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UROLOGY - REVIEW

Caffeine intake and the risk of incident kidney stones: a systematic review and meta-analysis

Jiaxi Zhao[1] · Yiqin Huang[1] · Xiaofeng Yu[1]

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Abstract

Background Kidney stone disease is increasingly common in the general population, with a high recurrence rate after stone removal. It has been proven that caffeine consumption can reduce the risk of diseases, such as stroke and dementia. However, the effect of caffeine intake on the incidence of kidney stones has not been determined. This systematic review and meta-analysis were performed to evaluate the association of caffeine intake with the risk of incident kidney stones.

Methods PubMed, Web of Science, Scopus, Cochrane and Google Scholar were searched using terms related to coffee, caffeine and kidney stones to find eligible articles up to December 2021. Articles with clear diagnostic criteria for kidney stone disease and the exact intake dose of caffeine were included. The incidence of kidney stone disease was the main outcome. Summarized risk estimates and 95% CIs for the highest and lowest categories of caffeine intake were calculated using a random effects model.

Results Seven studies were included in the final meta-analysis, with 9707 cases of kidney stones and a total of 772,290 cohort members. Compared with the lowest category of caffeine intake, the pooled relative risk (RR) was 0.68 ([95% CI 0.61–0.75], $I^2 = 57\%$) for the highest category of caffeine intake. Subgroup analyses showed that caffeine intake had an inverse relationship with the incidence of kidney stones in all subgroups.

Conclusion This study suggests that a higher caffeine intake may be associated with a lower risk of incident kidney stones.

Keywords Caffeine · Kidney stones · Systematic review · Meta-analysis

Introduction

Kidney stone disease is a common disease affecting people of all ages [1]. In industrialized countries, the prevalence is estimated to be approximately 14% [2], and nearly one-tenth of the people in the United States suffer from it at some stage in their lives. There is evidence that the number of patients is rising, which may be the result of changes in dietary habits and lifestyle [3]. Historically, the incidence of kidney stones in men is higher than that in women. However, in recent years, the disproportionate increase in female stone diseases indicates that the gender gap in stone diseases is narrowing [4]. The reason for the observed increase in stone diseases in women is still uncertain, but it has been found that obesity affects women more than men, and obesity plays an important role in kidney stones [5].

The treatment methods for kidney stones mainly include diet therapies, surgical treatment and pharmacologic therapies. Surgical treatment of stones is usually not the end of the disease duration because stones are likely to recur. At least 50% of patients relapse within 10 years [6]. Many studies have focused on diet therapies. Most medical references suggest strict control of sodium, calcium, oxalate-rich foods, nondairy animal protein, and increasing intake of fruits and vegetables. Monitoring fluid intake is a key part of preventing the formation of kidney stones. Guidelines suggest maintaining fluid intake so that both kidneys produce at least 2–2.5 L of urine per day [7, 8]. Treatment methods for kidney stones have been developed, however, studies on protective factors for the incidence of kidney stones are lacking [9].

Coffee is one of the most widely consumed beverages in the world. Caffeine is an alkaloid extracted from coffee

✉ Jiaxi Zhao
zhaojia_xi@126.com

Xiaofeng Yu
yuxiaofeng252@163.com

[1] Department of General Medicine, Huadong Hospital Affiliated to Fudan University, 221 Yan'an West Road, Jing'an District, Shanghai, People's Republic of China

beans. It is a central nervous system stimulant and can be found in many beverages, especially coffee [10]. There is increasing evidence that coffee and caffeine are good for health. Coffee and caffeine can resist oxidation and regulate cell growth, proliferation and apoptosis [9], and they can also regulate intestinal flora [11] and material metabolism [12, 13]. Previous epidemiological studies have found that coffee and caffeine are associated with a lower risk of many diseases, such as cancer, dementia, cardiovascular disease and Parkinson's disease [14, 15].

The effect of caffeine intake on the incidence of kidney stones has not been determined. A previous study showed that caffeine intake was associated with the risk of kidney stone recurrence in adults, especially in women, nonwhite individuals, and non-overweight subjects, compared with those whose kidney stones did not recur [16]. However, a study conducted by Ferraro, P M et al. showed that caffeine intake was independently associated with a lower risk of incident kidney stones [17]. There was a systematic review on this similar topic, the primary outcome of which was the role of tea and coffee in the development of kidney stone disease [2]. However, due to the heterogeneity of the results, only a narrative synthesis rather than a quantified meta-analysis of data was conducted. Given the limited results of that study, subgroup analyses were conducted to identify sources of heterogeneity in this systematic review and meta-analysis.

In this systematic review and meta-analysis, we discussed the association of caffeine intake with the risk of incident kidney stones and discussed the possible mechanisms behind the results in detail. We also performed subgroup analyses for risk assessment, exploring possible sources of heterogeneity.

Methods

Search strategy

Two independent authors (Yiqin, Xiaofeng) searched PubMed, Web of Science, Scopus, Cochrane and Google Scholar to determine the eligible articles published from January 1, 1990 to December 31, 2021. The search was conducted using medical subject heading (MeSH) words and related keywords, such as caffeine, coffee, *Coffea*, kidney calculi, kidney calculus, nephrolith, renal calculus, kidney stones, kidney stone, renal calculi, and kidney stone disease. The reference list was screened for relevant articles that were not retrieved using the search terms. This meta-analysis procedure is in adherence to the PRISMA guidelines [18].

Inclusion and exclusion criteria

Studies that met the following criteria were eligible: (1) there were clear diagnostic criteria for kidney stone disease; (2) the study reported the precise intake amount of caffeine or the consumption amount of coffee, which was converted into caffeine intake (250 ml of coffee was approximately 100 mg of caffeine), and caffeine intake was expressed in mg per day or per month; (3) the study presented the incidence of kidney stones as one of the outcomes; (4) the participants only suffered from kidney stone disease, rather than other underlying diseases. Repeated publications, studies involving unrelated topics, populations, and designs, as well as animal experiments and low-quality studies were excluded. Furthermore, unpublished articles, review articles, case reports or letters were removed. Two independent authors (Yiqin, Xiaofeng) carried out the above steps separately. If there were any disagreements, the third author (Jiaxi) then conferred with the other two to make a final decision. A total of 7 studies were finally included in the meta-analysis. When there were insufficient data or information in the study, we attempted to contact the corresponding author to request relevant data.

Data extraction

We extracted the following data from the eligible studies: name of first author, year of publication, study country, study design, population, sample size, follow-up time, number of kidney stone disease cases, degree of caffeine intake, primary study outcome, RR (OR or HR) and 95% CI. The above information is shown in a table. Two authors (Yiqin, Xiaofeng) independently extracted data from candidate studies and discussed them with the third author (Jiaxi) to reach a consensus when they encountered disagreements. Then, the three authors (Yiqin, Xiaofeng, Jiaxi) independently reviewed all the data and resolved relevant issues through discussion.

Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of candidate studies [19]. The criterion for high-quality studies was a score of ≥ 6. Two authors (Yiqin, Xiaofeng) independently assessed the quality of each study. If they could not reach an agreement, they discussed it with the third author (Jiaxi).

Statistical analysis

Data were analyzed using the Review Manager 5.3 software recommended by the Cochrane collaboration. In this meta-analysis, the estimated risk ratio (RR) was used to

measure the association between caffeine intake and the incidence of kidney stones. The Cochrane I^2 test was used to assess heterogeneity between relevant studies. $I^2 > 50\%$ suggested that statistical heterogeneity might exist, and the data were merged using a random effects model. $I^2 \leq 50\%$ was considered not heterogeneous, and the fixed effects model was used to merge the data (the smaller the I^2 value was, the smaller the difference between the results obtained by the two models). Subgroup analyses were conducted to identify sources of heterogeneity when $I^2 > 50\%$, the related variables include: country, sample size, follow-up years, adjustment for total fluid intake, number of cases, outcome assessment method and quality score. Differences between subgroups were analyzed using the chi-square test. To explore the effect of each study on the pooled outcomes, we also performed sensitivity analyses by sequentially excluding one study at a time and then repeating the meta-analysis method. In this meta-analysis, $P < 0.05$ was considered statistically significant and was two-sided.

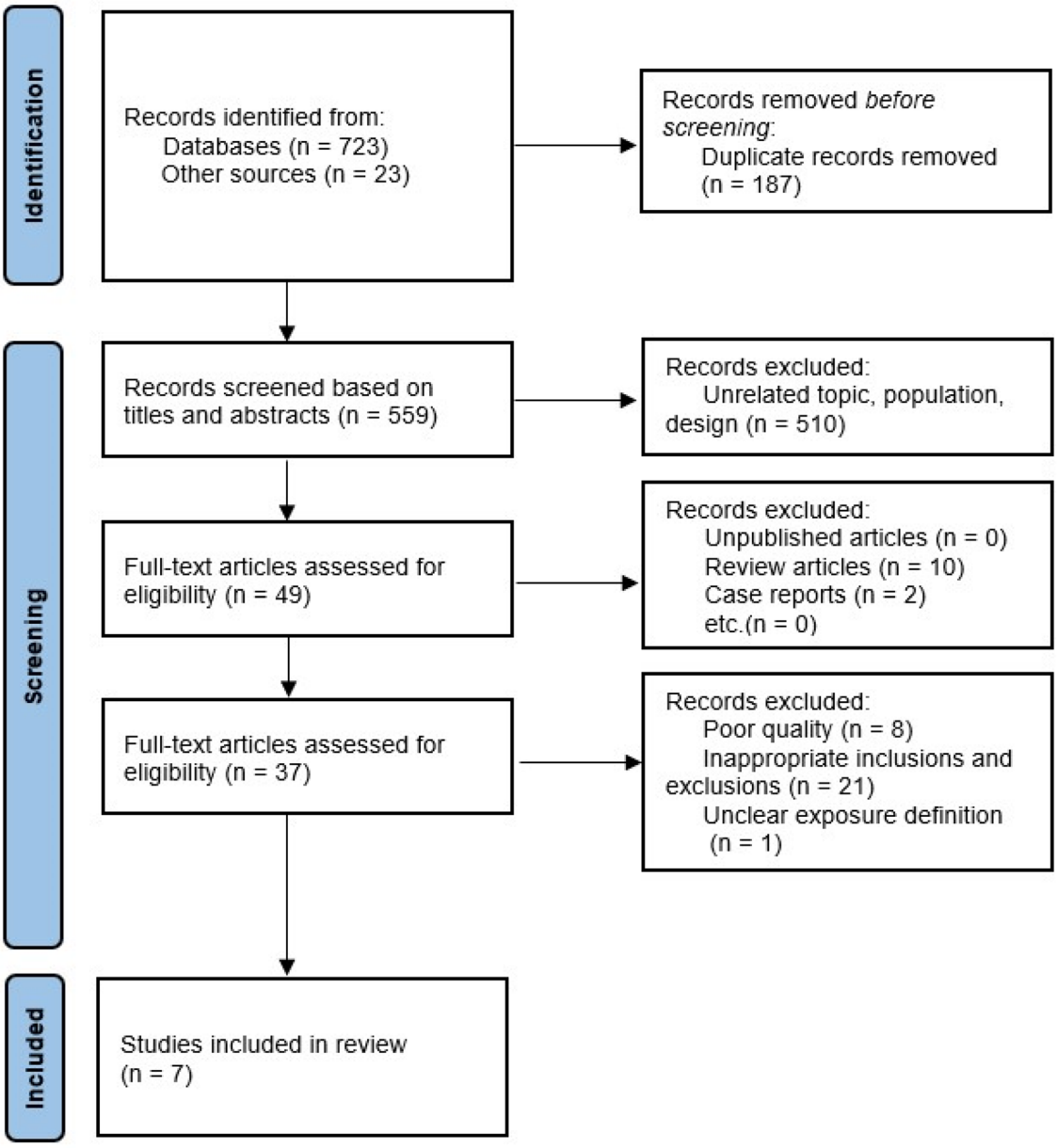

Fig. 1 Flow chart of literature screening

Results

Literature screening

The flow diagram of the literature screening process is shown in Fig. 1. After searching the database, we identified 723 records. In addition, 23 records were from other sources. After excluding 187 duplicate records, the titles and abstracts of 559 records were screened. After screening titles and abstracts, 510 records of unrelated topics, populations, and designs were excluded. After further full-text review of the remaining 49 studies, unpublished articles ($n=0$), review articles ($n=10$) and case reports ($n=2$) were excluded. Then, records with poor quality ($n=8$), unclear exposure definition ($n=1$), and inappropriate inclusions and exclusions ($n=21$) were excluded. Thus, seven studies were included in the final meta-analysis [17, 20–23]. It must be noted that 3 different studies with different populations were included in the same article [17].

Study characteristics and quality assessment

The brief characteristics of each selected study are shown in Table 1, and seven cohort studies were included in the meta-analysis. The eligible studies were conducted in the United Kingdom ($n=1$) and the United States ($n=6$) and were published between 1996 and 2020. The studies included a total of 772290 people, 9707 of whom developed kidney stones. The included studies were conducted among the general population ($n=1$), men ($n=1$), women ($n=1$), health professionals ($n=2$) and female nurses ($n=2$). The age ranged from 25 to 75. Detailed, comprehensive questionnaires were used in each study to assess caffeine intake. For outcome assessment, 4 studies used self-report questionnaires, 1 study used medical records, and 2 studies used self-report questionnaires and medical records. Four studies reported daily coffee intake rather than caffeine intake, and 3 studies reported daily caffeine intake directly. The results of the 7 studies were adjusted by age, profession, geographic region, use of thiazide diuretics, BMI, and dietary intake of calcium, animal protein, potassium, sodium, sucrose and vitamins. After a quality assessment was performed using the Newcastle–Ottawa Scale (NOS), 4 studies with a total score of ≥ 6 were considered to be of relatively high quality and have a low risk of bias. The quality score ranged from 5 to 8. Furthermore, all results of the included studies were adjusted for different elements.

Overall analyses, subgroup analyses and sensitivity analyses

Compared with the lowest category of caffeine intake, the pooled relative risk (RR) was 0.68 [(95% CI 0.61–0.75), $I^2=57\%$, $P<0.001$] for the highest category of caffeine intake using the random model (Fig. 2). Subgroup analyses are shown in Table 2. When stratified by country, the pooled RRs were 0.66 (95% CI 0.59–0.73) and 0.80 (95% CI 0.68–0.93) for studies conducted in the US and the UK, respectively. When stratified by sample size, the pooled RRs were 0.66 (95% CI 0.51–0.84) and 0.68 (95% CI 0.60–0.77) for study sample sizes $<50{,}000$ and $\geq 50{,}000$, respectively. When stratified by follow-up years, the pooled RRs were 0.67 (95% CI 0.55–0.82) and 0.67 (95% CI 0.59–0.75) for study follow-up years ≤ 8 and >8, respectively. When stratified by adjustment for total fluid intake, the pooled RRs were 0.66 (95% CI 0.59–0.73) and 0.80 (95% CI 0.68–0.93) for adjustment or no adjustment for total fluid intake, respectively. When stratified by the number of cases, the pooled RRs were 0.62 (95% CI 0.48–0.81) and 0.70 (95% CI 0.62–0.79) for studies with <1000 and ≥ 1000 cases, respectively. When stratified by outcome assessment methods and quality score, caffeine intake was significantly associated with a lower incidence rate of kidney stones.

Subgroup analyses indicated that country, sample size, follow-up years, adjustment for total fluid intake, number of cases, outcome assessment methods, and study quality score were sources of heterogeneity. Furthermore, the subgroup analyses showed that caffeine intake had an inverse relationship with incident kidney stones in all subgroups. No significant difference was found in country, sample size, follow-up years, adjustment for total fluid intake, number of cases, outcome assessment methods, and study quality score between the subgroups (Table 2).

In the sensitivity analysis where we excluded one study at a time and recalculated the pooled RRs of the remaining studies, the results did not change significantly. After omitting the studies by Ferraro et al. and Curhan et al., the pooled RRs ranged from 0.66 (95% CI 0.58–0.75) to 0.70 (95% CI 0.64–0.77), respectively.

Discussion

In this meta-analysis, a higher caffeine intake was associated with a lower risk of incident kidney stones. In the subgroup analyses stratified by country, sample size, follow-up years, adjustment for total fluid intake, number of cases, outcome assessment method and quality score, and in the sensitivity analysis, the results of the pooled relative risk (RR) were very robust. Considering that all the articles included in this meta-analysis were large population-based cohort studies,

Table 1 The brief characteristics of eligible studies

Author	Year	Country	Study design	Population	Sample size	Follow-up (years)	Cases	Degree of caffeine intake	Outcome	RR (95% CI)	Outcome assessment	Quality score	Adjustment
Curhan, et al	1996	US	Cohort	Men	45,289	6	753	< 100 mg per month ≥ 400 mg per day	Risk of incident kidney stones	1 0.54 (0.38,0.75)	Self-reported questionnaire	7	Age, dietary intake of calcium, animal protein and potassium, thiazide use, geographic region, profession and total fluid intake
Curhan, et al	1998	US	Cohort	Women	65,584	8	719	< 100 mg per month ≥ 400 mg per day	Risk of incident kidney stones	1 0.67 (0.50,0.91)	Questionnaire + medical records	7	Age, dietary intake of calcium, animal protein, potassium, sodium, sucrose, intake of supplemental calcium and intake of all 17 beverages
Ferraro, et al	2013	US	Cohort	Health professionals	4462	8	926	< 100 mg per week > 100 mg per day	Risk of incident kidney stones	1 0.74 (0.69,0.80)	Questionnaire + medical records	7	Age, race, region of residence, BMI, use of furosemide, use of thiazides, high blood pressure, diabetes, gout, intake of calcium, potassium, phytate, animal protein, vitamin C, total calories, profession and mutually adjusted for all the beverages

Table 1 (continued)

Author	Year	Country	Study design	Population	Sample size	Follow-up (years)	Cases	Degree of caffeine intake	Outcome	RR (95% CI)	Outcome assessment	Quality score	Adjustment
Ferraro, et al	2014	US	Cohort	Male health professionals	42,252	8.3	1581	7 mg per day 627 mg per day	Risk of incident kidney stones	1 0.74 (0.62,0.88)	Self-reported questionnaire	5	Age, BMI, use of thiazides, use of calcium supplements, and intakes of calcium, phosphate, sodium, potassium, magnesium, fructose, oxalate, phytate, total fluid, alcohol, and vitamins B-6, C, and D
				Female nurses	84,969	14	1859	31 mg per day 636 mg per day	Risk of incident kidney stones	1 0.71 (0.59, 0.85)		5	
				Female nurses	90,662	8.2	1812	17 mg per day 526 mg per day	Risk of incident kidney stones	1 0.69 (0.58, 0.82)		5	
Littlejohns, et al	2020	UK	Cohort	General population	439,072	6.1	2057	20 mg per day 300 mg per day	Risk of incident kidney stones	1 0.92 (0.88–0.95)	Medical records	8	Age, sex, Townsend deprivation score, education, ethnicity, smoking, BMI, and calcium supplementation

UK United Kingdom, *US* United States, *RR* relative risk, *CI* confidence interval, *BMI* body mass index

the results could suggest a benefit of caffeine intake in the primary prevention of kidney stones.

Several studies similar to the present one were found through the search process. Barghouthy et al. conducted a systematic review of 13 studies to investigate the relationship between the consumption of coffee and urolithiasis. The results suggested that moderate coffee consumption did not increase the risk of stone formation in healthy individuals [2]. However, this systematic review only included a qualitative analysis and not a quantitative analysis, and there was publication bias, so the conclusions drawn were limited. Relatively speaking, the present systematic review and meta-analysis used a more appropriate method to explore the association of caffeine intake with the risk of incident kidney stones. Subgroup and sensitivity analyses showed the stability of the outcomes. Xu et al. conducted a meta-analysis suggested that compared to no coffee consumption, 1–2 cups of coffee per day were associated with a lower risk of incident kidney stones (RR = 0.88, 95% CI 0.76–1.00, $I^2 = 54.7\%$). In a dose–response meta-analysis, the RR for every 110 mL increase in coffee consumption was 0.90 (95% CI 0.87, 0.93) [24]. However, the subgroup analysis only included study types and countries, which need further exploration and explanation. On this basis, our study added subgroups, such as sample size and quality, to make the results more reliable.

It is generally accepted that the vast majority (about 80%) of kidney stones formed in adults are calcium oxalate and calcium phosphate stones, followed by other stone components including uric acid, magnesium ammonium phosphate, and cysteine [25]. The mechanism of kidney stone disease is the formation, growth, aggregation, and retention of crystals in the kidneys due to oversaturation of minerals in the urine [26]. The main mechanism of stone formation involves free-particle and fixed-particle mechanism. In the free-particle mechanism, crystals form, grow and aggregate in the urine of the renal tubules. Once the crystals aggregate to form large particles, they are either too bulky to pass through the tubular lumen or remain in the kidney by attaching to the tubular epithelial cells. Another mechanism of stone formation is the fixed-particle mechanism, in which stones attach to calcified plaques on the papillary surface of the kidney, called Randall's plaques, which are initially formed by the deposition of calcium phosphate crystals in the renal interstitium [27, 28].

Caffeine is a stimulant of the central nervous system, has a positive effect on the cardiovascular system, can also promote gastric acid secretion and treat migraine and other diseases, and plays a wide range of roles in multiple systems of the body [29]. There are three main cell level's mechanisms of caffeine: inhibition of cellular phosphodiesterase; antagonism of cellular adenosine receptors, especially in the central nervous system; and mobilization of intracellular calcium stores [30].

There are some underlying mechanisms supporting the hypothesis that a higher caffeine intake is associated with a lower risk of incident kidney stones. Caffeine plays an important role in weakening the action of antidiuretic hormone (ADH), leading to increased urine flow and decreased maximal concentration [31, 32]. Caffeine also has an inhibitory effect on the formation of calcium oxalate stones and can reduce the adhesion of calcium oxalate crystals on the surface of renal tubular epithelial cells. Caffeine reduces the crystal-binding capacity of renal tubular epithelial cells by transferring annexin A1 (a crystal-binding protein) from the apical surface of renal tubular epithelial cells to the cytoplasm [33]. At the same time, fluid intake is increased, and urine flow is increased. However, several articles suggested that decaffeinated coffee could also play a protective role in kidney stone disease [20–23]. There are two main arguments to explain this observation. First, although caffeine may be protective against kidney stone disease, not every beverage containing caffeine may be so. In addition to caffeine, some beverages also contain a large amount of other substances, such as sugar and salt, which will adversely affect kidney function and cause kidney stone disease. Second, decaffeinated coffee still contains a small amount of caffeine; in addition to the caffeine effect, the presence of other protective bioactive compounds, such as trigonometric alkaloids [34], may exert similar protective effects. Therefore, the protective effect of caffeine in kidney stone formation cannot be denied accordingly.

Furthermore, the present study showed that the UK had a lower risk of incident kidney stones compared with the US. This could be related to the following potential reasons. First, a study by Cornelis et al. showed that UK participants had higher daily coffee intake than the US participants [35]. Second, participants in the UK and the US have different taste preferences of coffee. For example, the UK participants prefer sweetened and milked coffee; however, the US participants prefer black coffee without milk and sugar [35]. And previous studies showed that skim milk was inversely associated with risk of incident kidney stones [20, 21].

There were strengths and limitations of this study. One of the strengths was that the included studies were large sample studies, which could reduce sampling error to a certain extent. In addition, all the included studies were prospective cohort studies, compared with case–control studies, prospective cohort studies conform to the chronological order of cause and effect, with a strong ability to demonstrate causality and prevent bias. Furthermore, the included studies were of high quality and had a low risk of bias, which could further strengthen the current pooled results.

The meta-analysis also had several limitations. First, 4 of the studies included in the meta-analysis converted coffee consumption into caffeine intake, which may have led to bias because different coffee brands and coffee making

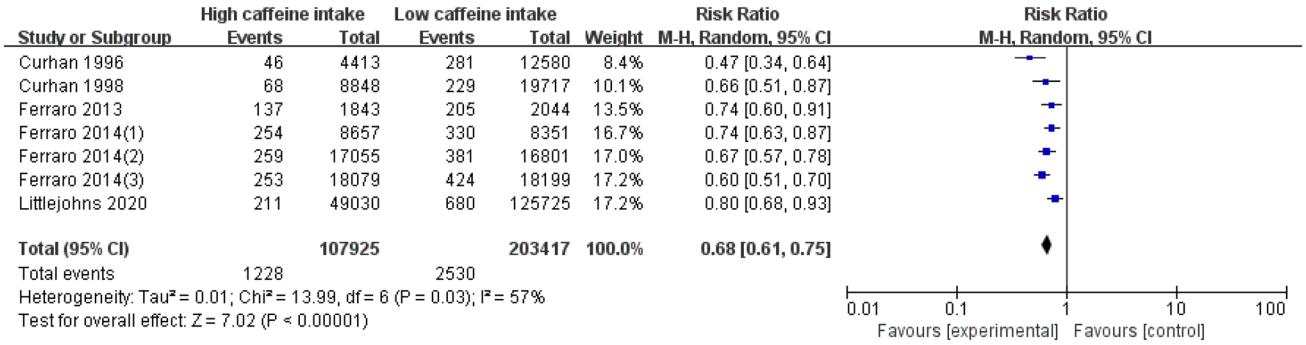

Fig. 2 Forest plot of the association of caffeine intake with the risk of incident of kidney stones

Table 2 Risk estimates for the association between degree of caffeine intake and incidence of kidney stones in subgroup analysis

	N	Pooled RR (95% CI)[a]	*P*-value (heterogeneity)	I^2 (%)	*P*-value
Total	7	0.68 (0.61,0.75)	0.03	57	
Country					0.05
US	6	0.66 (0.59,0.73)	0.09	48	
Non-US	1	0.80 (0.68,0.93)	NA	NA	
Sample size					0.79
< 50,000	3	0.66 (0.51,0.84)	0.02	73	
≥ 50,000	4	0.68 (0.60,0.77)	0.09	54	
Follow-up years					0.94
≤ 8	4	0.67 (0.55,0.82)	0.02	69	
> 8	3	0.67 (0.59,0.75)	0.18	43	
Adjustment for total fluid intake					0.05
Yes	6	0.66 (0.59,0.73)	0.09	48	
No	1	0.80 (0.68,0.93)	NA	NA	
The number of cases					0.44
< 1000	3	0.62 (0.48,0.81)	0.05	67	
≥ 1000	4	0.70 (0.62,0.79)	0.06	59	
Outcome assessment					0.11
Questionnaire	4	0.63 (0.54,0.74)	0.04	63	
Medical records	1	0.80 (0.68,0.93)	NA	NA	
Questionnaire + medical records	2	0.71 (0.60,0.84)	0.51	0	
Quality score					0.94
< 6	3	0.67 (0.59,0.75)	0.18	43	
≥ 6	4	0.67 (0.55,0.82)	0.02	69	

UK United Kingdom, *US* United States, *NA* not applicable, *CI* confidence interval, *RR* relative risk, *a* using random effects model

process have different caffeine content and other foods or supplements may also contain caffeine. And the subjects of the included studies may have ingested different kinds of beverages in the same period of time, such as tea, fruit juice, etc., these beverages may also have different effects on the risk of kidney stones [22], which may led to bias in the results of this study. Second, due to the relatively high coffee intake and incidence of kidney stones in the US and Europe, 6 cohorts from the US and 1 from the UK were included in this study, which may have exacerbated the bias. Third, different study sizes and follow-up times may have led to heterogeneous results that cannot be completely avoided. Finally, there was no information on stone composition, so it was not possible to investigate whether caffeine intake differentially affects kidney stone subtype formation, and future studies that subtype kidney stones are needed.

Conclusion

This study reports that a higher caffeine intake may be associated with a lower risk of incident kidney stones. Subgroup analysis showed that caffeine intake had an inverse relationship with incidence of kidney stones in all subgroups. Further research is still needed to explore the underlying mechanisms. And the effect of caffeine on stones of different composition still needs further exploration. More multicenter, large sample studies are needed in future, especially in Asian and African populations. If further research proves that the association is causal, it may encourage people to increase their caffeine intake and reduce their risk of developing kidney stones.

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Declarations

Conflict of interest Author Jiaxi Zhao declares that she has no conflict of interest. Author Yiqin Huang declares that he has no conflict of interest, Author Xiaofeng Yu declares that she has no conflict of interest. The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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