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Self-Fluid Management in Prevention of Kidney Stones: A PRISMA-Compliant Systematic Review and Dose–Response Meta-Analysis of Observational Studies

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Abstract: Epidemiologic studies have suggested that daily fluid intake that achieves at least 2.5 L of urine output per day is protective against kidney stones. However, the precise quantitative nature of the association between fluid intake and kidney stone risk, as well as the effect of specific types of fluids on such risk, are not entirely clear.

We conducted a systematic review and dose–response meta-analysis to quantitatively assess the association between fluid intake and kidney stone risk. Based on a literature search of the PubMed, Embase, and Cochrane Library databases, 15 relevant studies (10 cohort and 5 case–control studies) were selected for inclusion in the meta-analysis with 9601 cases and 351,081 total participants.

In the dose–response meta-analysis, we found that each 500 mL increase in water intake was associated with a significantly reduced risk of kidney stone formation (relative risk (RR)=0.93; 95% CI: 0.87, 0.98; $P < 0.01$). Protective associations were also found for an increasing intake of tea (RR = 0.96; 95% CI: 0.93, 0.99; $P = 0.02$) and alcohol (RR = 0.80, 95% CI: 0.75, 0.85; $P < 0.01$). A borderline reverse association were observed on coffee intake and risk of kidney stone (RR = 0.88; 95% CI: 0.76, 1.00; $P = 0.05$). The risk of kidney stones was not significantly related to intake of juice (RR = 1.02, 95% CI: 0.95, 1.10; $P = 0.64$), soda (RR = 1.03; 95% CI: 0.90, 1.17; $P = 0.65$), or milk (RR = 0.96; 95% CI: 0.88, 1.03; $P = 0.21$). Subgroup analysis and sensitivity analyses showed inconsistent results on coffee, alcohol, and milk intake.

Increased water intake is associated with a reduced risk of kidney stones; increased consumption of tea and alcohol may reduce kidney stone risk. An average daily water intake was recommended for kidney stone prevention.

(*Medicine* 94(27):e1042)

Editor: Kevin Harris.

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The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001042

Abbreviations: CI = confidence intervals, HR = hazard ratios, NOS = Newcastle Ottawa-Scale, ORs = odds ratios, RRs = relevant risks.

INTRODUCTION

Kidney stone is a common disease that has become increasingly prevalent over the past 2 decades.¹ Currently, the kidney stone prevalence rate worldwide is approximately 1.7% to 8.8%.^{2,3} It is more likely for men aged 60 to 69 to develop a kidney stone.⁴ Kidney stones can have serious clinical and economic consequences. Indeed, patients who suffer from large stones usually need surgical treatment, and in the year 2000, the cost of kidney stones was approximately \$2.81 billion in the United States alone.⁵

Increased fluid intake may help prevent the formation of stones by diluting urine concentration, decreasing urine acidity, and by taking away excess salt.^{6,7} These beneficial effects, however, may be offset by the tendency of increased fluid intake to dilute stone inhibitors such as magnesium, pyrophosphate, and glycosaminoglycan.^{8,9} A recent meta-analysis,¹⁰ based on the results of 2 randomized trials, concluded that high water intake decreased the long-term risk of kidney stone recurrence by approximately 60%. However, pooled evidence from only 2 studies is not conclusive. Additionally, data on the association between specific beverage types and risk of stone formation are sparse.

Accordingly, this study conducted a more extensive systematic review and meta-analysis of the quantitative relationship between fluid intake and risk of kidney stones, with a particular emphasis on examining the linear or nonlinear trends of the association. This study also examined the association of specific beverage types with kidney stone risk.

MATERIALS AND METHODS

This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA).¹¹ There are no ethical issues involved in our study for our data were based on published studies.

Search Strategy

Eligible studies were identified by searching the PubMed, Embase, and Cochrane Library databases for relevant studies of the association between fluid intake and risk of kidney stones. The search included studies that were published through February 15, 2015. A manual search of the references of the retrieved articles and relevant reviews was also conducted. In order to identify studies with relevant information on the exposure of interest (fluid intake), databases were searched

using the following terms: “water,” “fluid*,” “liquid*,” “beverage*,” “tea,” “alcohol,” “wine,” “beer,” “drink*,” “soda,” “milk,” “diet,” “coffee,” “juice*.” For the outcome of interest (kidney stone), search terms included: “kidney stone,” “kidney calculi,” “kidney calculus,” “renal stone,” “renal calculi,” “renal calculus,” and “nephrolithiasis.” The term “Humans” was used to limit the search results. No languages were limited during the search.

Study Inclusion and Exclusion Criteria

Studies were included in the meta-analysis if they: based on a cohort, case-control, or nested case-control design; defined kidney stone cases as patients diagnosed for the first time with a kidney stone without obvious bone disease; contained exposure information on at least one of the fluids of interest (water, coffee, tea, alcohol, juice, soda, milk); and had a sufficient data information. Additionally, to be included in the dose-response analyses, relevant studies were required to contain information on quantitative serving size with at least 3 quantitative categories. We excluded cross sectional studies, grey literature, and conference abstract. Studies which reported 24-hour urine biochemical changes after fluid intake were also excluded.

Data Extraction

Two reviewers conducted data extraction independent of one another. A standardized data collection form was used which extracted the following information: first author's name, publication year, country of study, follow-up, study design, sex, age range, number of cases, the total sample size or person-years of follow-up, quantitative serving size, effect size (odds ratio, relative risk, hazard ratio) with confidence intervals (CI), and control variables. When a given study presented models that adjusted for different numbers of control variables, data were extracted from the model that adjusted for the largest number of variables. Unadjusted results were extracted only when no other results were presented. When there was no information on serving size in an article, an assumption was made that a serving size of 1 cup (or glass) was equal to 150 mL. As for alcohol, 15.2 mL of alcohol, 120 mL wine, or 240 mL beer were assumed to contain approximately 12 g alcohol (1 standard drink).¹² Different periods of study (Stage I or Stage II) were regarded as 2 different studies. If multiple publications from the same data set or study were detected, we only included the publication with the longer follow-up period. Potential errors were checked by a third-party author and any divergences were resolved by discussion.

Statistical Analysis

The term “water,” “total fluids” were regarded as water intake in this article. The relative risk (RR) was used to measure the association between beverage intake and risk of kidney stones. Odds ratios and hazard ratios were regarded to be approximately equal to the RR, since the prevalence of kidney stones in the selected studies was approximately 10% or less.¹³

For dose-response analyses, we fitted both linear and nonlinear models to the data ($n \geq 3$). More specifically, we first estimated the RR of kidney stones per unit increment (500 mL for water, 110 mL for coffee and tea, 150 for juice, and 10 g for alcohol) of exposure within each study by generalized least-squares regression models. From these models, the regression coefficients were combined in a random-effects model, with fluid intake modeled as a continuous, linear variable.¹⁴ Then, to

model possible nonlinear exposure-outcome associations, we ran models in which the exposure was modeled as a restricted cubic spline with 3 fixed knots at 10th, 50th, and 90th percentile of the exposure distribution.¹⁵ The median values or middle point of each serving size were assigned to the corresponding relative risk for each study.¹⁶ When there were open-ended categories, we assumed the length of the open ended interval to be the same as that of the adjacent interval.¹⁷ When the lowest category was not analyzed as reference category (such as),¹⁸ the method of Hamling et al¹⁹ was used to convert the results. If a study reported incomplete data, we used the method of Bekkering et al²⁰ to evaluate the missing data. In the dose-response analyses, non-linearity was assessed by assuming that the regression coefficient of the second spline equaled zero, which is the Wald test.¹⁵

Not all studies reported dose-response information for specific fluids. Thus, we conducted analyses which analyzed the association of specific fluid intake modeled as a dichotomous variable (intake of 1–2 servings, or about 110–240 mL vs. no intake) with kidney stone risk. If a given study did not contain dose information at the 1 to 2 serving level, the results of the category nearest to that level was used in the pooled analysis. Further sensitivity analyses were conducted to evaluate whether this influenced the results. The I^2 statistics, which varied from 0% to 100%, were used to test heterogeneity, and were categorized as low (0–40%), moderate (30–60%), substantial (50–90%), and considerable (75–100%).²¹ A fixed-effects model was applied until slight heterogeneity ($I^2 < 30\%$) was detected; or a random-effect model was used. When the value of I^2 was $>75\%$, the combination would be terminated.²¹ When studies reported results separately by sex or other subtypes, the RRs were pooled using a fixed-effects model before adding the RRs to the overall meta-analysis.²² The inverse variance method was used to calculate the weight of each RR.

Egger's regression test was used to detect potential publication bias.²³ Subgroup analyses were used to detect possible sources of heterogeneity and potential difference among subgroups. Sensitivity analyses were also used to detect whether results were influenced by transformation of the data, the quality of included studies, and potential confounding factors. All P -values were 2-sided.

RESULTS

Search Results and Study Characteristics

An initial literature search identified 2739 studies. After removing duplicate and unrelated studies, 2 cross-sectional studies,^{24,25} and 1 case-control study²⁶ that included kidney stone cases with bone disease, 15 studies remained for the meta-analysis. A flow diagram illustrating how studies were selected is shown in Figure 1.

Among the included 15 studies, 10 were cohort studies, and 5 were case-control studies. The 15 studies combined had 9601 cases and 351,081 total participants (duplicate data from different studies were not counted). Three^{27–29} of the case-control studies described matching information that was utilized in matching controls to cases, while the other 2 case-control studies^{30,31} did not report such information. For cohort studies, the follow-up period ranged from 4 to 20 years. Nine of the studies were conducted in the United States, while 4 were conducted in China, 1 in Finland, and 1 in the United Kingdom.

Assessment of study quality was conducted according to the Newcastle Ottawa-Scale (NOS).³² The scale contains 9 items, and each item accounts for 1 point. Among the included studies, quality scores ranged from 3 to 8 points, with a mean

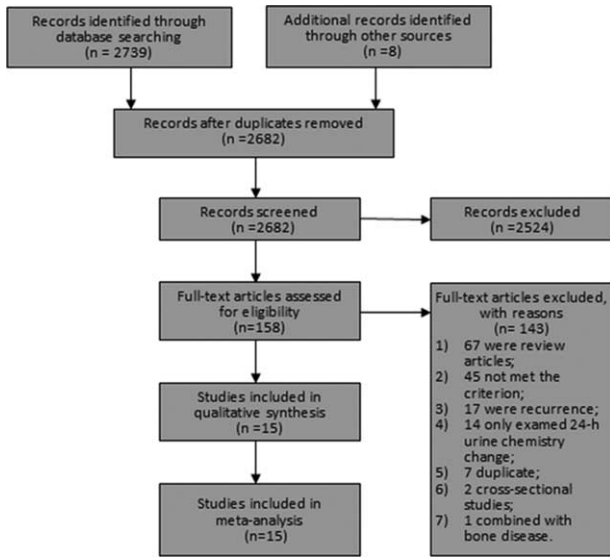


FIGURE 1. The flow diagram of study inclusion.

score of 7.3 for cohort studies and mean of 4.2 for case–control studies. The main characteristics of each study are shown in Table 1.

Water Intake and Risk of Kidney Stone

Nine studies^{27,30,31,33–38} reported on the association between water intake and risk of kidney stones, with 3 of the studies^{33,34,38} being multiple publications of study.³⁵ All of these studies included dose–response data. The combined RR for every 500 mL increment of water intake (linearity) a day was 0.93 (95% CI: 0.87, 0.98; $P < 0.01$; Figure 2). Substantial heterogeneity ($I^2 = 78.3\%$, $P < 0.01$) was detected among studies. Little evidence of nonlinear association was detected (P for nonlinearity test = 0.22). When using 1500 mL of daily water intake as the inference dose (RR = 1), the RRs of kidney stones for 1000 mL (approximate), 2000, 2500, and 3100 mL were 1.07 (95% CI: 1.05, 1.09), 0.92 (95% CI: 0.89, 0.95), 0.84 (95% CI: 0.78, 0.91), and 0.74 (95% CI: 0.65, 0.86), respectively.

Coffee Consumption and Risk of Kidney Stones

Seven studies^{6,29,30,36,38–40} investigated the relationship between coffee consumption and risk of kidney stones (Table 1). Two studies^{6,40} were identified as multiple publications of study.³⁸ From the remaining 5 studies, three^{30,38,39} reported dose–response relationship information, while two^{29,39} did not. Our meta-analysis showed that, compared to no coffee consumption, drinking 1 to 2 cups (about 110–240 mL) of coffee a day was associated with a RR of kidney stones of 0.88 (95% CI: 0.76, 1.00; $P = 0.05$; Figure 3). Moderate heterogeneity ($I^2 = 54.7\%$) was detected among studies. In dose–response meta-analysis, the RR for every 110 mL increment of coffee intake was 0.90 (95% CI: 0.87, 0.93; $P < 0.01$), and the Wald test showed nonsignificant of nonlinearity ($P = 0.77$).

Tea Consumption and Risk of Kidney Stones

Nine studies^{6,28,29,30,31,36,38–40} reported data on the association between tea consumption and kidney stones. Studies^{6,40}

were identified as the same publication of study.³⁸ After excluding multiple publications, 3 studies reported dose–response information.^{30,38,39} The meta-analysis showed that, compared to no tea consumption, those who consumed 1 to 2 cups of tea per day had a RR of kidney stones of 1.06 (95% CI: 0.94, 1.20; $P = 0.32$; $I^2 = 45.5\%$; Figure 4). When modeled as a continuous variable, each 110 mL/day increase in tea consumption was associated with a kidney stone RR of 0.96 (95% CI: 0.93, 0.99; $P = 0.02$), and there was some evidence this relationship was borderline nonlinear ($P = 0.07$ for nonlinearity test). The protective effect of tea consumption appeared to begin at an intake level of approximately 250 mL/day. Compared to the reference dose (0 mL), those whose daily tea intake was 102, 204, 257, 525, and 825 mL, had a RR of kidney stones of 1.02 (95% CI: 0.95, 1.09), 0.97 (95% CI: 0.90, 1.04), 0.91 (95% CI: 0.86, 0.99), 0.59 (95% CI: 0.39, 0.89), and 0.33 (95% CI: 0.13, 0.84), respectively.

Alcohol Intake and Risk of Kidney Stones

Nine studies^{6,18,27,29,30,36,38–40} with 7 of the studies being unique,^{18,27,29,30,36,38,39} reported on the association between alcohol intake and risk of kidney stones. Of these studies,^{18,30,36,38} reported dose–response information. Studies^{6,40} were identified as the same publication of study.³⁸ The meta-analysis showed that, compared to those who did not drink alcohol, those who drank about 1 standard drink (12 g) of alcohol per day had a RR of kidney stones of 0.80 (95% CI: 0.63, 1.01; $P = 0.06$; $I^2 = 67.1\%$; Figure 5). When modeled as a continuous variable, each 10 g/day increase in alcohol consumption was associated with a kidney stone RR of 0.80 (95% CI: 0.75, 0.85; $P < 0.01$), and there was no significant evidence that this association was nonlinear ($P = 0.73$ for nonlinearity test).

Other Beverages and Risk of Kidney Stones

After excluding multiple publications, 3 studies^{30,36,38} reported on the association between juice intake and risk of kidney stones, 4 studies^{29,30,36,38} reported on the association between soda intake and risk of kidney stones, and 5 studies^{30,31,36,38,39} reported on the association between milk consumption and kidney stone risk. Limited studies reported data that could be used for dose–response analyses. The overall meta-analysis showed that, compared to those with no juice consumption, those with 1 to 2 cups per day of juice intake had a RR of kidney stones of 1.02 (95% CI: 0.95, 1.10; $P = 0.64$; $I^2 = 0.0\%$); compared to those with no soda consumption, those with 1 to 2 cups per day of soda intake had a RR of kidney stones of 1.03 (95% CI: 0.90, 1.17; $P = 0.65$; $I^2 = 42.6\%$). Additionally, compared to those with no milk consumption, those who consumed 1 to 2 cups of milk per day had a kidney stone RR of 0.96 (95% CI: 0.88, 1.03; $P = 0.21$; $I^2 = 0.0\%$) (see Figure 6).

Subgroup Analysis and Sensitivity Analysis

Subgroup analyses were conducted on country, study design, and other subtypes (if reported, such as sex). Apart from coffee and alcohol, no substantial changes of the results were found between subgroups (Table 2).

For coffee intake, the kidney stone RR associated with 1 to 2 servings of coffee per day was not significant in the subgroup of case–control studies (RR = 0.85, 95% CI: 0.64, 1.13; $P = 0.26$; $I^2 = 41.7\%$). A subgroup analysis showed that alcohol intake was not associated with a lower risk of kidney stones (RR = 0.76, 95% CI: 0.46, 1.25; $P = 0.28$; $I^2 = 86.6\%$) in case–

TABLE 1. Detailed Characteristic of Included Studies

Author	Country	Research	Describe	Types of Beverages	Main Findings	Adjusted Item	Quality Score
Curhan ³³	America (1993)	Nurses' Health Study I	Cohort study; 4 years follow-up (1986–1990); mean age were 40–75; use semi-quantitative frequency questionnaire with 131 items	Total fluids intake	RR of highest vs. lowest levels of water intake was 0.71 (0.52, 0.97)	Age, profession, use of thiazide diuretics, alcohol, dietary intake of calcium, animal protein, potassium, and total fluid	7
Curhan ³⁴	America (2004)	Nurses' Health Study II	Cohort study; 8 years follow-up (1991–1999); mean age were 40–75; use self-reported frequency questionnaire	Total fluids intake	RR of highest vs. lowest levels of water intake was 0.68 (0.56, 0.83)	Age, body mass index, family history, and intake of supplemental calcium, dietary calcium, animal protein, potassium, sodium, sucrose, phytate, and fluid	7
Curhan ⁴⁰	America (1996)	Health Professionals Follow-up Study	Cohort study; cases were men; 6 years follow-up; mean age were 40–75; use semi-quantitative frequency questionnaire	Alcohol Milk, juice, soda, coffee, tea	R Rs were 0.54 (95% CI: 0.38, 0.75) for caffeinated coffee, 0.77 (95% CI: 0.50, 1.19) for decaffeinated coffee, 0.53 (95% CI: 0.23, 1.19) for highest vs. lowest tea intake	Age, profession, geographic region, thiazide, diuretics, dietary intake of calcium, protein, potassium, and all 21 beverages	8
Curhan ⁶	America (1998)	Nurses' Health Study	Cohort study; cases were women; 8 years follow-up; mean age were 40–75; use semi-quantitative frequency questionnaire	Alcohol milk, juice, soda, coffee, tea	R Rs were 0.67 (95% CI: 0.50, 0.91) for caffeinated coffee, 0.83 (95% CI: 0.55, 1.25) for decaffeinated coffee, 0.78 (95% CI: 0.60, 1.01) for highest vs. lowest tea intake	Age, dietary intake of calcium, animal protein, potassium, sodium, and sucrose; intake of supplemental calcium; and 17 beverages	7
Dai ³⁰	China (2013)	China's area study	Case-control study; hospital-based controls without description of match; use interviewer administered questionnaire suit for china participants; 8 years follow-up; participants were health male aged 40–75; use self-reported FFQs with 130 items	Water, alcohol, coffee, tea, juice, dairy products, soda	R Rs of highest vs. lowest levels of water intake were 0.53 (0.31, 0.90) and 0.72 (0.36, 1.43) for men and women	Age, BMI, smoke status, occupation, education, and history of hypertension	5
Ferraro ³⁸	America (2013)	Health Professionals Follow-Up and Nurses' Health Study	Cohort study; 8 years follow-up; participants were health male aged 40–75; use self-reported FFQs with 130 items	Water, alcohol, coffee, tea, juice, milk, soft drink	R Rs of highest vs. lowest levels of water, alcohol intake were 0.90 (0.81, 1.00) and 0.89 (0.82, 0.97) respectively	Age, race, region, body mass index, use of furosemide, thiazides, high BP, diabetes, gout, intake of calcium, potassium, phytate, animal protein, vitamin C, total calories, profession; all the beverages	8
Goldfarb ³⁹	America (2004)	Vietnam Era Twin (VET) Registry	Case-cohort study; cases and controls were twins aged from 34 to 50 years; matched with age, sex, gene	Alcohol, coffee, tea, milk	RR of current drinkers was 1.6 (0.6, 4.4); R Rs of highest vs. lowest levels of tea, coffee intake were 1.2 (0.4, 3.2) and 0.4 (0.2, 0.8)	Body mass index, hypertension, and smoking; N = 251 pairs with complete information on all covariates	6
Hirvonen ³⁶	Finland (1999)	National Public Health Institute	Cohort study; mean 6.1 years of follow-up (1985–1993); participants were male smoker aged 50–69; use self administered diet questionnaire with 276 food items	Water, alcohol, coffee, tea, juice, milk, soft drink	R Rs of highest vs. lowest levels of water, alcohol intake were 0.95 (0.67, 1.35) and 0.51 (0.36, 0.72) respectively	Age, supplementation group, vocational training, marital status, and intakes of magnesium, fiber, and alcohol	7
Krieger ²⁹	Puget Sound (2013)	Group Health Cooperative	Case-control study; sex- and age-matched hospital-based controls; use structured questionnaire by interviewers	Beer, coffee, tea, soda	RR was 0.44 (95% CI: 0.31, 0.63) and 0.71 (95% CI: 0.49, 1.02) for beer and coffee intake	Age	4
Liu ²⁷	China (2009)	China's area study	Case-control study; sex- and age-matched hospital-based controls; use structured questionnaire by interviewers	Total fluids and alcohol intake	R Rs of highest vs. lowest levels of water, alcohol intake were 0.90 (0.81, 1.00) and 0.89 (0.82, 0.97) respectively	Age, sex	4
Sorensen ³⁷	America (2012)	Women's Health Initiative Observational Study	Cohort study; mean follow-up was 8 year (from 1993); participants were woman aged 50–79; use self-reported WHI food questionnaire	Total water intake	RR of highest vs. lowest levels of water intake was 0.80 (0.66, 0.96)	Adjusted for age, race/ethnicity, education, geographic region, calcium supplementation, and current estrogen use	8
Taylor ³⁵	America (2004)	Nurses' Health Study I and II	Cohort study; 14 years follow-up (1986–1999); mean age were 40–75; use self-reported frequency questionnaire with 131 items	Total fluids intake	RR of highest vs. lowest levels of water intake was 0.71 (0.59, 0.85)	Age, body mass index, use of thiazide diuretics, fluid intake, alcohol use, calcium supplement use, dietary intake of animal protein, calcium, potassium, sodium, vitamin C, and magnesium	7

Author	Country	Research	Describe	Types of Beverages	Main Findings	Adjusted Item	Quality Score
Turney ¹⁸	British (2014)	European Prospective Investigation into Cancer and Nutrition	Cohort study; participants aged from 20 to 90 years; follow-up 20 years (1997–2007); self-reported	Alcohol	RR was 0.65 (95% CI: 0.47, 0.91) for highest vs. lowest alcohol intake	Sex, method of recruitment, region of residence and long-term medical treatment and adjusted for smoking, alcohol consumption, BMI, self-reported prior diabetes, and energy intake	8
Wang ²⁸	China (2013)	China's area study	Case-control study; hospital-based controls matched with age and sex; use interviewer-administered questionnaire	Constantly drinking tea	RR was 1.46 (1.03, 1.07) for constantly drinking tea vs. none	Adjusted for age, sex, labor intensity, source of tap water and boiled water, drinking habit, fresh vegetables, family history	3
Zhao ³¹	China (2012)	China's area study	Case-control study; controls are volunteers had annual routine physical examinations without description of match	Total fluids, tea, milk	RRs of highest vs. lowest levels of fluid, tea, milk were 0.60 (0.30, 0.90), 1.3 (1.0, 1.8), 0.9 (0.6, 1.6) for women	Fluid intake, smoking status, gender, bladder management, race, neurologic level	5

CI, confidence interval; RR, relative risk.

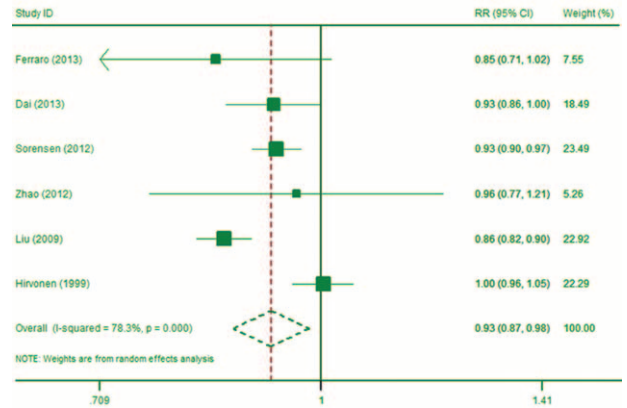


FIGURE 2. The forest plot of the linear association between water intake and risk of kidney stone (every 500 mL increment).

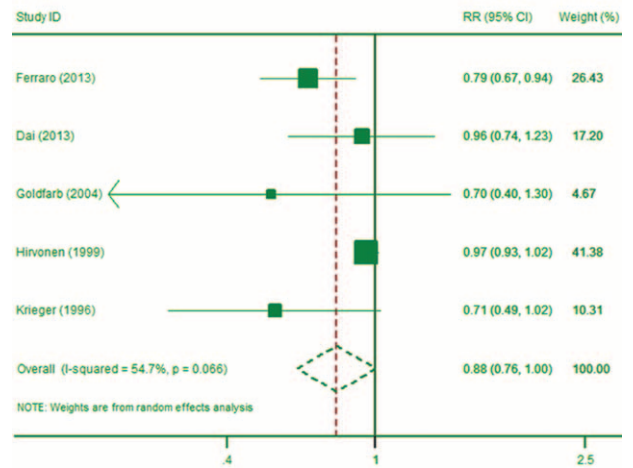


FIGURE 3. The forest plot of the association between coffee intake and risk of kidney stone (1–2 servings).

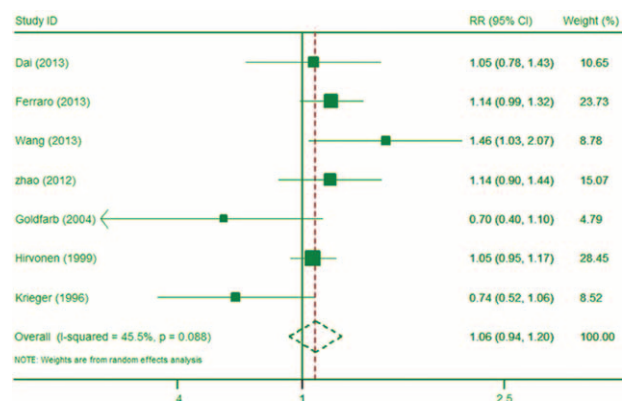


FIGURE 4. The forest plot of the association between tea intake and risk of kidney stone (1–2 servings).

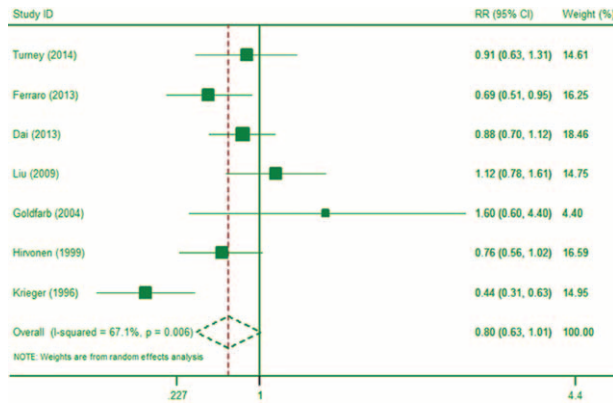


FIGURE 5. The forest plot of the association between alcohol intake and risk of kidney stone (1–2 servings).

control studies. Variation among other subgroups could not be assessed reliably due to small numbers.

As to heterogeneity of results, in most cases, the case–control studies showed a greater heterogeneity than cohort studies. Additionally, studies conducted in the United States showed mild heterogeneity, while considerably greater degrees of heterogeneity were observed in studies conducted in other countries (Finland, British).

Sensitivity analyses were conducted by omitting 1 study at a time to see whether the omission of the study influenced the overall results. We found that, for alcohol intake (about 12 g), 2 studies^{27,39} substantially influenced the results, as omitting either study led the results to become statistically significant (RRomit²⁷ = 0.78, 95% CI: 0.61, 0.99; RRomit³⁹ = 0.77, 95% CI: 0.61, 0.97). For milk intake, when omitting study,³⁰ the results reached to statistical significant (RR = 0.90, 95% CI: 0.82, 0.98). Other fluids showed robust results.

Publication Bias

The meta-analysis results for water, tea, and alcohol intake were examined for publication bias (there were not enough studies to conduct publication bias analyses for other

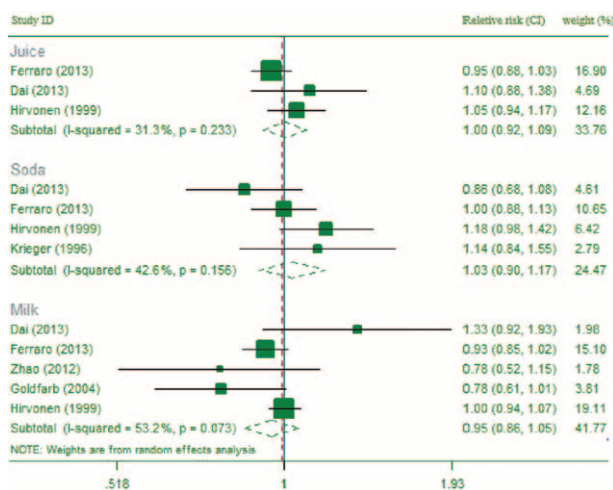


FIGURE 6. The forest plot of the association between other beverages intake and risk of kidney stone (1–2 servings).

beverages). Egger’s regression test of publication bias did not show strong evidence of publication bias (P for water = 0.92, P for tea = 0.55, P for alcohol = 0.76).

DISCUSSION

This is the first meta-analysis to have investigated the association of different types of beverages with risk of kidney stones. The meta-analysis confirmed that water intake was associated with a reduced risk of kidney stones. It also found that coffee, tea, and alcohol intake may reduce the risk of kidney stones. In contrast, juice, soda, and milk intake were not associated with kidney stone risk. Further subgroup analyses and sensitivity analyses showed unstable results for coffee and alcohol.

By increasing urine volume, increased water intake can dilute urine concentration, reduce CaOx super saturation, decrease urine acid, and remove salt.^{6,41} The European Association of Urology guidelines⁴² suggest that daily water intake should achieve at least 2.5 L of urine volume in order to prevent kidney stones. The present meta-analysis found no obvious threshold at which water intake began to be associated with reduced kidney stone risk. Instead, any increase in water intake, even at low levels of intake, was associated with reduced kidney stone risk. Thus, an average daily water intake should be recommended. The results of the present meta-analysis are partly consistent with a previous meta-analysis,¹⁰ which found that increased fluid intake (>2000 mL/day) was associated with a 61% reduction in the risk of kidney stones. Another conference abstract⁴³ comparing the highest versus lowest level of total fluid intake, observed a 60–80% decreased risk of kidney stone in the highest level group. In our meta-analysis, greater than 2000 mL of water intake per day reduced the risk of first kidney stone occurrence risk by at least 8% compared to 1500 mL daily intake, and the highest (3100 mL) category showed a 26% reduction of kidney stone risk compared to the reference category (1500 mL). Compared to the earlier meta-analysis, our meta-analysis quantitatively evaluated the effects of different doses of water intake and thus provides more refined information.

Caffeine, which is present in both in coffee and tea, is a potential risk factor for kidney stones because it may increase the urinary calcium/creatinine ratio.⁴⁴ In our study, coffee and tea intake were associated with a reduced risk of kidney stones when modeled as a continuous variable but not as a dichotomous variable. This may suggest a dose-dependent relationship between coffee (and tea) intake in prevention of stones. It is possible that some beneficial substances in coffee and tea (such as calcium)³⁴ offset the influence of caffeine. But this result may be influenced by the inconsistency between different study designs. Further studies, especially based on cohort design, were needed.

Tea consumption appeared to show a borderline nonlinear relationship with kidney stone risk, with a reduction in risk seen mostly at intake levels above 250 mL/day. Animal experiments support this result.^{45,46} In rats, green tea consumption significantly decreased urinary oxalate excretion and calcium oxalate deposit formation, possibly by the antioxidative action of epigallocatechin gallate and the activity of superoxide dismutase.^{45,46} However, it is difficult to explain why a reduction in kidney stone risk would only occur above a certain threshold of tea consumption, though increased consumption of water might partially explain such a threshold effect.

Our meta-analysis on alcohol consumption showed inconsistent results. Although 12 g of alcohol intake showed no

TABLE 2. Results of Subgroup Analysis

Subgroup Analysis	Study Type		Country			Other Subtypes	
	Case-Control	Cohort	America	China	Others		
Water						—	—
Study number	4	3	2	4	1	—	—
RR* (95% CI)	0.90 (0.85, 0.96)	0.96 (0.92, 0.99)	0.94 (0.93, 0.96)	0.89 (0.84, 0.95)	1.00 (0.96, 1.05)	—	—
P-value	<0.01	0.02	<0.01	<0.01	1	—	—
Heterogeneity (I ²)	38.50%	74.50%	0.00%	38.50%	—	—	—
Coffee						Caffeinated	Decaffeinated
Study number	2	3	3	1	1	1	1
RR† (95% CI)	0.85 (0.64, 1.13)	0.90 (0.82, 0.98)	0.75 (0.60, 0.93)	0.93 (0.77, 1.12)	0.97 (0.93, 1.12)	0.84 (0.77, 0.91)	0.74 (0.69, 0.80)
P-value	0.26	0.01	<0.01	0.43	0	—	—
Heterogeneity (I ²)	41.70%	51.20%	51.40%	—	—	—	—
Tea						Men	Women
Study number	4	3	3	3	1	2	2
RR† (95% CI)	1.07 (0.84, 1.37)	1.06 (0.93, 1.21)	0.88 (0.62, 1.06)	1.18 (1.0, 1.39)	1.05 (0.95, 1.17)	0.85 (0.49, 1.48)	0.80 (0.64, 1.12)
P-value	0.57	0.41	0.49	0.06	0	0.57	0.07
Heterogeneity (I ²)	59.40%	44.00%	29.90%	2.50%	—	78.3%‡	0.00%
Alcohol						Beer	Wine
Study number	3	4	4	2	1	2	1
RR† (95% CI)	0.76 (0.46, 1.25)	0.80 (0.71, 0.91)	0.79 (0.65, 0.96)	0.67 (0.45, 1.01)	0.96 (0.77, 1.19)	0.64 (0.31, 1.30)	0.78 (0.63, 0.96)
P-value	0.28	<0.01	0.02	0.7	0	0.22	0.02
Heterogeneity (I ²)	86.6%‡	5.30%	36.00%	15.60%	77.10%‡	89.60%‡	—
Soda						With sugar	Without sugar
Study number	2	2	2	1	1	1	1
RR† (95% CI)	0.97 (0.73, 1.28)	1.07 (0.91, 1.26)	1.02 (0.91, 1.05)	0.86 (0.68, 1.08)	1.17 (1.00, 1.37)	1.15 (0.95, 1.17)	0.98 (0.92, 1.04)
P-value	0.83	0.41	0.76	0.18	0	—	—
Heterogeneity (I ²)	54.00%	52.40%	0.00%	—	—	—	—
Milk						Whole milk	Skim milk
Study number	2	3	2	2	1	2	2
RR† (95% CI)	1.02 (0.60, 1.73)	0.94 (0.86, 1.04)	0.89 (0.77, 1.03)	1.02 (0.60, 1.73)	1.00 (0.94, 1.07)	0.96 (0.91, 1.01)	0.98 (0.93, 1.04)
P-value	0.94	0.23	0.11	0.94	1	0.14	0.52
Heterogeneity (I ²)	74.10%	55.10%	34.30%	74.10%	—	0.00%	2.70%

CI, confidence interval; RR, relative risk.
 *RR was the results of linearity dose–response meta-analysis of water intake.
 †RR was the results of about 1 to 2 servings of beverages intake.
 ‡ Indicated considerable heterogeneity (>75%).

prevention effect on stone formation, the dose–response meta-analysis indicates alcohol intake was associated with a reduced risk of kidney stones. Our subgroup analysis also showed inconsistent results by study design and country, indicating the potential benefit effect on stone prevention. There are limited studies focusing on the mechanism by which alcohol intake could affect kidney stone risk. One possible mechanism may be the diuretic action of alcohol.⁴⁷ This hypothesis may also partly explain why tea and coffee are associated with a reduced risk of kidney stones. But our results for alcohol were not particularly stable, and should therefore be interpreted with caution.

For juice intake, the overall meta-analysis showed no association between juice intake and risk of kidney stones. But the limited number of studies may result in bias. Moreover, the present study did not have sufficient data on the relation of lemon juice, cranberry juice, or pomegranate juice to kidney stone risk, though previous studies have reported that these juices are associated with a reduction in kidney stone risk.^{48–51} Further studies are needed.

Regarding soft drinks, the meta-analysis of Fink et al¹⁰ showed that decreased soft drink intake lowered the risk of kidney stones in patients with a high baseline consumption of soft drinks. In our meta-analysis, 110 to 240 mL of soda intake per day was not associated with stone risk. But the present study had no more data on other doses intake and the risk of stones.

In our meta-analysis, milk intake (about 1–2 servings a day) was not associated with kidney stone risk. Subgroup analyses also failed to find associations of whole or skim milk with kidney stone risk. The effect of higher doses of milk intake is still not known. But in the large cohort study of Goldfarb et al,³⁹ intake of 5 or more cups of milk intake a day was not associated with stone risk.

We should note that confounding factors may have influenced our results.⁵² The most important confounder is water intake, for each type of beverage contains large amounts of water. It is difficult to control for the confounding influence of water, either by study design or by statistical adjustment. Therefore, the effects of coffee, tea, and alcohol may be overestimated while the effects of juice, soda, and milk may be underestimated. That is, coffee, tea, and alcohol may actually be less protective against kidney stone risk than our results suggest. Conversely, juice, soda, and milk intake may increase the risk of kidney stone more than is suggested by our results, since water may offset part of the risk associated with those beverages. Other variables, such as genetic factors,⁵³ hardness of drinking water,⁵⁴ concentration of beverages, body mass index,³⁵ and geographical environment⁵⁵ (such as desert) may also potentially confound the association between fluid intake and kidney stone risk. However, our sensitivity analyses showed that our results were robust, which suggests that the influence of confounders in our study was mild.

Strength and Limitations

The present study's comprehensive literature search, and strict study design, lends credibility to the study's results. Linear and nonlinear dose–response meta-analysis quantitatively evaluated the association of different levels of beverages intake on kidney stone risk, providing a more refined analysis than some prior studies. Additionally, subgroup and sensitivity analyses suggested that our study's results were robust in most cases, which strengthens the conclusions of our study.

This present study had some limitations. One limitation was that our evaluation and transformation of the raw data was fairly crude. A second limitation was that there were limited numbers of cohort studies focusing on the association between fluid intake and the risk of kidney stones. This small number of cohort studies is potentially problematic, since some research indicates that random errors induced by a small number of trials may cause bias in the results of meta-analyses.^{56,57} A third limitation was that different categories of fluid intake among studies made it difficult to pool results across studies. Indeed, some studies only reported the effect of any versus no fluid intake, or high versus no intake, while others reported 110 mL versus no intake of fluids. Although dose–response meta-analysis was used to overcome this problem, for soda and milk, there were limited studies reporting relevant data that could be used in a dose–response analysis. Furthermore, differences in how studies categorized fluid intake may have contributed to some of the heterogeneity we observed in our results, especially for juice intake. A fourth limitation was that, in our meta-analysis, most of the studies were conducted in the United States and China, and may not be generalizable to other countries. Fifth, we did not examine interactions among subgroups because the subgroup sample sizes were too small for such analyses to produce statistically reliable results.

CONCLUSIONS

Increased water are associated with a reduced risk of developing kidney stones; increased intake of coffee, tea, and alcohol showed potential benefits on stones prevention, but needs to be confirmed further. Soda and milk intake appeared to be unrelated to stone risk. Current evidence is insufficient for definitively determining the relationship between juice intake and risk of kidney stones.

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