspect should be kept in mind when assessing the reliability of our conclusions. Fourth, we could include studies conducted in only 4 countries (United States, China, Norway, and Sweden), as no eligible studies were available for other countries that met the inclusion criteria. Finally, we did not have access to data regarding different types of kidney stones, and thus could not assess the effect of the type of stone on the relationship with CHD and stroke. Further studies are warranted to address such limitations.
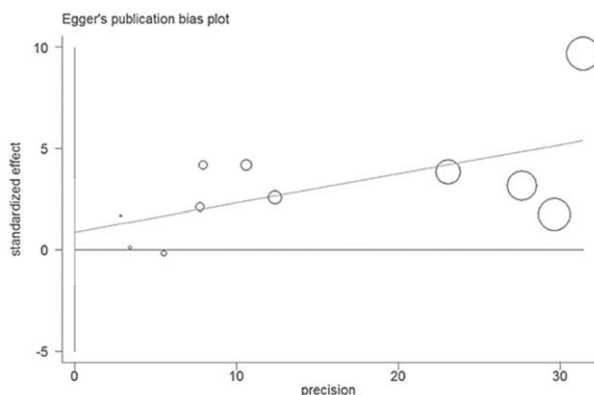
5. Conclusion

In conclusion, kidney stones may associate with an increased risk of CHD and stroke, and the effect varies with sex, follow-up year, and geographic region. Men with kidney stones may have a higher risk of CHD, while women with kidney stones may have a higher risk for stroke. Asian and American individuals with kidney stones may be more susceptible to CHD and stroke.

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