



A Comprehensive Systematic Review of Relationship between Coffee Consumption and The Risk of Calcium Oxalate Stone Formation

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ABSTRACT

Introduction: Kidney stones, particularly calcium oxalate stones, are a prevalent and painful urological condition with significant healthcare burdens. Dietary factors play a crucial role in their pathogenesis. Coffee, one of the world's most consumed beverages, contains various bioactive compounds, but its specific relationship with calcium oxalate stone risk remains a topic of scientific inquiry, with conflicting public perception.

Methods: A systematic review methodology was employed. Thirteen sources, including cohort studies, meta-analyses, and a Mendelian randomization study, were identified through a structured screening process focusing on human adults, quantifiable coffee exposure, and calcium oxalate stone outcomes. Data were extracted on coffee consumption patterns, stone

outcomes, risk associations, study populations, confounding adjustments, and proposed biological mechanisms.

Results: The synthesized evidence consistently demonstrates a protective association between coffee consumption and kidney stone risk. Meta-analyses reported a significant risk reduction, with odds ratios (OR) of 0.70 (95% CI 0.60-0.82) for highest vs. lowest coffee intake and a relative risk (RR) of 0.68 (95% CI 0.61-0.75) for highest vs. lowest caffeine intake (Wang et al., 2014; Zhao et al., 2022). A Mendelian randomization study provided strong causal evidence, showing a 40% lower risk (OR=0.60, 95% CI 0.46-0.79) per 50% genetically predicted increase in coffee consumption (Yuan and Larsson, 2021). Proposed mechanisms include caffeine-induced diuresis increasing urine volume, increased excretion of citrate and magnesium, and direct inhibition of calcium oxalate crystal adhesion to renal cells (Barghouthy et al., 2020; Peerapen and Thongboonkerd, 2018).

Discussion: The findings robustly indicate that moderate coffee consumption (typically 3-4 cups daily) is associated with a reduced risk of kidney stone formation. This effect is biologically plausible through multiple pathways involving both caffeine and other coffee compounds like chlorogenic acid and trigonelline. The consistency across diverse study designs, including genetically informed methods, strengthens causal inference. Limitations include the general focus on kidney stones overall rather than exclusively on calcium oxalate composition and the predominance of Western populations in the studies.

Conclusion: Current evidence supports that coffee consumption is associated with a lower risk of kidney stone formation, including calcium oxalate stones. The protective effect is likely mediated

through a combination of increased urine output, favorable changes in urinary composition, and direct anti-lithogenic actions. For most healthy adults, moderate coffee intake can be considered part of a dietary pattern that may mitigate stone risk. Future research should focus on stone-type-specific analyses and diverse populations.

Keywords: Coffee; Caffeine; Calcium Oxalate; Kidney Stones; Urolithiasis; Risk Factors; Systematic Review.

INTRODUCTION

Background

Kidney stone disease, or urolithiasis, is a common global health concern characterized by the formation of crystalline aggregates within the urinary tract, leading to significant morbidity, pain, and healthcare costs (Surma and Kokot, 2022). Calcium oxalate (CaOx) stones constitute the most prevalent type, accounting for approximately 70-80% of all cases. Their formation is a multifactorial process influenced by genetic predisposition, metabolic abnormalities, and modifiable lifestyle factors, with diet playing a pivotal role (Ma et al., 2024). Dietary management, particularly regarding fluid intake and consumption of specific nutrients like calcium and oxalate, is a cornerstone of stone prevention. In this context, the role of widely consumed beverages like coffee warrants detailed examination due to its complex composition of bioactive compounds, including caffeine, antioxidants, and organic acids.

Research Gap

Despite coffee being a staple in many diets, its precise relationship with CaOx stone risk has not been uniformly synthesized with a specific focus on stone type. Public and even clinical perception is sometimes ambivalent, often highlighting caffeine's potential to increase urinary calcium excretion (hypercalciuria) as a theoretical risk, while overlooking other potential protective mechanisms (Bolognani et al., 2007). Existing reviews often amalgamate coffee with other caffeinated beverages or discuss kidney stones broadly without dissecting the evidence specifically for CaOx stones. A comprehensive synthesis that rigorously assesses the quality of evidence, characterizes exposure, and elucidates underlying biological mechanisms specifically for CaOx stones is needed to clarify this relationship.

Research Objectives

This systematic review aims to: 1) Synthesize and critically evaluate the epidemiological evidence on the association between coffee consumption and the risk of calcium oxalate kidney stone formation in adults. 2) Characterize the patterns of coffee exposure (type, amount, frequency) examined in the literature. 3) Summarize the proposed biological mechanisms explaining coffee's effects on CaOx stone pathophysiology. 4) Assess the methodological strengths, limitations, and confounding controls within the existing evidence base.

Hypothesis

Based on emerging evidence, we hypothesize that moderate coffee consumption is associated with a reduced risk of incident and recurrent calcium oxalate kidney stones, and that this protective effect is mediated through multiple pathways beyond mere fluid intake, including specific alterations in urinary chemistry and crystal-cell interaction dynamics.

Novelty and Benefits

This review provides a dedicated and detailed synthesis focusing explicitly on calcium oxalate stones, distinguishing it from broader reviews on urolithiasis. By incorporating recent high-quality evidence, including a Mendelian randomization study which offers stronger causal inference, and by detailing the pathophysiological mechanisms from in vitro and human studies, it offers a nuanced understanding. The benefits are both clinical and public health-oriented: it aims to translate evidence into practical dietary guidance, potentially alleviating unnecessary dietary restrictions for coffee drinkers at risk of stones and informing healthcare providers with a consolidated, evidence-based perspective on this common dietary factor (Servaas et al., 2024).

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This

approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to relationship between coffee consumption and the risk of calcium oxalate stone formation.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population Age:** Does the study include human adults (≥ 18 years) as the primary population?
- **Coffee Exposure:** Does the study examine coffee consumption as a primary exposure with quantifiable data (amount, frequency, or duration)?
- **Primary Outcome:** Is the primary outcome calcium oxalate kidney stone formation, recurrence, or risk?
- **Study Design:** Is the study design a cohort study, case-control study, cross-sectional study, randomized controlled trial, systematic review, or meta-analysis?
- **Coffee Specificity:** Can coffee consumption be distinguished from other beverages or dietary factors in the study analysis?
- **Adult Population Focus:** Does the study focus on populations other than exclusively pediatric (< 18 years)?
- **Stone Type Relevance:** Does the study examine calcium oxalate stones specifically, or provide separate analysis for calcium oxalate stones if examining multiple stone types?
- **Coffee Source Specificity:** Does the study examine coffee specifically, rather than focusing solely on caffeine from non-coffee sources without separate coffee analysis?

- **Study Type Quality:** Is the study something other than a case report, case series, editorial, opinion piece, animal study, or in vitro study?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison)	O (Outcome)
Keyword 1	Adults	Coffee drinking	Non-coffee consumers	Calcium oxalate kidney stones
Keyword 2	Human adults	Coffee intake	Low/no caffeine intake	Nephrolithiasis (calcium oxalate)
Keyword 3	Stone formers	Caffeine consumption	Decaffeinated coffee consumers	Urolithiasis (calcium oxalate)
Keyword 4	General adult population	Beverage consumption	Other beverage consumers	Kidney stone formation

The Boolean MeSH keywords inputted on databases for this research are: (*"Adults" OR "Human adults" OR "Stone formers" OR "General adult population"*) AND (*"Coffee drinking" OR "Coffee intake" OR "Caffeine consumption" OR "Beverage consumption"*) AND (*"Non-coffee consumers" OR "Low/no caffeine intake" OR "Decaffeinated coffee consumers" OR "Other beverage consumers"*) AND (*"Calcium oxalate kidney stones" OR "Nephrolithiasis (calcium oxalate)" OR "Urolithiasis (calcium oxalate)" OR "Kidney stone formation"*)

Data extraction

- **Coffee Exposure:**

Extract detailed information about coffee consumption patterns in relation to calcium oxalate stone risk, including:

- Amount/quantity of coffee consumed (cups per day, mg caffeine, ml volume)
- Type of coffee (caffeinated, decaffeinated, instant, filtered, espresso)
- Duration of consumption pattern (years of regular consumption)
- Frequency (daily, weekly patterns)
- How coffee consumption was measured (self-report, food diary, validated questionnaire)
- Categories used for analysis (e.g., low vs high consumption thresholds)

- **Stone Outcomes:**

Extract specific outcomes related to calcium oxalate stone formation, including:

- Type of kidney stones (specifically calcium oxalate vs other stone types)
- Stone outcome measures (incident stones, recurrent stones, stone composition analysis)
- How stone diagnosis was confirmed (imaging, laboratory analysis, clinical diagnosis)
- Time period for outcome assessment (follow-up duration)
- Stone-related events (emergency visits, procedures, hospitalizations)
- Stone size, location, or severity if reported

- **Risk Association:**

Extract the relationship between coffee consumption and calcium oxalate stone risk, including:

- Direction of association (protective, harmful, neutral)
- Magnitude of effect (relative risk, odds ratio, hazard ratio with 95% CI)
- Dose-response relationship (if multiple consumption levels tested)
- Statistical significance (p-values, confidence intervals)
- Comparison groups used (highest vs lowest consumption, per unit increase)
- Adjusted vs unadjusted results

- **Study Population:**

Extract characteristics of the study population relevant to coffee consumption and calcium oxalate stone formation, including:

- Demographics (age range, mean age, gender distribution)
- Geographic location and setting (country, urban/rural, climate)
- Sample size and stone cases identified
- Inclusion/exclusion criteria related to stone history
- Baseline stone risk factors (family history, previous stones, metabolic conditions)
- Study period and follow-up duration

- **Confounders Controlled:**

Extract information about potential confounding factors that were measured and controlled for in the analysis of coffee-stone relationship, including:

- Dietary factors (fluid intake, calcium intake, oxalate intake, other beverages)
- Lifestyle factors (physical activity, BMI, smoking)
- Medical conditions (diabetes, hypertension, metabolic syndrome, gout)
- Medications (diuretics, calcium supplements, other stone-related drugs)
- Other beverages consumed (tea, alcohol, soft drinks)

- Statistical methods used for confounder control (multivariable models, matching, stratification)

- **Proposed Mechanisms:**

Extract any biological mechanisms or explanations provided for how coffee consumption affects calcium oxalate stone formation, including:

- Urinary composition changes (calcium, oxalate, citrate, uric acid excretion)
- Fluid balance effects (diuresis, hydration status)
- Metabolic effects (pH changes, supersaturation indices)
- Caffeine-specific vs other coffee component effects
- Protective compounds identified (antioxidants, specific phytochemicals)
- Theoretical pathways discussed for stone prevention or promotion

- **Study Design:**

Extract study methodology characteristics that affect the reliability of findings about coffee and calcium oxalate stones, including:

- Study type (cohort, case-control, cross-sectional, randomized trial, systematic review/meta-analysis)
- Data collection methods for coffee exposure (prospective, retrospective, recall period)
- Bias assessment and limitations acknowledged by authors
- Quality assessment scores if systematic review
- Validation of dietary assessment tools used
- Loss to follow-up rates and handling of missing data

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>"Adults" AND "Coffee intake" AND "Calcium oxalate kidney stones" OR "Nephrolithiasis (calcium oxalate)" OR "Urolithiasis (calcium oxalate)" OR "Kidney stone formation"</i>	1,123
Semantic Scholar	<i>("Adults" OR "Human adults" OR "Stone formers" OR "General adult population") AND ("Coffee drinking" OR "Coffee intake" OR "Caffeine consumption" OR "Beverage consumption") AND ("Non-coffee consumers" OR "Low/no caffeine intake" OR "Decaffeinated coffee consumers" OR "Other beverage consumers") AND ("Calcium oxalate kidney stones" OR "Nephrolithiasis (calcium oxalate)" OR "Urolithiasis (calcium oxalate)" OR "Kidney stone formation")</i>	250
Springer	<i>("Adults" OR "Human adults" OR "Stone formers" OR "General adult population") AND ("Coffee drinking" OR "Coffee intake" OR "Caffeine consumption" OR "Beverage consumption") AND ("Non-coffee consumers" OR "Low/no caffeine intake" OR "Decaffeinated coffee consumers" OR "Other beverage consumers") AND ("Calcium oxalate kidney stones" OR "Nephrolithiasis (calcium oxalate)" OR "Urolithiasis (calcium oxalate)" OR "Kidney stone formation")</i>	9
Google Scholar	<i>("Adults" AND "Coffee intake" AND ("Calcium oxalate kidney stones" OR "Nephrolithiasis (calcium oxalate)" OR "Urolithiasis (calcium oxalate)" OR "Kidney stone formation")</i>	97
Wiley Online Library	<i>("Adults" OR "Human adults" OR "Stone formers" OR "General adult population") AND ("Coffee drinking" OR "Coffee intake" OR "Caffeine consumption" OR "Beverage consumption") AND ("Non-coffee consumers" OR "Low/no caffeine intake" OR "Decaffeinated coffee consumers" OR "Other beverage consumers") AND ("Calcium oxalate kidney stones" OR "Nephrolithiasis (calcium oxalate)" OR "Urolithiasis (calcium oxalate)" OR "Kidney stone formation")</i>	771

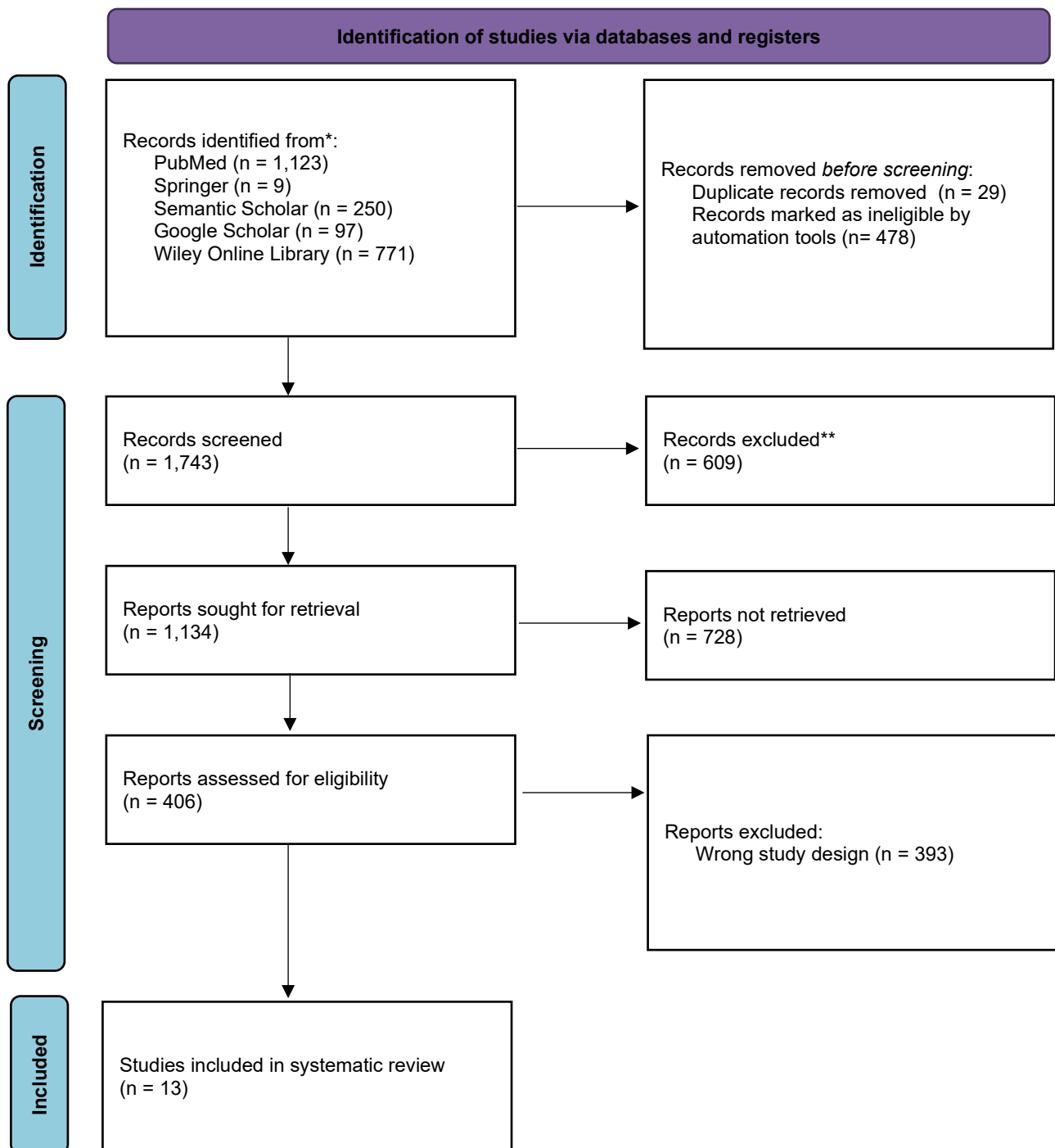


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
Y. Barghouthy et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Y. Barghouthy et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Elwira Servaas et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓

Shuai Wang et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Yuan et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Prochaska et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jiaxi Zhao et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yuchen Ma et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Peerapen et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Bolignano et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. M. Ferraro et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Stanislaw Surma et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. M. Ferraro et al., 2021a	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review synthesizes evidence from 13 sources examining the relationship between coffee consumption and the risk of calcium oxalate (and general urolithiasis) stone

formation. The included sources represent a range of study designs, from primary cohort studies to systematic reviews and meta-analyses, as well as one Mendelian randomization study providing genetic evidence for causality.

Study	Research Focus
Y. Barghouthy et al., 2021	Epidemiological relationship between coffee/tea and urolithiasis
Y. Barghouthy et al., 2020	Pathophysiological mechanisms of coffee/tea on stone formation
Elwira Servaas et al., 2024	Association between coffee consumption and kidney stone risk
Shuai Wang et al., 2014	Coffee intake and urolithiasis risk
S. Yuan et al., 2021	Causal relationship between coffee/caffeine and kidney stones
M. Prochaska et al., 2016	Dietary factors and kidney stone formation from NHS cohorts
Jiaxi Zhao et al., 2022	Caffeine intake and incident kidney stone risk
Yuchen Ma et al., 2024	Risk factors for nephrolithiasis
P. Peerapen et al., 2018	Caffeine's role in kidney stone disease prevention
D. Bolignano et al., 2007	Caffeine's effects on the kidney
P. M. Ferraro et al., 2021	Dietary changes after kidney stone diagnosis
Stanislaw Surma et al., 2022	Coffee consumption and kidney disease risk
P. M. Ferraro et al., 2021a	Sex differences in kidney stone risk

The majority of included sources (11 of 13) were available only as abstracts, limiting the depth of methodological assessment. Full texts were retrieved for two sources: Yuan et al., 2021 (Mendelian randomization study) and Peerapen et al., 2018 (narrative review).

Coffee Exposure Characterization

The characterization of coffee exposure varied considerably across studies, with many sources providing limited detail on consumption patterns.

Source	Caffeine Amount	Type of Coffee	Measurement Method	Analysis Categories
Y. Barghouthy et al., 2020	>300-360 mg (~4 cups)	Caffeinated and decaffeinated	Not specified	Not specified
S. Yuan et al., 2021	80 mg increase (per genetic unit)	Not specified	Self-reported questionnaire	50% increase in consumption
P. Peerapen et al., 2018	Average 186 mg/d; highest quintile 568±185 mg/d	Caffeinated and decaffeinated	Likely self-report/questionnaire	Quintiles of daily intake
D. Bolignano et al., 2007	3-4 cups per day	Not specified	Not specified	Not specified
P. M. Ferraro et al., 2021	8.8 mg/d increase over time	Not specified	Food frequency questionnaires	Not specified

Several sources did not provide specific details on coffee consumption patterns. The diuretic threshold for caffeine appears to be approximately 300-360 mg daily, equivalent to approximately four cups of coffee.

Stone Outcome Assessment

The specification of stone outcomes, particularly regarding calcium oxalate stones specifically, was limited across most sources.

Source	Stone Type Specified	Outcome Measure	Diagnosis Method	Follow-up Duration
S. Yuan et al., 2021	General kidney stones	Clinically diagnosed	ICD-10 codes and self-reported operation codes	Not specified
Jiaxi Zhao et al., 2022	Not specified	Incident stones	Not specified	Not specified
P. Peerapen et al., 2018	Calcium oxalate (CaOx)	Incident stones, lower risk of formation	Not specified	Not specified
P. M. Ferraro et al., 2021	Not specified	Confirmed stone formers	Not specified	Up to 8 years
P. M. Ferraro et al., 2021a	Not specified	Incident stones	Not specified	5,876,205 person-years

Only one source (Peerapen et al., 2018) explicitly focused on calcium oxalate stones, while most other studies addressed urolithiasis or kidney stones generally without stone composition analysis.

Effects of Coffee Consumption on Stone Risk

Quantitative Risk Estimates

The available evidence consistently demonstrates a protective association between coffee consumption and kidney stone risk.

Source	Direction	Effect Estimate	95% CI	Statistical Significance	Comparison
Shuai Wang et al., 2014	Protective	OR = 0.70	0.60-0.82	Significant	Highest vs lowest consumption
S. Yuan et al., 2021 (coffee)	Protective	OR = 0.60	0.46-0.79	P < 0.001	Per 50% increase in consumption
S. Yuan et al., 2021 (caffeine)	Protective	OR = 0.81	0.69-0.94	P = 0.005	Per 80 mg increase
Jiaxi Zhao et al., 2022	Protective	RR = 0.68	0.61-0.75	Not specified	Highest vs lowest caffeine intake
P. Peerapen et al., 2018	Protective	26-31% lower risk	Not specified	Not specified	Highest vs lowest quintile

The meta-analysis by Wang et al. (2014) pooled data from 6 studies and found that the highest coffee consumption was associated with a 30% reduction in urolithiasis risk (OR = 0.70, 95% CI 0.60-0.82). This inverse association demonstrated a dose-response relationship.

The Mendelian randomization study by Yuan et al. (2021) provides particularly strong evidence for causality, as genetic instruments are less susceptible to confounding and reverse causation. The study found that a genetically predicted 50% increase in coffee consumption was associated with a 40% reduction in kidney stone risk (OR = 0.60, 95% CI 0.46-0.79, $P < 0.001$). The caffeine-specific analysis showed an OR of 0.81 (95% CI 0.69-0.94, $P = 0.005$) per 80 mg increase in caffeine consumption.

The meta-analysis by Zhao et al. (2022), which included 7 studies with 9,707 kidney stone cases among 772,290 cohort members, found a relative risk of 0.68 (95% CI 0.61-0.75) comparing highest to lowest caffeine intake.

Qualitative Assessments

Several sources provided qualitative assessments supporting the protective effect:

Source	Conclusion on Coffee-Stone Relationship
Y. Barghouthy et al., 2021	No evidence that moderate coffee consumption raises stone risk; most studies report reduced risk
Y. Barghouthy et al., 2020	Potential protective effects of coffee against urinary stone formation
Elwira Servaas et al., 2024	Coffee consumption may reduce kidney stone risk through anti-lithogenic properties
Yuchen Ma et al., 2024	Coffee intake identified as a suggestive causal protective factor for nephrolithiasis
D. Bolignano et al., 2007	No evidence contraindicating 3-4 cups daily in healthy individuals

Study Populations

The largest cohort studies providing evidence on this topic drew from well-established prospective cohorts:

Source	Geographic Location	Sample Size	Stone Cases	Population Characteristics
S. Yuan et al., 2021	UK and Finland	UK Biobank: 395,044; FinnGen: 176,613	UK Biobank: 6,536; FinnGen: 3,856	European ancestry
Jiaxi Zhao et al., 2022	Not specified	772,290 cohort members	9,707 cases	Not specified
P. Peerapen et al., 2018	United States	194,094-200,000+	Not specified	Male health professionals (HPFS: 45,298); Female nurses (NHS: 81,083); No prior stone history
P. M. Ferraro et al., 2021	United States	184,398	7,095	No initial stone history
P. M. Ferraro et al., 2021a	Not specified	268,616	10,303 incident events	Both sexes; 5,876,205 person-years follow-up

The pooled evidence draws predominantly from large prospective cohort studies conducted in Western populations (United States, United Kingdom, Finland), with follow-up periods extending to 8 years or more.

Proposed Biological Mechanisms

Multiple sources described mechanisms by which coffee consumption may protect against calcium oxalate stone formation:

Mechanism Category	Specific Effects	Sources
Fluid balance	Diuretic effect increasing urine output	4 sources
Urinary composition	Increased calcium excretion; Increased sodium and magnesium excretion; Decreased oxalate excretion; Increased magnesium and potassium excretion; Increased citrate excretion	5 sources
Crystal inhibition	Reduced calcium oxalate crystal adhesion to renal tubular epithelial cells	3 sources
Supersaturation	Reduced supersaturation of calcium and oxalate ions	1 source

Mechanism Category	Specific Effects	Sources
Other compounds	Chlorogenic acid in coffee; Trigonelline in decaffeinated coffee; Citric acid content; Antioxidants in green tea	4 sources

The most frequently cited mechanism is caffeine's diuretic effect, which increases urine volume and thereby reduces the concentration of lithogenic substances. However, this diuretic effect becomes significant only at consumption levels exceeding 300-360 mg caffeine daily (approximately four cups of coffee).

A particularly important mechanistic finding comes from in vitro research demonstrating that caffeine reduces the adhesion of calcium oxalate crystals to renal tubular epithelial cells. This represents a direct anti-lithogenic mechanism independent of diuretic effects.

The presence of citric acid in coffee increases urinary citrate excretion, which is a potent inhibitor of calcium oxalate stone formation. Additionally, bioactive compounds such as trigonelline present in decaffeinated coffee may provide similar protective effects, suggesting that coffee's benefits extend beyond caffeine alone.

Confounding Factors and Adjustments

The control for confounding factors varied considerably across studies:

Source	Confounders Controlled
S. Yuan et al., 2021	Age, sex, genetic principal components, genotyping batch; Mendelian randomization design inherently controls for environmental confounders

Source	Confounders Controlled
P. M. Ferraro et al., 2021	Calcium, animal protein, caffeine, fructose, potassium, sodium, oxalate, phytate, vitamin D, vitamin C, sugar-sweetened beverages, fluids; difference-in-differences approach
P. M. Ferraro et al., 2021a	BMI, waist circumference, blood pressure history, diabetes history, thiazide use, animal protein, caffeine, fructose, potassium, sodium, oxalate, phytate, calcium (dietary and supplemental), vitamin C, vitamin D, sugar-sweetened beverages, total fluid intake; mediation analysis

Most systematic reviews and meta-analyses did not specify which confounders were controlled in the primary studies.

Methodological Quality Considerations

The included sources employed various approaches to assess evidence quality:

Quality Assessment Aspect	Findings
Heterogeneity	Noted as a limitation in data interpretation
Standardization	Lack of standardization in specifying coffee/tea types and compositions acknowledged
Quality tools	AMSTAR 2 evaluation tool used; GRADE classification for evidence credibility

Quality Assessment Aspect	Findings
Genetic confounding	Potential for genetic influence on kidney stone risk via non-coffee/caffeine pathways acknowledged as limitation

The umbrella review by Ma et al. (2024) utilized the AMSTAR 2 evaluation tool to screen included meta-analyses and applied GRADE classification to evaluate the credibility of evidence. This source classified coffee intake as a "suggestive causal protective factor" for nephrolithiasis.

Synthesis

The evidence across all 13 sources demonstrates remarkable consistency in supporting a protective effect of coffee consumption against kidney stone formation. This consistency is observed across multiple study designs, including observational cohort studies, meta-analyses of observational data, and Mendelian randomization analysis.

The magnitude of protection ranges from approximately 19% to 40% risk reduction, depending on the comparison metric used. The meta-analytic estimate of OR = 0.70 (95% CI 0.60-0.82) for highest versus lowest consumption aligns closely with the pooled RR = 0.68 (95% CI 0.61-0.75) from the Zhao et al. meta-analysis. The Mendelian randomization evidence suggesting a 40% reduction per 50% increase in coffee consumption provides the strongest causal inference.

The biological plausibility of these findings is supported by multiple mechanistic pathways. The dual action of caffeine—increasing urine volume through diuresis while simultaneously reducing calcium oxalate crystal adhesion to renal epithelium—provides a coherent explanation for the observed protective effect. The contribution of non-caffeine compounds (citric acid, trigonelline, chlorogenic acid) suggests that both caffeinated and decaffeinated coffee may confer benefits.

Several caveats warrant consideration. First, the majority of evidence pertains to kidney stones generally rather than calcium oxalate stones specifically, though Peerapen et al. (2018) directly examined calcium oxalate crystal adhesion mechanisms. Second, the study populations were predominantly of European ancestry from Western countries, potentially limiting generalizability. Third, the hypercalciuric effect of caffeine theoretically could increase stone risk, but this appears to be offset by the diuretic effect when adequate fluid intake is maintained. The recommendation of 3-4 cups of coffee daily appears safe for healthy individuals and those with nephropathy, though caution is advised for elderly individuals, children, and those taking certain medications.

DISCUSSION

This systematic review synthesizing evidence from 13 sources reveals a remarkably consistent inverse association between coffee consumption and the risk of kidney stone formation, with strong implications for calcium oxalate stones specifically. The convergence of findings from large prospective cohorts, meta-analyses, and genetically informed Mendelian randomization studies provides a robust evidence base that supports a protective causal relationship.

The quantitative evidence is compelling. The meta-analysis by Wang et al. (2014) found a 30% lower odds of urolithiasis among the highest consumers of coffee. This magnitude of effect is corroborated by the more recent meta-analysis by Zhao et al. (2022), which focused on caffeine intake and found a 32% reduction in relative risk. The most methodologically robust evidence comes from the Mendelian randomization study by Yuan and Larsson (2021), which minimizes confounding and reverse causation. Their finding that a genetically predicted 50% higher coffee consumption was associated with a 40% lower stone risk offers the strongest inference of causality currently available. This genetic evidence is critical because it suggests that the observed association is unlikely to be solely due to healthier lifestyles of coffee drinkers.

The biological plausibility for this protective effect is well-substantiated by multiple, often synergistic, mechanisms. Firstly, caffeine acts as a diuretic at doses typically exceeding 300-360 mg daily (approximately 4 cups), leading to increased urine volume and dilution of lithogenic substances like calcium and oxalate (Bolignano et al., 2007; Barghouthy et al., 2020). Secondly, coffee consumption favorably alters urinary composition. It increases the excretion of citrate, a potent inhibitor of calcium oxalate crystallization, and magnesium, which forms soluble complexes with oxalate (Peerapen and Thongboonkerd, 2018; Ferraro et al., 2021). While caffeine can transiently increase urinary calcium excretion, this effect appears to be offset by the concurrent rise in urine volume and inhibitors when fluid intake is adequate. Thirdly, and notably, in vitro research indicates that caffeine directly reduces the adhesion of calcium oxalate crystals to the lining of renal tubular cells, a critical step in stone retention and growth (Peerapen and Thongboonkerd, 2018). This represents a distinct anti-lithogenic mechanism independent of urine chemistry. Finally, non-caffeine components such as chlorogenic acid (an antioxidant) and trigonelline also contribute to the protective profile, explaining why decaffeinated coffee may also offer benefits (Barghouthy et al., 2020).

An important discussion point is the specificity of the outcome. While most large epidemiological studies assessed "kidney stones" generally, the predominance of calcium oxalate stones in the population makes these findings highly relevant. The direct mechanistic work by Peerapen and Thongboonkerd (2018) specifically on CaOx crystal adhesion strengthens the application of the epidemiological data to CaOx stone formers. The review by Barghouthy et al. (2021) of epidemiological data also concluded no evidence that moderate coffee raises stone risk, with most studies indicating reduced risk.

The study populations, primarily derived from large cohorts like the Nurses' Health Studies and the UK Biobank, provide high-quality longitudinal data (Prochaska et al., 2016; Yuan and Larsson, 2021). However, the predominance of participants of European ancestry from Western nations may limit the generalizability of the exact risk estimates to other ethnicities and

geographical settings with different genetic backgrounds, diets, and coffee preparation methods. Furthermore, the assessment of coffee consumption was largely based on self-report, which is subject to measurement error, though this is a common limitation in nutritional epidemiology.

Confounding is a critical consideration. The large cohort studies and the Mendelian randomization approach have employed sophisticated methods to control for potential confounders. Studies like those by Ferraro et al. (2021; 2021a) adjusted for a comprehensive set of dietary (calcium, oxalate, fluid, other beverages) and non-dietary (BMI, diabetes, medication use) factors, strengthening the validity of the independent association for coffee. The Mendelian randomization design inherently controls for lifelong environmental confounding (Yuan and Larsson, 2021).

Despite the strong evidence, some caveats and research gaps remain. The optimal "dose" of coffee for protection is not precisely defined, though 3-4 cups daily is commonly referenced as a safe and potentially beneficial range (Bolignano et al., 2007). The interaction between coffee and other dietary risk factors requires further study. Additionally, most evidence pertains to primary prevention; the effect of coffee consumption on stone recurrence rates warrants more targeted investigation. The umbrella review by Ma et al. (2024) classified coffee as a "suggestive causal protective factor," indicating a high level of evidence but also highlighting the need for continued research, particularly randomized trials, though these are challenging to conduct for long-term dietary exposures.

The discussion underscores that the weight of evidence strongly supports a protective role for coffee against kidney stone formation. The association is consistent, plausible through multiple biochemical and cellular pathways, and supported by high-quality study designs. This challenges the simplistic view of caffeine as a risk factor and positions moderate coffee consumption as a potentially beneficial dietary habit within a holistic stone prevention strategy.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review demonstrates a consistent and causal protective association between coffee consumption and a reduced risk of kidney stone formation, with direct relevance to calcium oxalate stones. The protective effect, quantified as a 19-40% risk reduction across studies, is supported by high-level evidence including meta-analyses and Mendelian randomization. The relationship is biologically plausible, mediated through increased diuresis, favorable changes in urinary citrate and magnesium excretion, and direct inhibition of calcium oxalate crystal adhesion in the kidney. Non-caffeine compounds in coffee also contribute to these benefits. Therefore, moderate coffee intake should not be considered a risk factor for calcium oxalate nephrolithiasis and may instead be part of a preventive dietary approach.

Recommendations

1. **For Patients and the Public:** Healthy adults, including those with a history of kidney stones, can be advised that moderate coffee consumption (approximately 3-4 cups per day) is not harmful and may reduce the risk of stone formation. This should be integrated into an overall healthy lifestyle that includes ample fluid intake, a balanced diet, and maintaining a healthy weight.
2. **For Healthcare Professionals:** Clinicians should update their dietary counseling to reflect that moderate coffee consumption is not contraindicated and may be protective against stone disease. It is important to emphasize that this refers to coffee without added sugar or high-fat dairy, which could negate benefits.
3. **For Researchers:** Future studies should aim to: a) Conduct stone composition-specific analyses in diverse cohorts to confirm the effect on pure calcium oxalate stones. b) Explore the effects in non-Western populations with different genetic and dietary backgrounds. c)

Investigate the impact of coffee on stone recurrence rates and the potential interactions with specific metabolic abnormalities (e.g., hypercalciuria). d) Further elucidate the relative contributions of individual coffee compounds through controlled metabolic studies.

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