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Association between Sleep Disorders and Urolithiasis: A Meta-Analysis

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Abstract: *To evaluate the relationship between sleep disorders and the risk of urolithiasis using a meta-analysis method. We searched PubMed, The Cochrane Library, Web of Science, Medline, CNKI, and Wanfang Data for relevant English and Chinese articles published from their inception to June 2024. Two researchers independently completed the literature screening, data extraction, and assessment of the risk of bias in the included studies. Meta-analysis was performed using Stata 12.0 software. A total of 8 studies were included, with a combined sample size of 86,419 cases. The meta-analysis results showed that individuals with obstructive sleep apnea (OSA) had a 1.41-fold increased risk of urolithiasis compared to those without OSA, with a statistically significant difference (odds ratio, OR = 1.41, 95% confidence interval, CI = 1.19–1.67, P < 0.001). Individuals with insufficient sleep duration (<7 hours) had a 1.19-fold increased risk of urolithiasis (OR = 1.19, 95% CI = 1.10–1.29, P < 0.001). Day dozing had a 1.16-fold increased risk of urolithiasis (OR = 1.16, 95% CI = 1.07–1.27, P < 0.01). Additionally, individuals with insomnia had a 1.10-fold increased risk of urolithiasis (OR = 1.10, 95% CI = 1.06–1.15, P < 0.001). OSA, insufficient sleep duration (<7 hours), daytime dozing, and insomnia may be risk factors for urolithiasis.*

Keywords: *Sleep disorders; Obstructive sleep apnea; Sleep duration; Daytime Dozing; Insomnia; Urolithiasis; Urinary tract stones; Meta-analysis*

1. Introduction

Urolithiasis is an ancient disease that affects nearly 10% of the global population, imposing a significant burden on patients and their families in terms of both health and economics. However, the pathogenesis of kidney stones remains unclear, and treatment options are limited[1]. Moreover, urolithiasis has a high recurrence rate, with a 50% recurrence rate within five years[2]. Therefore, kidney stones have long been considered an important public health issue and have become a serious threat to human health[3]. The etiology of kidney stones is multifactorial, requiring exploration of its mechanisms and risk factors to identify potential targets for intervention[4]. Recent epidemiological studies have shown that there is a close association between lifestyle factors and kidney stones, including sleep, physical activity, and diet[4] [5] [6].

Sleep is a complex process that occupies approximately one-third of the human lifespan. Poor sleep habits have a significant impact on global public health[7]. Research has indicated that poor sleep habits are associated with diseases such as stroke[8], coronary heart disease[9], malignant tumors[10], and diabetes[11]. However, the primary evidence linking sleep issues and kidney stones comes from observational studies, and there is a lack of robust meta-analyses. Therefore, this study employs a meta-analysis approach to investigate the relationship between sleep disorders and urolithiasis.

2. Materials and Methods

2.1 Inclusion and Exclusion Criteria

The criteria for inclusion in the study are as follows: (1) Age > 18 years; (2) The study clearly describes the relationship between sleep disorders and urolithiasis; (3) The study cohort is compared and analyzed with healthy controls; (4) Cross-sectional or longitudinal design. Conversely, the exclusion criteria for this study are described as follows: (1) Conference abstracts, case reports,

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editorials, commentaries, or reviews; (2) Insufficient controls or raw data to calculate odds ratios (ORs) or relative risks (RRs); (3) Studies conducted in homogeneous populations.

2.2 Literature Search Strategy

Two researchers independently searched studies on the relationship between sleep issues and kidney stones published in databases including PubMed, The Cochrane Library, Web of Science, Medline, CNKI, and Wanfang. The Chinese and English search terms included: urolithiasis, urinary stones, kidney stones, ureteral stones, bladder stones, lower urinary tract stones, sleep, sleep disorders, sleep quality, sleep duration, insomnia, sleep apnea, and sleep disorders (Obstructive Sleep Apnea Syndrome, OSA). The English search terms included: Urinary Calculi, Urinary Stone Disease, Kidney stone, Nephrolithiasis, Calculi, Sleep, Insomnia, Sleep apnoea, Sleeplessness, Daytime Dozing, Sleep Duration, Sleep Disorders, and Obstructive Sleep Apnea Syndrome. The search period spanned from the inception of the databases to June 2024, and studies meeting the criteria were collected based on the search results.

2.3 Data Extraction

Two researchers will independently screen studies based on the included literature, extract data, and perform cross-verification. In case of disagreements, a third researcher will be involved to reach a consensus. Data extraction includes: author, publication year, study type, data source, sample characteristics and size, sleep issue type, and definition criteria.

2.4 Quality Assessment of Included Literature

Two authors used the Newcastle-Ottawa Scale (NOS) to assess the quality and risk of bias in cohort and case-control studies, with scores ranging from 0 to 9 (high quality: 7–9, medium quality: 4–6, low quality: 0–3). Cross-sectional studies were evaluated using the Agency for Healthcare Research and Quality (AHRQ) scale, with scores ranging from 0 to 12 (high quality: 7–12, medium quality: 4–6, low quality: 0–3), ensuring comprehensive evaluation and robust analysis. The basic characteristics and model features of the included literature are presented in Table 1.

2.5 Statistical Analysis

Odds ratios (ORs), relative risks (RRs), and hazard ratios (HRs) were calculated, and their respective 95% confidence intervals (CIs) were comprehensively adjusted to account for most covariates. In longitudinal studies, if relative risks (RRs) were not provided, they were estimated based on odds ratios (ORs) and the incidence rate in the control group, along with their corresponding 95% confidence intervals[12]. Additionally, if odds ratios (ORs) were not provided in cross-sectional studies, they were derived using raw data on exposure and outcome, along with their corresponding 95% confidence intervals. Since hazard ratios (HRs) are very close to relative risks (RRs), HRs were treated as RRs. In cross-sectional studies, odds ratios (ORs) and their corresponding 95% confidence intervals were used to explore the associations between sleep quality, sleep disorders, sleep duration, and the occurrence of urolithiasis. In longitudinal studies, relative risks (RRs) and their respective 95% confidence intervals were used to analyze the relationship between sleep issues and the occurrence of urolithiasis[13].

Cochran's Q test and the I^2 index were used to assess heterogeneity among studies. Heterogeneity was considered present if $I^2 \geq 50\%$ or $p < 0.05$. If significant heterogeneity was observed, a random-effects model (DerSimonian and Laird method) was applied. Conversely, if no significant heterogeneity was found, a fixed-effects model was used. Sensitivity analysis was conducted to explore the presence of heterogeneity and to evaluate the robustness and consistency of the study results. Publication bias was assessed using funnel plots and Egger's test. Analyses were performed using Stata software (version 12.0), and a two-sided P-value less than 0.05 was considered statistically significant.

2.6 Definition of Sleep Disorders

The definitions of sleep disorders addressed in this article are as follows: 1. OSA refers to obstructive sleep apnea; 2. Sleep duration: refers to the average nightly sleep time of an individual, typically measured in hours; 3. Daytime dozing: refers to an individual experiencing fatigue and

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drowsiness during the day; 4. Insomnia: a common sleep disorder characterized by difficulty falling asleep, maintaining sleep, or waking up too early and being unable to fall back asleep, leading to impaired daytime functioning or significant distress; 5. Use of sleep-related medications: an individual has used sleep medications within the past month.

3. Results

3.1 Literature Search Results and Basic Characteristics

A total of 96 Chinese literature and 109 English literature were retrieved. After reviewing the titles, abstracts, and full texts, 44 duplicate articles were excluded. Based on the inclusion and exclusion criteria, 8 articles were ultimately included.

Table 1. Model Characteristics of the Included Literature

Author	Country	Sex (male %)	Age	Design	Kind of sleep disorders	Methods of sleep disorders ascertainment	Methods of urolithiasis ascertainment	NOS/AHRQ Score
Chung SD[14] (2016)	China	100.0	47.80 ±13.80	CS	OSA	ICD	ICD	7
Kang JH[15] (2012)	China	63.3	48.10	CS	OSA	ICD	ICD	10
LI XK[16] (2023)	UK	46.6	56.78	LS	OSA, Sleep Duration, Daytime Dozing, Insomnia	Healthy Sleep Score	ICD	8
Tsai SH[17] (2018)	China	62.0	43.30 ±15.10	LS	OSA	ICD	ICD	7
Wang H[18] (2022)	China	41.1	52.0±10.7	LS	OSA, Sleep Duration, Daytime Dozing, Insomnia, Medications	Healthy Sleep Score	ICD	9
Wang S[19] (2017)	China	46.6	66.64	CS	Sleep Duration	National Sleep Foundation	ICD	7
Wang S[20] (2022)	China	33.9	56.16±10.95	CS	Sleep Duration, Daytime dozing, Medications	Pittsburgh Sleep Quality Index	Self-report	8
Yin S[4] (2022)	USA	48.6	47.67±16.99	CS	Sleep Duration	Joint Consensus Statement of the American Academy of Sleep Medicine and the Sleep Research Society	Self-report	8

Note: Obstructive Sleep Apnea Syndrome (OSA); International Statistical Classification of Diseases and Related Health Problems (ICD); Cross-sectional Study (CS); Longitudinal Study (LS).

3.2 Basic characteristics and risk of bias of the included literature

Among the 8 included studies, there were 3 cohort studies and 5 cross-sectional studies. Three articles used the International Statistical Classification of Diseases and Related Health Problems (ICD) to assess sleep issues; six articles employed the ICD to evaluate urolithiasis; six studies originated from China, one from the United States, and one from the United Kingdom; five studies explored the relationship between obstructive sleep apnea (OSA) and urolithiasis, five studies investigated the association between sleep duration and urolithiasis, one study examined the link between sleep disorders and urolithiasis, and two studies simultaneously explored the relationships of OSA and sleep duration with urolithiasis. The Newcastle-Ottawa Scale (NOS) quality assessment results showed an

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average score of 8 points for the included studies, indicating high quality. Similarly, the Agency for Healthcare Research and Quality (AHRQ) quality assessment results also showed an average score of 8 points, confirming the high quality of the included studies. The basic characteristics and NOS scores of the included studies are presented in Table 1.

3.3 Subgroup analysis and Meta-regression

Subgroup analyses were conducted based on region, age, sample size, sleep issue assessment tools, and urolithiasis evaluation tools. Additionally, meta-regression analysis was performed by adjusting for the aforementioned five variables. Significant heterogeneity was observed among the studies focusing on OSA, insufficient sleep duration, and daytime sleepiness. However, the source of heterogeneity could not be identified through subgroup and meta-regression analyses.

3.4 Meta-analysis results

A total of 8 studies involving 86,419 cases were included. Five studies explored the relationship between OSA and urolithiasis, with significant heterogeneity observed among the studies (I^2=96.9%, P<0.001). A random-effects model was used for analysis. The results indicated that the risk of urolithiasis in individuals with OSA was 1.41 times higher than in those without OSA [OR=1.41, 95% CI (1.19, 1.67), P<0.001]. Five studies examined the relationship between sleep duration and urolithiasis. Individuals with insufficient sleep duration (<7 hours) had a 1.19 times higher risk of urolithiasis [OR=1.19, 95% CI (1.10, 1.29), P<0.001; heterogeneity: I^2=69.1%, P<0.05, analyzed using a random-effects model]. However, the increased risk of urolithiasis in individuals with excessive sleep duration (≥9 hours) was not statistically significant. Individuals with daytime sleepiness had a 1.16 times higher risk of urolithiasis [OR=1.16, 95% CI (1.07, 1.27), P<0.01, heterogeneity: I^2=66.9%, P<0.05]. Additionally, individuals with insomnia had a 1.1 times higher risk of urolithiasis [OR=1.10, 95% CI (1.06, 1.15), P<0.001; heterogeneity: I^2=0.0%, P=0.823, analyzed using a fixed-effects model]. However, the risk of urolithiasis in individuals taking sleep-related medications was not statistically significant. The above results are presented in Table 2.

Table 2. Meta-Analysis Results

sleep disorders	Number of Studies	OR(95%CI)	P	Heterogeneity	
				I2	P
OSA	5	1.41(1.19,1.67)	<0.001	96.90%	<0.001
Insufficient sleep duration	5	1.19(1.10,1.29)	<0.001	69.10%	0.011
Excessive sleep duration	3	1.09(0.87,1.37)	0.464	66.00%	0.053
Daytime dozing	3	1.16(1.07, 1.27)	0.001	66.90%	0.049
Insomnia	2	1.10(1.06,1.15)	<0.001	0.00%	0.823
Medications	2	1.03(0.90,1.17)	0.662	0.00%	0.407

3.5 Sensitivity analysis and publication bias

In this study, a sensitivity analysis was conducted using the leave-one-out method on the aforementioned meta-analysis results, and no significant changes were observed, indicating the stability of the findings. Publication bias: In the study examining the relationship between sleep issues and the risk of urolithiasis, both Egger's test and Begg's test were employed to assess publication bias, and the results showed no evidence of publication bias.

4. Discussion

This study investigated the relationship between sleep disorders and urolithiasis using meta-analysis methods. The results revealed that the incidence of urolithiasis was significantly higher in individuals with OSA, insufficient sleep duration (<7 hours), daytime sleepiness, and insomnia compared to the normal population. The study found no significant publication bias, and sensitivity analysis confirmed the stability of the findings.

OSA is associated with an increased risk of urolithiasis development, and while the underlying mechanisms have not been thoroughly investigated, the connection between the two further supports the close relationship between urinary stones and vascular and metabolic disorders[17]. Studies have shown that the prevalence of metabolic syndrome is notably high in individuals with OSA (ranging from 50% to 87%), and there appears to be a dose-response relationship between the severity of sleep

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apnea and the further deterioration associated with metabolic syndrome[21]. Some scholars [16], after adjusting for variables related to metabolic syndrome, found that the risk of developing urolithiasis decreased by 8% in the non-snoring group, confirming from the perspective of healthy sleep that OSA is associated with an increased risk of stone development. The reason for the increased risk of urolithiasis development associated with OSA may be that OSA leads to intermittent tissue hypoxia, induces oxidative stress, and causes insulin resistance in the body, thereby increasing uric acid and decreasing urinary citrate, thus promoting the formation of kidney stones. In addition, OSA is also associated with subacute and chronic systemic inflammation. Elevated circulating inflammatory mediators, including C-reactive protein, interleukin-6, interleukin-8, tumor necrosis factor-alpha, and adhesion molecules, have been detected in OSA, and inflammation promotes crystal aggregation to damaged urothelium or shed Randall's plaques, increasing the risk of stone development[22] [23].

The reasons for the increased prevalence of urolithiasis among individuals with short or long sleep durations remain unclear. In this study, the incidence of urolithiasis was significantly higher among those with insufficient sleep duration (<7 hours). Sleep is crucial for maintaining metabolic homeostasis and energy balance in the body. Sleep deprivation may stimulate appetite and prolong eating times. This situation could not only lead to an increase in body mass index (BMI) but also raise the risk of developing diabetes, both of which are associated with the formation of kidney stones[24]. However, a study [4] found that even after adjusting for BMI and diabetes, insufficient sleep duration (<7 hours) remained significantly associated with kidney stones, which aligns with the conclusions drawn in this study, suggesting the possibility of other underlying mechanisms. Additionally, sleep deprivation and insomnia not only lead to increased sympathetic nervous system activity but also upregulate pro-inflammatory factors in the kidneys, such as tumor necrosis factor-alpha and interleukin-6, through the activation of adrenergic α2 receptors, thereby inducing renal inflammation[25]. Simultaneously, the activation of these receptors also promotes fibrosis in renal tissues, further exacerbating the progression of chronic kidney injury and ultimately increasing the risk of kidney stone formation[26]. These physiological changes not only impact kidney health but may also negatively affect systemic metabolic and inflammatory states, further increasing the risk of other chronic diseases. Therefore, ensuring adequate sleep duration and good sleep quality is of significant importance for preventing kidney stones and other metabolic disorders.

Previous studies have indicated that poor sleep quality may be associated with drowsiness and fatigue, which could indirectly lead to reduced physical activity during the day[27]. Furthermore, research[28] has found that physical activity is a protective factor against urinary stones. However, insomnia can lead to a decline in sleep quality, and daytime drowsiness is one of the specific manifestations of poor sleep quality. This may explain how poor sleep quality results in daytime drowsiness and reduced physical activity, thereby increasing the incidence of urolithiasis. From the perspective of inflammation being one of the risk factors for the formation of urinary stones, the levels of inflammatory factors such as tumor necrosis factor alpha, interleukin-1, interleukin-6, interleukin-18, and C-reactive protein are significantly increased in the serum of patients with chronic insomnia[29]. Insomnia-induced inflammation within the body provides a potential condition for the formation of urinary stones.

Although this study is the first to conduct a Meta-analysis on the association between sleep issues and urolithiasis, it still has certain limitations: Firstly, only eight articles were included in the Meta-analysis, which is relatively insufficient and lacks prospective studies. Therefore, future research should include more high-quality, prospective studies. Secondly, only studies in Chinese and English were included, which may introduce language bias. Thirdly, the included studies used different designs (cohort studies, cross-sectional studies), and the diversity of study designs may affect the internal validity of the Meta-analysis. Finally, due to the limited number of studies that could be included for each sleep issue, we were unable to analyze the sources of heterogeneity. We discussed and analyzed the reasons, summarized as follows: 1. The limited number of studies that could be included made subgroup analysis difficult and may have introduced bias; 2. The mechanisms of sleep issues and urolithiasis formation are complex, which may lead to confounding bias. The strengths of this study: Firstly, it is the first to use Meta-analysis to investigate the association between sleep issues and urolithiasis. Secondly, the included studies have relatively large sample sizes and cover a wide geographical area. Finally, this study integrates multiple sleep issues, providing more comprehensive evidence on the relationship between sleep and urolithiasis.

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5. Conclusion

Finally, there is a significant correlation between unhealthy sleep and the prevalence of urolithiasis. Sleep disorders, such as obstructive sleep apnea (OSA), insufficient sleep duration (<7 hours), daytime drowsiness, and insomnia, are all associated with the onset of urolithiasis. The findings of this study indicate that future public health guidelines need to be developed to formulate detailed strategies for improving sleep quality. These strategies may include the prevention and intervention of risk factors affecting sleep quality, as well as recommending optimal sleep durations, thereby effectively reducing the incidence of urolithiasis.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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