

Impact of Smoke Exposure on Kidney Stone Formation: A Systematic Review

Siti Noor Aqilla Maharani^{1*}, Alexander Rafael Satyadharma², Ayu Saraswati³

¹Cipaku Community Health Center, Ciamis, West Java, Indonesia, 46252

²Tebet Regional Public Hospital, South Jakarta, Indonesia, 12810

³Kramat Jati Community Health Center, East Jakarta, Indonesia, 13510

*Corresponding Author

Siti Noor Aqilla Maharani
Cipaku Community Health Center, Ciamis, West Java, Indonesia, 46252
Email: aqillanoor72@gmail.com

Introduction. Nephrolithiasis, or kidney stone disease (KSD), involves crystal formation in the kidneys and may increase the risk of end-stage renal failure. More than 1 in 5 of the Indonesian population identifies as smokers. Smoking is known to be the culprit of multisystem disease and conditions. In the urologic field, smoking is thought to increase the risk of nephrolithiasis; nonetheless, this association has not yet been extensively studied. This study aims to assess the association between smoking and nephrolithiasis.

Methods. A systematic search was conducted in PubMed, Cochrane, Scopus, and ResearchGate (October 10–12, 2024), including systematic reviews, meta-analyses, cohort, case-control, and cross-sectional studies. Studies found were then underwent quantitative analysis using RevMan version 5.4.

Results. Seven studies showed a significant association between smoking and nephrolithiasis; two found no link. Quantitative analysis from five studies showed that smoking exposure was associated with a significantly increased risk of nephrolithiasis (OR 2.36, 95% CI 1.18–4.73, $p = 0.02$, $I^2 = 98\%$).

Conclusion. Smoke exposure is significantly linked to increased risk of nephrolithiasis.

Keywords: kidney stones, nephrolithiasis, smoke, smoking

Introduction

Kidney stone disease involves the formation of crystals, typically in the kidneys, and is associated with an elevated risk of advancing to end-stage renal failure. Over the past 30 years, its incidence and prevalence have significantly increased [1-2]. Prevalence varies between developed and developing nations, partly due to more frequent detection of asymptomatic kidney stones in developed countries. Studies report a prevalence of 5.0–19.1% in West Asia, Southeast Asia, South Asia, South Korea, and Japan. The prevalence in other parts of East and North Asia is lower, ranging from 1–8% [2].

The global distribution of kidney stones is influenced by geography, socioeconomic status, and climate, as well as by factors like age, gender, race, and diet. Obesity and metabolic syndrome are major risk factors, while the stone composition and recurrence rate vary based on these factors [2]. Calcium oxalate remains the primary component of kidney stones worldwide. Smoking, meanwhile, is a well-known risk factor for early mortality and disability, accounting for 148 million disability-adjusted life-years (DALYs) per year.

According to the World Health Organization (WHO), smoking causes 12% of male and 6% of female deaths worldwide [3]. In Indonesia, a national health survey conducted in 2023 revealed 22.46% of the population aged ≥ 10 years smokes every day while 4.56% smokes occasionally within the last month [4]. Smoking is estimated to have cost the country between Rp 17.9 and Rp 27.7 trillion in 2019 for healthcare expenditure alone [5].

There is ongoing debate about whether smoking exposure contributes to kidney stone risk. A systematic review examining lifestyle factors, such as smoking, alcohol use, and physical activity, found a potential link between smoking and kidney stone formation, though further research is needed to clarify this relationship [6]. Smoking is thought to induce lithogenesis by indirectly exerting an antidiuretic effect and facilitating crystal formation [7-9]. Identifying modifiable risk factors for kidney stones is essential to reducing their socioeconomic impact and enhancing prevention and treatment. This systematic review and meta-analysis thus aims to analyze existing evidence on the association between smoking and kidney stones, providing valuable insights for clinical practice and recommendations for nephrolithiasis prevention.

Materials and Method

Clinical Question

We identified the etiology-type clinical question “Does smoke exposure increase the risk of nephrolithiasis in adult patients?” to conduct our study. Based on the clinical question, we used the eligibility criteria using the PICO (Population, Intervention, Comparisons, Outcome) model. These criteria include: (i) the population, consisted of adult patients; (ii) intervention, consisted of smoke exposure; (iii) the comparison, consisted of without smoke exposure; (iv) the outcome, which was nephrolithiasis.

Search Strategy

This study follows the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) criteria (Figure 1). We conducted literature searches on 10th-12th October 2024. Cochrane, PubMed, Scopus, and Researchgate databases were used for the search. The search strategy used in each database is described in Table 1. The keywords and Medical Subject Headings (MeSH) used were smoking, smoker, tobacco,

cigarette, vape, electric cigarette, active smoke, secondhand smoke, nephrolithiasis, lithiasis, kidney stone, stone, calculi, calculus, and urolithiasis. We used the tools provided in the databases to exclude articles published before the year 2000, review articles, and conference papers. Article selection was independently performed by three reviewers. Any discrepancies were resolved through discussion until consensus was reached.

Eligibility Criteria

Inclusion criteria was study on humans with similar PICO with one of the following study designs: cohort, case control, cross-sectional, systematic review, and meta analysis. We did not set a specific definition of kidney stone or smoker classification. Only adults are included in this study due to potential differences in underlying pathophysiology in the pediatric population [10]. Studies involving individuals younger than 18 years old, urinary stone in site other than kidney, and studies written in languages other than Bahasa Indonesia and English were excluded. Studies that were editorials, commentaries, review articles, conference abstracts, or other non-original documents were excluded from the analysis.

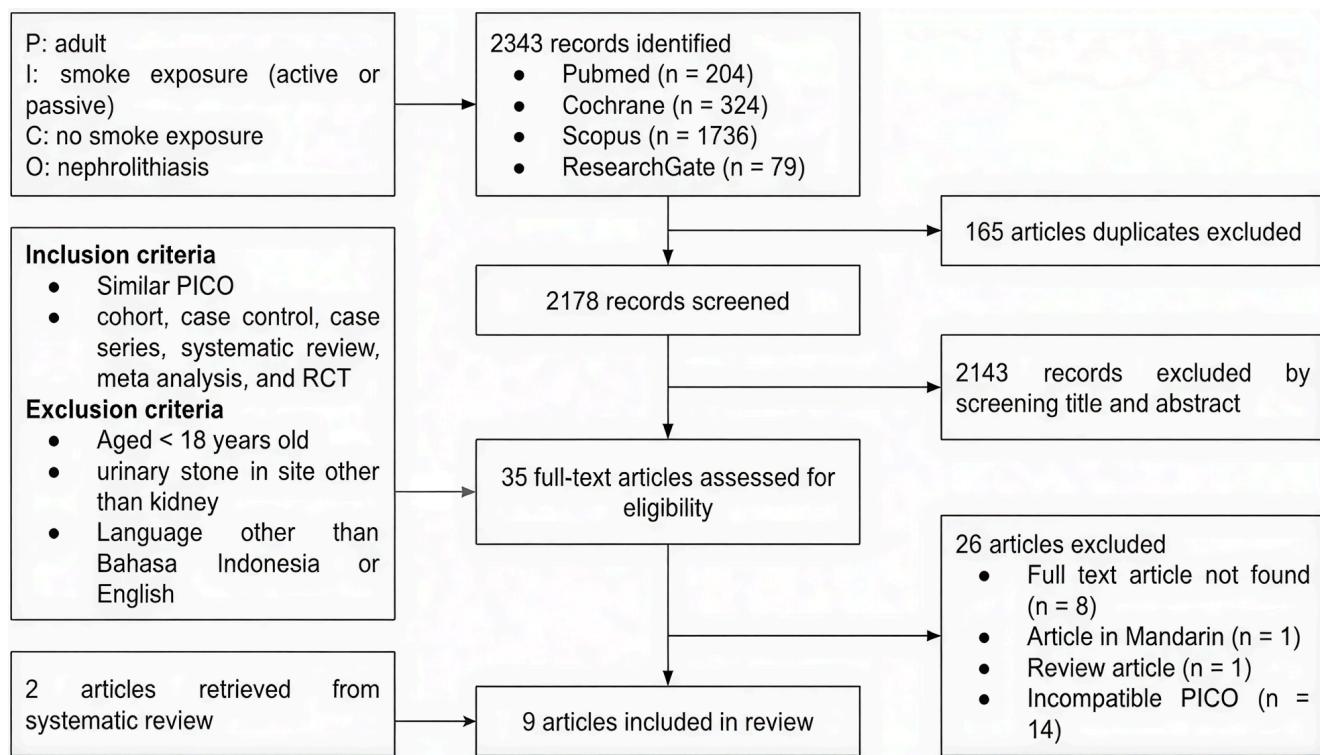


Figure 1. PRISMA Flowchart

Table 1. Literature searching strategy

Database	Search Strategy	Articles Found
Scopus	("smoking" OR "smoke" OR "smoker" OR "tobacco" OR "cigarette" OR "vape" OR "electric cigarette" OR "active smoke" OR "secondhand smoke" OR "smoke exposure") AND ("nephrolithiasis" OR "lithiasis" OR "kidney stone" OR "stone" OR "calculi" OR "calculus" OR "urolithiasis" OR "kidney stone disease")	1736
PubMed	(Smoking OR smoke OR smoker OR tobacco OR cigarette OR vape OR electric cigarette OR active smoke OR secondhand smoke) AND (Nephrolithiasis OR lithiasis OR kidney stone OR stone OR calculi OR calculus OR urolithiasis)	204
Cochrane	(Smoking OR smoke OR smoker OR tobacco OR cigarette OR vape OR electric cigarette OR active smoke OR secondhand smoke OR smoke exposure) AND (Nephrolithiasis OR lithiasis OR kidney stone OR stone OR calculi OR calculus OR urolithiasis OR kidney stone disease)	324
ResearchGate	(Smoking OR smoke OR smoker OR tobacco OR cigarette OR vape OR electric cigarette OR active smoke OR secondhand smoke) AND (Nephrolithiasis OR lithiasis OR kidney stone OR stone OR calculi OR calculus OR urolithiasis)	79

Quality Assessment

The quality and risk of bias of all included studies were evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists, selected according to the study design (cross-sectional, case-control, or cohort) [11]. Each checklist covers domains such as comparability of groups, validity and reliability of exposure and outcome measurement, identification and management of confounding factors, adequacy of follow-up (for cohort studies), and appropriateness of statistical analysis. The assessment was conducted independently by three reviewers, with disagreements resolved by discussion until agreements were achieved. Each checklist item was recorded as "Yes", "No", or "Unclear".

Statistical Analysis

Review Manager (RevMan) 5.4 was used for quantitative statistical analysis and data synthesis to evaluate the association between smoking exposure and nephrolithiasis. Two-by-two tables of exposure (smoke exposure versus no smoke exposure) and outcome (nephrolithiasis versus no nephrolithiasis) were extracted or reconstructed from the published data. These were pooled using the Mantel-Haenszel method under a random-effects model, with odds

ratios (ORs) and 95% CIs as the effect measure. Heterogeneity was evaluated using the I^2 statistic. Cross-sectional studies were excluded from quantitative synthesis because they do not establish temporality, but their findings were summarized narratively to complement the overall evidence.

Result

We found 204 articles from Pubmed, 324 articles from Cochrane, 1736 articles from Scopus, and 79 articles from ResearchGate, totalling 2343 articles from 4 databases. The title of all studies were compiled in Google Sheets. We then eliminated article duplicates manually. After 165 article duplicates were removed, we screened the title and abstract of the remaining 2178 articles and found 35 studies with similar PICO. We did not get access to the full text of 8 articles. We excluded 1 review article and 1 article written in Mandarin. Fourteen articles were excluded due to unsuitable PICO. We then proceeded to hand-search individual studies incorporated in the studies and found 2 articles matching our PICO. A total of 9 articles were included in this review. Figure 1 summarized the overall selection process

Risk of bias assessment demonstrated a low risk from all the studies included in this review,

with most meeting the majority of methodological quality criteria (Figure 2, 3, 4). The main sources of potential bias were related to reliance on self-reported exposures and outcomes, recall bias in dietary and lifestyle variables, and incomplete reporting of follow-up information in some cohort studies. On the positive side, the majority of studies clearly defined inclusion criteria, identified and

adjusted for relevant confounders, and applied appropriate statistical analyses, which strengthened the validity of their findings.

In this study, a total of 8430 participants were exposed to smoking with 893 participants also having nephrolithiasis. From 9 studies included, we found 7 studies supporting the notion of smoking as

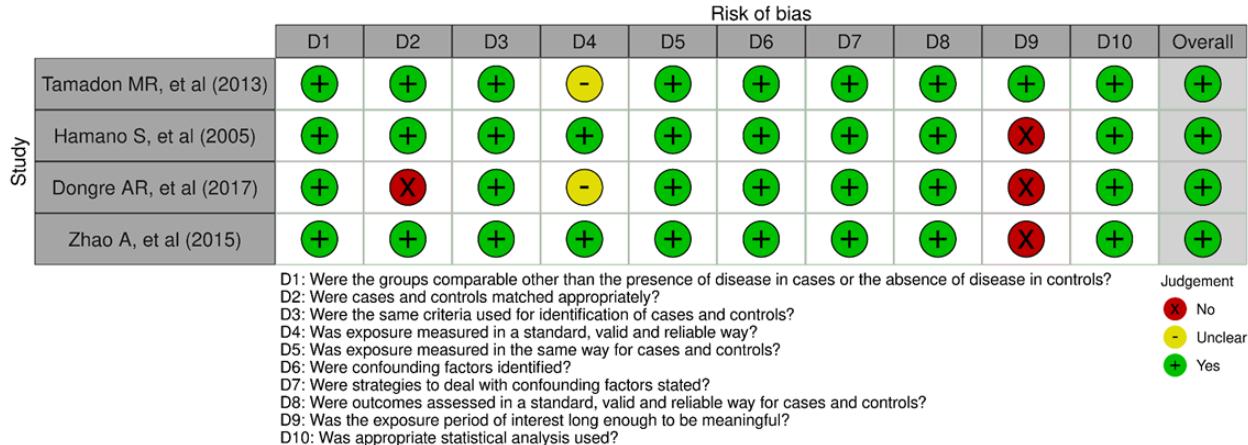


Figure 2. Risk of bias assessment for case control studies using JBI

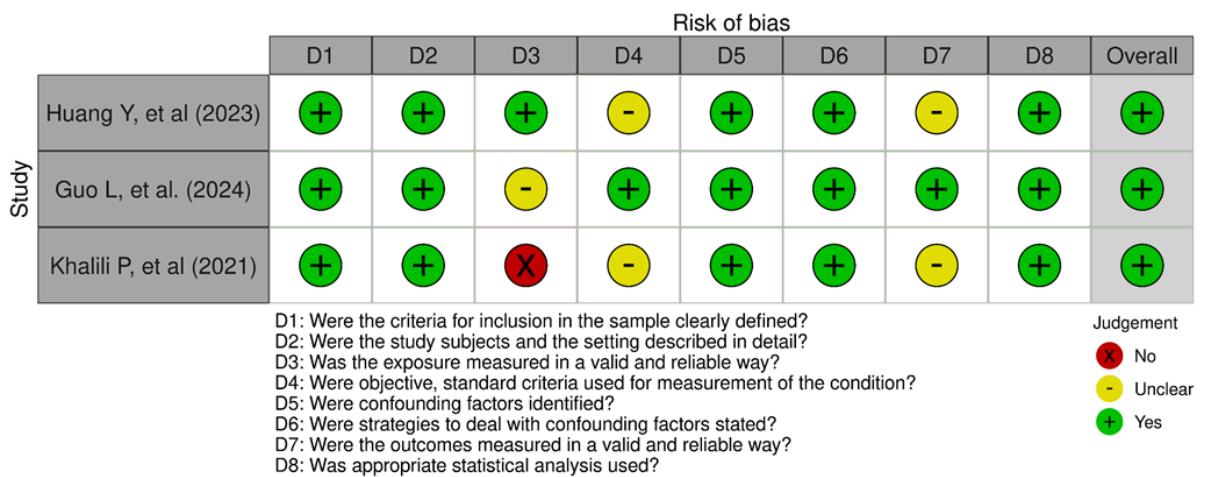


Figure 3. Risk of bias assessment for cross-sectional studies using JBI

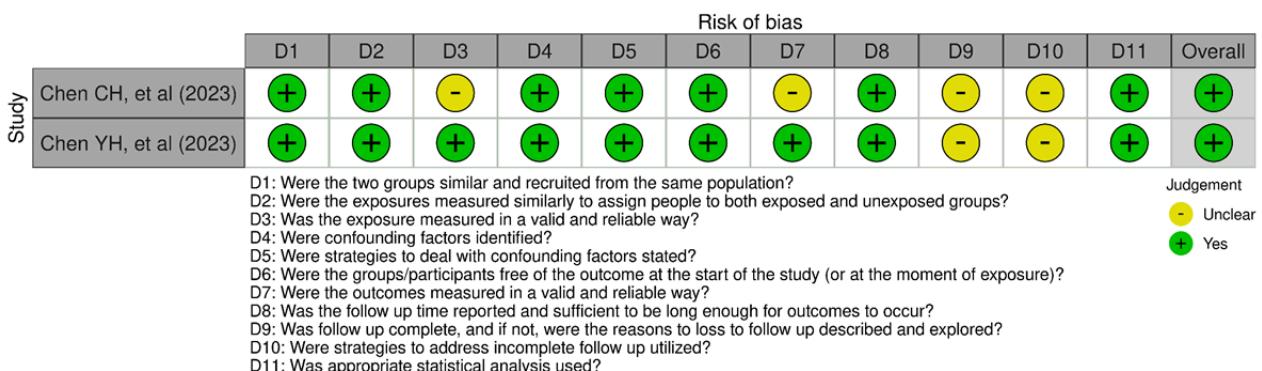


Figure 4. Risk of bias assessment for cohort studies using JBI

a risk factor for kidney stone formation. Most studies compared current smokers and non smokers, while Chen CH and Chen YG studies also measure secondhand smoke exposure. Table 2 summarizes the main results from each study.

For statistical analysis, both case-control and cohort studies were eligible. Since the primary measure of association across case-control designs is the odds ratio (OR), we selected ORs as the common effect estimate for pooling. Notably, the included cohort studies (Chen CH, 2021; Chen YH, 2023) also reported ORs, as they applied logistic regression to model kidney stone occurrence, rather than Cox regression or risk ratio estimates. This ensured consistency of effect measures across study designs, permitting direct meta-analysis.

Since both Chen CH (2021) and Chen YH (2023) studies were also conducted on overlapping populations, only Chen YH (2023) was included in the primary meta-analysis owing to its larger sample size, longer follow-up, and broader exposure categories (active and passive smoking). Furthermore, for Chen YH (2023) study, we combined ever-smokers and secondhand smoke (SHS)-exposed never-smokers into a single “smoke-exposed” group by summing events and totals, compared against never-smokers without SHS exposure. In this meta-analysis of cohort and case-control studies, smoking exposure was associated with a significantly increased risk of nephrolithiasis (OR 2.36, 95% CI 1.18–4.73, $p=0.02$, $I^2 = 98\%$), presented in Figure 5.

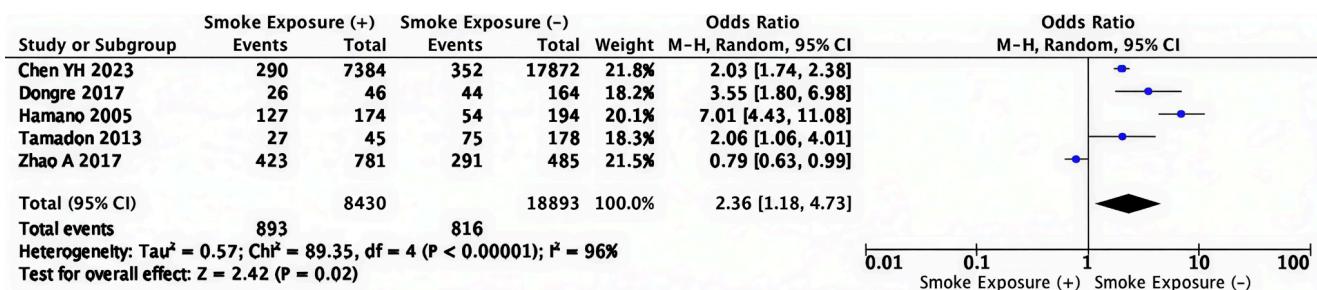


Figure 5. Forest plot of smoke exposure and nephrolithiasis

Discussion

With the rising incidence of nephrolithiasis and the widespread prevalence of smoking, understanding their potential connections is crucial. While previously smoking is not established as a direct risk factor for nephrolithiasis, it is well-documented as a contributor to various morbidities and mortalities. In our study, smoke exposure was associated with a significantly increased risk of nephrolithiasis (OR 2.36, 95% CI 1.18–4.73, $p = 0.02$). This finding indicates that individuals with active or passive tobacco exposure have 2.36 higher odds of developing kidney stones compared with non-smokers.

Huang et al. reported association between serum cotinine level (a major metabolite of nicotine) and kidney stone incidence. When compared to group with serum cotinine level of <0.05 ng/ml, serum cotinine levels of 0.05–2.99 compared to group with serum cotinine level of <0.05 ng/ml, serum cotinine levels of 0.05–2.99 ng/ml [OR = 1.15 (1.03–1.29), $P = 0.013$] and ≥3.00 ng/ml [OR = 1.22 (1.10–1.37), $P < 0.001$] were found to be of higher risk of nephrolithiasis (p for trend < 0.001) [6, 20-21]. Although Tamadon et

al. suggested smoking to be an independent risk factor of kidney stone disease, they did not find an association between years of smoking and kidney stone incidence ($p = 0.536$) [12]. Hamano et al. reported that smoking may be a stronger risk factor for calcium oxalate stones formation than hypertension, hypercholesterolemia, and high BMI [13]. While Khalili et al. reported no association between cigarette smoking and kidney stones, they discovered hookah smoking to be associated with kidney stones (OR = 1.22; 95%CI 1.08-1.37). Moreover, subjects in the case group had a higher proportion of cigarette smoker (26.25% vs 25.38%) and hookah smoker (19.48% vs 16.60%) when compared to the control group [17].

Findings from a longitudinal cohort study using data from Taiwan Biobank (TWB) found that secondhand smoking is also a risk factor for developing kidney stones. Chen CH et al. found that the group exposed to secondhand smoke (SHS) for ≥1.2 hours a week experienced greater risk for kidney stones (OR 1.92, [1.29-2.86], $p = 0.02$) compared with no exposure group [18]. Furthermore, Chen YH et al. reported that the risk for nephrolithiasis was higher in secondhand

Table 2. Summary of Reviewed Articles

Study Design	Author, Year	Country	Sample	Nephrolithiasis Diagnosis	Smoking Criteria	Main Result
Cross Sectional	Huang et al., 2023	China	34,836	Questionnaire	Current smokers, smokers, non-smokers	Current smoker is at more risk for nephrolithiasis (OR = 1.17 [95% CI 1.04-1.31], p = 0.009)
	Guo et al., 2024	China	5,115	Radiology	Current Smokers or non-smokers	No association between smoking status with nephrolithiasis (OR = 1.38 [95% CI 0.86-2.05], p = 0.200)
	Khalili et al., 2021	Iran	9,932	Questionnaire	Yes (currently or formerly a smoker) and No (never a smoker)	Hookah smoking as a risk factor for nephrolithiasis (OR = 1.22 [95% CI 1.08-1.37])
Case Control	Tamadon et al., 2013	Iran	223	Radiology	Had smoked ≥ 5 cigarettes /day for at least 6 months or not	Cigarette smoking more common in stone formers (OR = 2.06 [95% CI 1.06-4.01], p = 0.034)
	Hamano et al., 2005	Japan	368	Diagnosis from institution	Current Smokers or non-smokers	Smoking habit associated with stone formation (OR 4.29 [95% CI 2.68-6.86], p < 0.0001)
Cohort	Dongre et al., 2017	India	210	Diagnosis from institution	Current Smokers or non-smokers	Odds of nephrolithiasis higher among current smokers (OR = 3.55 [95% CI 1.71-7.39])
	Zhao et al., 2012	China	1,266	Diagnosis from institution	Nonsmoker (has not smoked for ≥ 3 years or never smoke), Current smoker (smoke ≥ 1 cigarette/day)	No association between smoking status and nephrolithiasis (OR = 1.0 [95% CI 0.8-1.4])
Cohort	Chen CH et al., 2023	Taiwan	19,430	Questionnaire	No exposure, ≤ 1.2 hours/week, >1.2 hours/ week	Higher risk in group exposed to SHS ≤ 1.2 hours/week (OR 1.40 [95% CI 0.90-2.18], p = 0.14) and >1.2 hours/week (OR 1.92 [95% CI 1.29-2.86], p = 0.002) than no exposure

Study Design	Author, Year	Country	Sample	Nephrolithiasis Diagnosis	Smoking Criteria	Main Result	
	Chen YH et al., 2023	Taiwan	25,256	Questionnaire	Never-smokers, never-smokers with SHS exposure, never smokers with no SHS exposure	ever-smokers, with SHS	Higher risk of nephrolithiasis among eversmokers (OR 2.124 [95% CI 1.80-2.51], p < 0.001) and nonsmoker with SHS exposure (OR 1.69 [95% CI 1.25-2.29], p = 0.001)

Notes: OR, Odds Ratio; CI, Confidence Interval.

smoker (OR 1.622, 95% CI 1.225 to 2.255 p = 0.001) and eversmoker (OR, 1.282; 95% CI, 1.044 to 1.574, p = 0.018) than the never-smokers group (have never smoked and have not been exposed to secondhand smoke for at least 5 minutes).

In addition, never-smokers with SHS exposure had similar effects on the development of KSD than ever-smokers (OR, 1.223; 95% CI, 0.852 to 1.756, p = 0.275) [19]. These findings can be explained by previous study, which found that nonsmokers exposed to secondhand smoke also inhale a significant amount of toxic substances from tobacco. For individuals over the age of 14, secondhand smoke (SHS) exposure can be equivalent to smoking up to 20 cigarettes per month — roughly one pack of cigarettes [22]. Hence, in statistical analysis, we combined the secondhand-smoker group with active smokers in Chen YH et al. study as a single “smoke-exposed” category because both are exposed to similar toxic constituents. Grouping them together therefore provides a more comprehensive estimate of the overall impact of tobacco exposure on nephrolithiasis risk.

The association of smoking with nephrolithiasis can be explained by several possible mechanisms. It is believed that smoking causes an increase in arginine vasopressin hormone (AVP), which is a strong antidiuretic [23-24]. Thus, decreased urinary output occurs, subsequently leading to stone formation [2-4,25]. This AVP hormone is also increased more at night, resulting in a greater lithogenic risk by the end of the night [2-4,12]. Reactive oxygen species (ROS) and oxidative stress are also elevated in smokers. These substances can cause renal injuries, leading to increased nucleation, aggregation, and retention of crystals [12, 18, 26-27]. Another potential explanation is that smoking could reduce the amount of calcium excreted in the urine, and lower urinary calcium levels have been linked to a higher risk of developing kidney stones [12, 18, 24].

Two studies found no association between nephrolithiasis and smoking, both relying on questionnaires and noting potential limitations, such as recall bias, which may have affected the accuracy of certain measurements. Guo et al. did not adjust for other confounding variables in their analysis, which may have contributed to the nonsignificant result. Additionally, this study focused on a specific population—medical staff—who may have unique risk factors related to their work environment, such as long hours and shift work [16]. Similarly, the study by Zhao et al. involved only volunteers from a single hospital in

China, making the results susceptible to volunteer bias [15].

In our meta-analysis of cohort and case-control studies, smoking exposure was associated with a significantly increased risk of nephrolithiasis (2.36, 95% CI 1.18–4.73, p=0.02). However, heterogeneity was high ($I^2 = 96\%$), reflecting substantial variability across studies. The inconsistency may be attributed to differences in study design, population characteristics, exposure classification (active vs passive smoking), or adjustment for confounders. Chen YH et al (2023) and Zhao et al (2017), both contributing a relatively large share of the total sample, reported conflicting results [15,19]. The findings entail further investigation into population-specific or methodological factors since the incidence of nephrolithiasis was already high (>50%) in both smokers and nonsmokers in the study conducted by Zhao et al [15]. Despite this heterogeneity, the overall direction of evidence consistently supports smoking as an independent risk factor for nephrolithiasis.

From that result, efforts to tackle smoking habits are key to reducing the risk of nephrolithiasis. This is especially relevant in Indonesia, which has a large number of smokers and is classified as part of the stone-belt, i.e. regions where nephrolithiasis is prevalent [29]. Avoiding and/or stopping smoking should be advocated to the general population, particularly to those with risk factors of developing nephrolithiasis. On a higher level, the government should also enforce stricter smoking-free zones and mandate cigarette enterprises to mention kidney stone disease as one of the risks of cigarette smoking.

Several limitations should be acknowledged. Heterogeneity across studies was very high ($I^2 = 96\%$), which may reflect differences in study design, populations, exposure definitions, or outcome measurement. Studies included in this review varied in their criteria for defining smoking and case definition of nephrolithiasis. Subjective reporting of smoking history may not truly reflect smoking exposure as opposed to cotinine measurement. Confounding factors may not have been fully accounted for across the included studies. The small number of eligible studies restricted our ability to perform subgroup analyses to further investigate sources of heterogeneity.

Conclusion

In conclusion, smoke exposure is significantly linked to increased risk of nephrolithiasis. To address this issue, it is crucial to implement health promotion to cease smoking and/or regulate smoking. Future research focusing on e-cigarettes consumption and using serum cotinine level as an objective measurement of smoking exposure may provide stronger insight regarding association between nephrolithiasis and smoking.

Conflict of Interest

The authors declare no conflict of interest.

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