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ORIGINAL RESEARCH

Self-Reported Symptoms of Obstructive Sleep Apnea are Associated with Increased Risk of Kidney Stones: A Cross-Sectional Study from NHANES 2015-2020

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Objective: To investigate whether self-reported symptoms of obstructive sleep apnea (OSA), including snoring, snorting/stopping breathing, and sleepiness, are associated with increased risk of kidney stones.

Methods: This cross-sectional study was conducted based on the 2015–2020 National Health and Nutrition Examination Survey (NHANES). Self-reported symptoms of OSA and history of kidney stones were diagnosed via questionnaires. Multivariable logistic regression was used to determine the associations between self-reported symptoms of OSA and kidney stones. Subgroup analyses and interaction tests were performed to address this issue further.

Results: A total of 9,973 participants were enrolled, and the prevalence of kidney stones was 10.76%. Although no significant association was observed between frequent snoring and kidney stones after covariate adjustments (OR 1.033, 95% CI 0.726, 1.469 p = 0.850), frequent snorting/stopping breathing was associated with a greater risk of kidney stones after covariate adjustments (OR 1.655, 95% CI 1.262, 2.172, p = 0.002). Participants who often or almost always felt sleepy also had a greater risk of kidney stones after covariate adjustment (OR 1.651, 95% CI 1.222, 2.229; p = 0.004). The interaction tests suggested that marital status (p = 0.015) and smoking status (p < 0.001) significantly interacted with the association between snorting/stopping breathing and kidney stones.

Conclusion: Self-reported frequent snorting/stopping breathing and sleepiness may be associated with increased risk of kidney stones. Although these findings may emphasize prevention of kidney stones in these people, further research was still needed to verify our results.

Keywords: obstructive sleep apnea, snoring, snorting/stopping breathing, sleepiness, kidney stones, NHANES

Introduction

Kidney stones, caused by the abnormal accumulation of crystalline substances in the kidney, are widely prevalent and pose a growing global public health challenge globally.[1] A recent study revealed that the prevalence of kidney stones was 11.0%, and there was a substantially greater 12-month incidence of kidney stones in the United States.[2] In China, a meta-analysis of 18 articles with 115,087 individuals revealed that the pooled overall prevalence of kidney stones reached 7.54%, which increased with age.[3] Moreover, the economic burden of kidney stones is comparable to the combined cost of prostate and bladder cancers.[4] However, the pathogenesis and risk factors of kidney stones are complicated and not fully understood.

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Accounting for 1/3 of human life, sleep is essential for maintaining multisystem homeostasis and the health status of humans.[5] Sleep disorders, such as insomnia, circadian rhythm disruption and sleep-disordered breathing, are now recognized as essential health problems worldwide.[6] Sleep disorders have been reported to be associated with multiple diseases such as chronic obstructive pulmonary disease and cancers.[7,8] Recent studies have suggested a potential link between sleep disorders and kidney stones.[9,10] A cross-sectional study revealed a greater risk of kidney stones in participants who slept less than seven hours per day.[9] Another study indicated that circadian rhythm disturbances may affect the pathogenesis of kidney stones through multiple pathways, including microbiota dysbiosis and metabolic disorders.[10] However, current studies in this field are still limited, and it is still unclear which kinds of sleep disorders significantly increase the risk of kidney stones.

Obstructive sleep apnea (OSA) was a highly prevalent sleep disorder characterized as persistent upper airway obstruction and intermittent hypoxia.[11] Although OSA was reported to have shared risk factors of kidney stones such as male sex and obesity, whether OSA was associated with increased risk of kidney stones was still unclear.[11,12] Therefore, this study tried to determine the association between OSA and kidney stones based on the National Health and Nutrition Examination Survey (NHANES). However, the accurate diagnosis of OSA was not available in NHANES due to lack of polysomnography results. To address this issue, the frequency of self-reported typical symptoms of OSA, including snoring, snorting/stopping breathing and excessive daytime sleepiness, was applied as an alternative to OSA diagnosis.

Methods

Study Population

The NHANES is designed to evaluate the health status of the American population and includes approximately 5000 participants to form a nationally representative sample each year.[13] The NHANES program was approved by the Ethics Review Board of the National Center for Health Statistics (Protocol #2018-01 and Protocol #2011-17). In this study, data were obtained from NHANES 2015 to 2020, as only these cycles included complete data on self-reported symptoms of OSA. The exclusion criteria were as follows: (1) Unavailable questionnaire data on the occurrence of OSA-related symptoms. (2) Unavailable questionnaire data on the diagnosis of kidney stones. (3) Patients younger than 20 years, pregnant, or without data of other covariates.

Exposure and Outcome

Data on self-reported symptoms of OSA were obtained from the questionnaires. Participants enrolled in this study were asked, "How often do you snore? (Never/Rarely (1–2 times/week)/Occasionally (3–4 times/week)/Frequently (more than 5 times/week))", "How often do you snort or stop breathing? (Never/Rarely (1–2 times/week)/Occasionally (3–4 times/week)/Frequently (more than 5 times/week))" and "How often do you feel overly sleepy during the day? (Never/Rarely (1/month)/Sometimes (2–4/month)/Often or almost always (more than 5/month))?". The diagnosis of kidney stones was obtained from another questionnaire, "Ever had kidney stones (yes/no)".

Covariates

Covariates, which included demographic characteristics (sex, age, race, education status, marital status, poverty-to-income ratio (PIR), body mass index (BMI), and smoking status), comorbidities (hypertension and diabetes), and biochemical profiles (serum calcium, creatine, and uric acid), were selected based on previous studies and data availability from the NHANES database. Never smoking was defined as smoking <100 cigarettes throughout one's life. The diagnoses of comorbidities were obtained from the questionnaire data. Measurements of standard biochemical profiles can be found in P_BIOPRO (cdc.gov).

Statistical Analysis

Considering the complex probability sampling design of the NHANES database, all statistical analyses were conducted with regard to survey design parameters, including primary sample units and strata. As the NHANES 2017-March 2020

pre-pandemic cycle represented a period of 3.2 years, when combining the NHANES 2015–2016 cycle with this cycle, the weight of NHANES 2015–2016 cycle was multiplied by 2/5.2, while the weight of NHANES 2017-March 2020 pre-pandemic cycle was multiplied by 3.2/5.2, according to the NHANES guidelines (NHANES Analytic Guidance and Brief Overview for the 2017-March 2020 Pre-pandemic Data Files (cdc.gov)). Continuous variables were evaluated using *t*-tests and presented as means with standard errors (SEs). Categorical variables were evaluated using the chi-square test and presented as percentages with SEs. Multivariate logistic regression analysis was performed to evaluate the association between self-reported symptoms of OSA and kidney stones. The results were analyzed based on the three models. Model 1: Crude model without covariate adjustments. Model 2: Minimally adjusted for sex, age and race. Model 3: Fully adjusted for sex, age, race, education status, marital status, PIR, BMI, smoking status, hypertension status, diabetes status and serum calcium, creatine and uric acid levels. Subgroup analyses and interaction tests were performed to evaluate this association further. The sample size was estimated to ensure the statistical power and reduce the risk of type II errors. The specific effect sizes were evaluated referring to previous related publications, and the probability to detect type II errors was 0.2. All analyses were conducted using R and Empowerstats software (EmpowerStats | Data Analysis for Biostatistics & Epidemiology), and a p value <0.05 was regarded as statistically significant.

Results

Baseline Characteristics of Eligible Participants

A total of 9,973 eligible participants were selected from the NHANES 2015–2020, the process of which was presented in Figure 1. The baseline characteristics of eligible participants were presented in Table 1, with a weighted prevalence of kidney stones of 10.76%. Compared to those without kidney stones, the baseline characteristics of patients with kidney stones were significantly different, except for serum calcium (p = 0.252), PIR (p = 0.549), and snoring (p = 0.090).

Association Between Self-Reported Symptoms of OSA and Kidney Stones

Table 2 shows the associations between self-reported symptoms of OSA and the presence of kidney stones. Although frequent snoring (OR 1.425, 95% CI 1.042,1.948; p=0.033) was positively associated with kidney stones, this association disappeared after covariate adjustments (OR 1.033, 95% CI 0.726, 1.469; p = 0.850). Positive associations were observed for those who frequently snorted/stopped breathing (crude model: OR 2.248, 95% CI 1.711, 2.954, p < 0.001; minimally adjusted model: OR 2.153, 95% CI 1.620, 2.860, p < 0.001; fully adjusted model: OR 1.655, 95% CI 1.262, 2.172, p = 0.002) and those who often or almost always felt sleepy (crude model: OR 1.929, 95% CI 1.463, 2.544, p < 0.001; minimally adjusted model: OR 1.978, 95% CI 1.484, 2.638, p < 0.001; fully adjusted model: OR 1.651, 95% CI 1.222, 2.229, p = 0.004), which were still significant after covariate adjustments.

Subgroup Analyses and Interaction Tests

The results of subgroup analyses and interaction tests are presented in Tables 3–4, with all covariates adjusted. Regardless of statistical significance, frequent snorting/stopping breathing was also associated with a greater risk of kidney stones in most subgroups, except for those who were never married (Table 3). Participants who often or almost always felt sleepy also had a greater risk of kidney stones than those who never felt sleepy in all subgroups (Table 4). The results of the interaction tests suggested that marital status (p = 0.015) and smoking status (p < 0.001) significantly interacted with the relationship between snorting/stopping breathing and kidney stones, while no variables significantly interacted with the relationship between sleepiness and kidney stones (all p > 0.05).

Discussion

In this cross-sectional study, we observed that participants who frequently snorted/stopped breathing and often/almost always felt sleepy, rather than those who snored, were at greater risk of kidney stones in American adults. Results of this study suggest that prevention of kidney stones should be given more attention to those with obvious symptoms of snorting/stopping breathing and sleepiness.

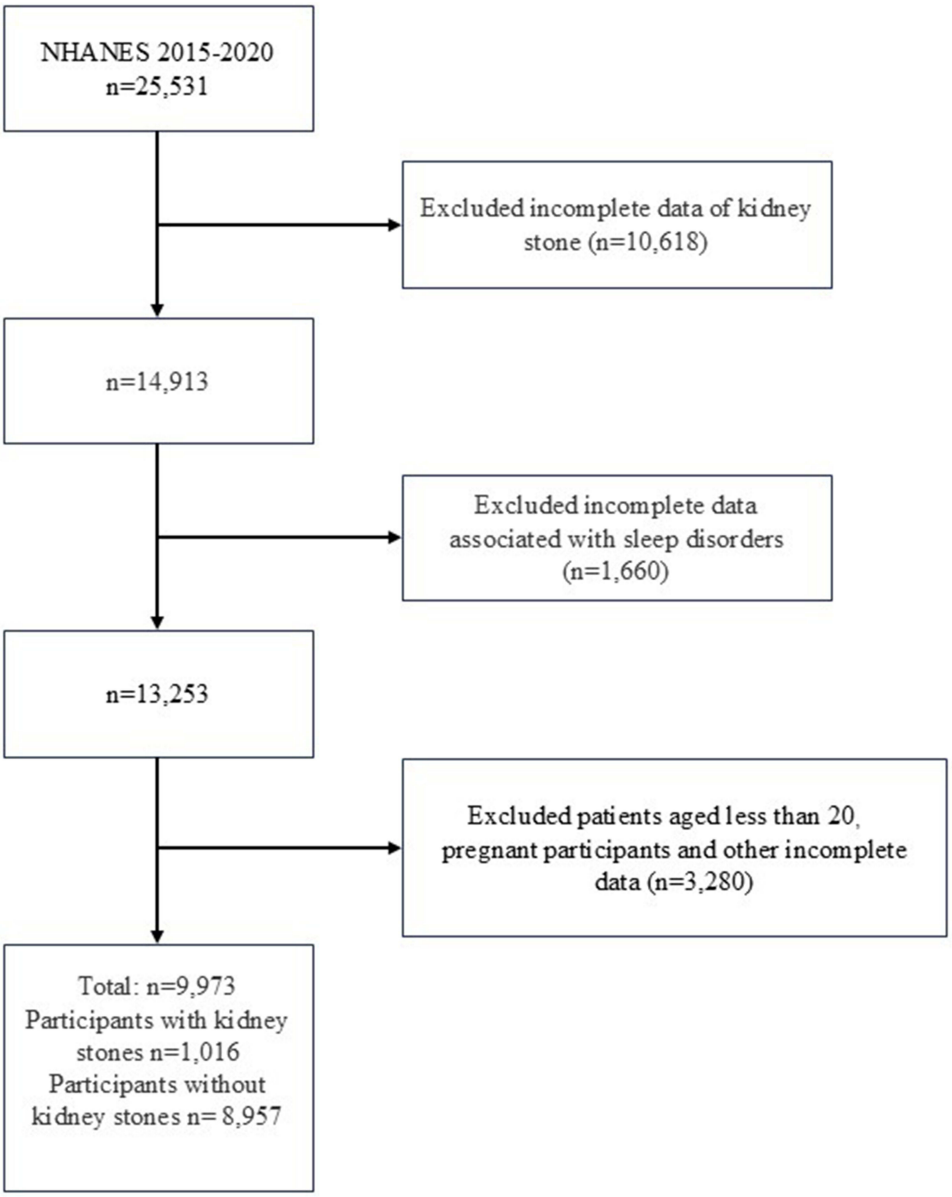

Figure 1 Selection of participants from NHANES 2015–2020.

There are several types of kidney stones, the majority of which include calcium, uric acid, struvite, and cystine stones. Although previous studies have reported multiple factors that may contribute to kidney stone formation, the specific mechanisms involved warrant further investigation.[14] Diet has been regarded as an important factor contributing to the pathogenesis of kidney stones. A recent umbrella review suggested that fructose intake and dietary sodium may serve as risk factors, while intake of coffee and alcohol may serve as protective factors for kidney stones.[15] Another study revealed that dietary vinegar enhanced histone acetylation in tubular cells, which may enhance citrate excretion and inhibit calcium excretion in urine, thereby reducing formation of kidney stones.[16] Apart from dietary effects, recent studies have also suggested a potential link between sleep disturbances and kidney stone development. Patients with obstructive sleep apnea were reported to have significantly greater levels of 24-h urinary oxalate, uric acid, sodium, potassium, phosphorous, chloride, and sulfate, which may promote kidney stone formation.[17] A population-based cohort study suggested that sleep apnea is associated with an increased risk of nephrolithiasis, especially in male participants with metabolic-related comorbidities.[18] Short sleep duration and circadian rhythm disruption may also serve as risk

Table 1 Baseline Characteristics of Eligible Participants in This Cross-Sectional Study

	Kidney Stones	Without Kidney Stones	P-value
Gender (%)			0.006
Male	55.42 (2.17)	48.32 (0.75)	
Female	44.58 (2.17)	51.68 (0.75)	
Age (%)			<0.001
<60	63.55 (2.26)	73.58 (1.17)	
≥60	36.45 (2.26)	26.42 (1.17)	
Race (%)			<0.001
Hispanic	12.45 (1.53)	14.93 (11.43)	
Non-Hispanic White	73.56 (2.44)	64.79 (2.09)	
Other race	13.99 (1.66)	20.28 (1.52)	
Education (%)			0.029
Under high school	12.09 (1.33)	10.75 (0.74)	
High school or equivalent	19.61 (1.68)	24.43 (1.06)	
Above high school	68.31 (2.10)	64.82 (1.47)	
Marital status (%)			<0.001
With partner	70.60 (2.10)	65.75 (1.11)	
Widowed, divorced or separated	18.92 (1.70)	15.74 (0.64)	
Never married	10.48 (1.31)	18.52 (0.82)	
PIR (%)			0.549
PIR<1.3	16.70 (1.33)	18.71 (0.91)	
1.3≤PIR<3.5	36.16 (2.22)	35.17 (1.10)	
PIR≥3.5	47.14 (3.21)	46.12 (1.52)	
BMI (%)			<0.001
BMI<25	19.50 (1.53)	28.11 (0.98)	
25≤BMI<30	30.22 (2.12)	31.91 (0.62)	
BMI≥30	50.29 (2.10)	39.98 (1.08)	
Hypertension (%)			<0.001
Yes	46.09 (2.78)	29.64 (0.96)	
No	53.91 (2.78)	70.36 (0.96)	
Diabetes (%)			<0.001
Yes	21.24 (1.44)	12.09 (0.56)	
No	78.76 (1.44)	87.91 (0.56)	
Smoking (%)			<0.001
Never smoker	49.48 (2.20)	58.92 (0.92)	
Former smoker	31.97 (1.64)	24.70 (0.86)	
Current smoker	18.55 (1.36)	16.38 (0.76)	
Snoring (%)			0.090
Never	21.79 (1.74)	26.26 (0.93)	
Rarely (1–2/week)	28.43 (1.87)	28.61 (0.72)	
Occasionally (3–4/week)	19.20 (1.57)	19.27 (0.66)	
Frequently (≥5/week)	30.58 (2.66)	25.87 (0.64)	
Snorting or stop breathing (%)			<0.001
Never	67.23 (2.10)	75.33 (0.63)	
Rarely (1–2/week)	15.09 (1.27)	13.46 (0.44)	
Occasionally (3–4/week)	7.82 (1.39)	6.30 (0.32)	
Frequently (≥5/week)	9.86 (1.32)	4.92 (0.32)	
Sleepiness (%)			<0.001
Never	10.25 (1.29)	13.78 (0.71)	
Rarely (1/month)	17.11 (1.56)	24.83 (0.77)	
Sometimes (2–4/month)	35.33 (2.00)	35.41 (0.84)	
Often and almost always (≥5/week)	37.31 (1.70)	25.98 (0.88)	

(*Continued*)

Table 1 (Continued).

	Kidney Stones	Without Kidney Stones	P-value
Calcium (mmol/L)	2.33 (0.005)	2.33 (0.002)	0.252
Creatinine (mmol/L)	81.69 (1.17)	76.92 (0.48)	<0.001
Uric acid (μmol/L)	331.50 (3.65)	318.62 (1.46)	<0.001

Notes: Participants with kidney stones: n=1,016 before weighted, n=18,670,971 after weighted Participants without kidney stones: n=8,957 before weighted, n=154,877,554 after weighted. Continuous variables were presented as means with standard errors (SEs). Categorical variables are presented as percentages with SEs.

Table 2 Relationship Between Symptoms of OSA and Kidney Stones

Variables	Crude model OR (95% CI) p	Minimally adjusted OR (95% CI) p	Fully adjusted OR (95% CI) p
Snoring			
Never	Ref	Ref	Ref
Rarely (1–2/week)	1.198 (0.918, 1.562) 0.191	1.171 (0.899, 1.525) 0.251	1.067 (0.797, 1.430) 0.644
Occasionally (3–4/week)	1.201 (0.882, 1.636) 0.253	1.121 (0.825, 1.525) 0.470	0.934 (0.649, 1.344) 0.696
Frequently (≥5/week)	**1.425 (1.042, 1.948) 0.033**	1.337 (0.977, 1.830) 0.078	1.033 (0.726, 1.469) 0.850
P for trend	**0.043**	0.109	0.967
Snorting or stop breathing			
Never	Ref	Ref	Ref
Rarely (1–2/week)	**1.256 (1.026, 1.538) 0.033**	**1.230 (1.010, 1.497) 0.048**	1.115 (0.917, 1.356) 0.291
Occasionally (3–4/week)	1.391 (0.947, 2.045) 0.101	1.309 (0.900, 1.903) 0.169	1.135 (0.788, 1.635) 0.505
Frequently (≥5/week)	**2.248 (1.711, 2.954) <0.001**	**2.153 (1.620, 2.860) <0.001**	**1.655 (1.262, 2.172) 0.002**
P for trend	**<0.001**	**<0.001**	**0.002**
Sleepiness			
Never	Ref	Ref	Ref
Rarely (1/month)	0.926 (0.679, 1.261) 0.627	0.922 (0.669, 1.270) 0.622	0.842 (0.610, 1.161) 0.308
Sometimes (2–4/month)	1.341 (0.957, 1.878) 0.097	1.337 (0.948, 1.887) 0.108	1.191 (0.835, 1.698) 0.348
Often and almost always (≥5/month)	**1.929 (1.463, 2.544) <0.001**	**1.978 (1.484, 2.638) <0.001**	**1.651 (1.222, 2.229) 0.004**
P for trend	**<0.001**	**<0.001**	**<0.001**

Notes: Crude model: No covariates was adjusted. Minimally adjusted: Adjusted for sex, age and race. Fully adjusted: Adjusted for sex, age, race, education status, marital status, PIR, BMI, smoking status, hypertension, diabetes, serum calcium, creatine and uric acid. Significant results were presented in BOLD type.

factors for kidney stones.[9,10] Consistent with previous studies, this cross-sectional study indicated that self-reported snoring was not significantly associated with kidney stones, whereas frequent snorting/stopping breathing and often/always sleepiness were significantly associated with kidney stones, suggesting that severe symptoms of OSA may significantly increase the risk of nephrolithiasis.

The potential mechanisms by which sleep disorders affect the pathogenesis of kidney stones are summarized in Figure 2. Sleep disorders may increase the risk of kidney stones through multiple pathways including microbiota alteration, systematic inflammation, and circadian rhythm disruption. Alterations in the microbiota have been reported

Table 3 Subgroup Analysis of Relationship Between Snorting/Stopping Breathing and Kidney Stone

Snorting or Stop Breathing	Never	Rarely (1–2 times/week)		Occasionally (3–4 times/week)		Frequently (≥5/week)		p Interaction
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	
Gender								0.710
Male	Ref	1.279 (0.988, 1.656)	0.060	1.238 (0.783, 1.958)	0.340	**1.716 (1.254, 2.349)**	**0.002**	
Female	Ref	0.876 (0.546, 1.407)	0.591	0.988 (0.570, 1.714)	0.966	1.704 (1.093, 2.655)	0.029	
Age								0.661
<60	Ref	1.204 (0.915, 1.586)	0.201	1.065 (0.664, 1.708)	0.796	**1.839 (1.335, 2.532)**	**0.001**	
≥60	Ref	0.913 (0.591, 1.412)	0.666	1.240 (0.551, 2.791)	0.584	1.414 (0.678, 2.949)	0.334	
Race								0.445
Hispanic	Ref	1.334 (0.866, 2.057)	0.178	1.299 (0.709, 2.388)	0.380	1.235 (0.758, 2.013)	0.376	
Non-Hispanic White	Ref	1.106 (0.838, 1.460)	0.455	1.108 (0.627, 1.959)	0.711	**1.510 (1.084, 2.013)**	**0.017**	
Other races	Ref	1.000 (0.624, 1.602)	1.000	1.234 (0.735, 2.072)	0.436	**3.050 (1.773, 5.247)**	**<0.001**	
Education								0.696
Under high school	Ref	1.525 (0.934, 2.491)	0.107	1.774 (0.806, 3.902)	0.170	**2.402 (1.776, 4.905)**	**0.026**	
High school or equivalent	Ref	1.003 (0.612, 1.645)	0.991	1.199 (0.388, 3.709)	0.756	1.630 (0.823, 3.227)	0.176	
Above high school	Ref	1.087 (0.843, 1.401)	0.529	1.028 (0.676, 1.562)	0.899	**1.555 (1.103, 2.193)**	**0.020**	
Marital status								**0.015**
With partner	Ref	1.164 (0.920, 1.472)	0.220	1.156 (0.710, 1.882)	0.566	**1.745 (1.272, 2.394)**	**0.003**	
Widowed, divorced or separated	Ref	1.253 (0.794, 1.979)	0.313	0.824 (0.386, 1.757)	0.598	**2.071 (1.053, 4.074)**	**0.036**	
Never married	Ref	0.412 (0.147, 1.153)	0.107	1.622 (0.596, 4.411)	0.355	0.659 (0.240, 1.805)	0.426	
PIR								0.668
<1.3	Ref	0.945 (0.499, 1.788)	0.854	1.348 (0.902, 2.014)	0.135	**1.879 (1.173, 3.010)**	**0.011**	
1.3≤PIR<3.5	Ref	1.183 (0.885, 1.581)	0.271	1.045 (0.583, 1.872)	0.885	**2.034 (1.454, 2.847)**	**<0.001**	
≥3.5	Ref	1.077 (0.744, 1.559)	0.681	1.058 (0.597, 1.873)	0.839	1.345 (0.782, 2.314)	0.267	
BMI								0.180
BMI<25	Ref	0.936 (0.554, 1.582)	0.808	1.308 (0.708, 2.415)	0.401	**2.817 (1.159, 6.844)**	**0.033**	
25≤BMI<30	Ref	1.202 (0.746, 1.937)	0.429	1.200 (0.705, 2.043)	0.482	2.026 (0.995, 4.125)	0.051	
BMI≥30	Ref	1.112 (0.820, 1.508)	0.501	1.053 (0.657, 1.689)	0.832	1.377 (0.996, 1.903)	0.067	
Hypertension								0.875
Yes	Ref	1.041 (0.667, 1.625)	0.853	1.077 (0.550, 2.106)	0.820	1.484 (0.975, 2.258)	0.063	
No	Ref	1.175 (0.869, 1.588)	0.308	1.214 (0.764, 1.929)	0.421	**1.889 (1.284, 2.778)**	**0.004**	
Diabetes								0.417
Yes	Ref	0.788 (0.484, 1.283)	0.317	1.522 (0.825, 2.808)	0.166	1.567 (0.764, 3.215)	0.205	
No	Ref	1.180 (0.920, 1.514)	0.179	1.032 (0.663, 1.604)	0.884	**1.659 (1.225, 2.247)**	**0.002**	
Smoking								**<0.001**
Never smoker	Ref	**0.652 (0.457, 0.930)**	**0.020**	1.312 (0.714, 2.413)	0.362	1.019 (0.614, 1.693)	0.937	
Former smoker	Ref	**1.854 (1.265, 2.717)**	**0.003**	0.955 (0.460, 1.985)	0.897	**2.190 (1.028, 4.662)**	**0.042**	
Current smoker	Ref	1.521 (0.868, 2.665)	0.133	1.055 (0.506, 2.199)	0.881	**2.629 (1.588, 4.352)**	**<0.001**	

Notes: Adjusted for sex, age, race, education status, marital status, PIR, BMI, smoking status, hypertension, diabetes, serum calcium, creatine and uric acid. Significant results were presented in BOLD type.
Abbreviations: PIR, poverty-to-income ratio; BMI, body mass index.

in patients with sleep disorders. Shimizu et al noted that shorter sleep duration led to alterations in the gut microbiota via reduced secretion of human defensin 5.[19] Matenchuk et al suggested that hypothalamus-pituitary-adrenal axis activation and immune system regulation may serve as potential pathways between sleep disorders and microbiota alterations.[20] Evidence also indicates the role of hypoxia in inducing gut microbiota dysbiosis.[21] Moreover, alterations in microbiota may also be associated with the development of kidney stones. Al et al compared the gut, oral, and urinary microbiota of 30 healthy controls and 83 stone formers and suggested that multisite microbiota alterations may serve as effective indicators of kidney stone development.[22] Mechanistically, oxalate-degrading bacteria, including *Oxalobacter formigenes*, have been shown to reduce the formation of kidney stones by promoting degradation and modulating the function of the oxalate transporter SLC26A6.[9,23] Short-chain fatty acids, a common group of microbiota-derived metabolites, may

Table 4 Subgroup Analysis of Relationship Between Sleepiness and Kidney Stone

Sleepiness	Never	Rarely (1/month)		Sometimes (2–4/month)		Often or Almost Always (≥5/month)		p Interaction
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	
Gender								0.126
Male	Ref	1.091 (0.680, 1.752)	0.702	1.411 (0.982, 2.030)	0.061	**1.716 (1.154, 2.551)**	**0.010**	
Female	Ref	0.605 (0.345, 1.063)	0.097	0.960 (0.575, 1.604)	0.879	1.529 (0.972, 2.405)	0.082	
Age								0.230
<60	Ref	1.108 (0.703, 1.746)	0.663	1.401 (0.872, 2.251)	0.180	**2.036 (1.327, 3.124)**	**0.004**	
≥60	Ref	**0.568 (0.345, 0.936)**	**0.028**	1.023 (0.590, 1.772)	0.932	1.287 (0.731, 2.265)	0.361	
Race								0.161
Hispanic	Ref	0.884 (0.511, 1.529)	0.643	1.155 (0.646, 2.064)	0.610	1.021 (0.694, 1.502)	0.912	
Non-Hispanic White	Ref	0.796 (0.478, 1.327)	0.392	1.253 (0.764, 2.053)	0.382	**1.822 (1.164, 2.852)**	**0.016**	
Other races	Ref	0.967 (0.533, 1.752)	0.912	1.011 (0.599, 1.705)	0.968	1.396 (0.818, 2.382)	0.236	
Education								0.636
Under high school	Ref	1.098 (0.608, 1.984)	0.745	1.325 (0.742, 2.365)	0.321	**2.574 (1.352, 4.899)**	**0.006**	
High school or equivalent	Ref	1.016 (0.470, 2.196)	0.968	1.387 (0.762, 2.526)	0.297	**1.975 (1.127, 3.462)**	**0.028**	
Above high school	Ref	0.730 (0.463, 1.152)	0.164	1.065 (0.643, 1.765)	0.796	1.382 (0.890, 2.146)	0.140	
Marital status								0.719
With partner	Ref	0.823 (0.542, 1.249)	0.372	1.157 (0.759, 1.766)	0.505	**1.516 (1.063, 2.160)**	**0.032**	
Widowed, divorced or separated	Ref	0.739 (0.401, 1.363)	0.345	1.306 (0.743, 2.297)	0.365	1.647 (0.914, 2.968)	0.112	
Never married	Ref	1.020 (0.364, 2.857)	0.968	1.145 (0.416, 3.150)	0.782	2.421 (0.947, 6.190)	0.063	
PIR								0.299
<1.3	Ref	0.808 (0.473, 1.380)	0.415	1.359 (0.834, 2.215)	0.203	1.469 (0.801, 2.692)	0.199	
1.3≤PIR<3.5	Ref	0.871 (0.551, 1.377)	0.534	0.898 (0.549, 1.469)	0.652	**1.710 (1.151, 2.541)**	**0.010**	
≥3.5	Ref	0.807 (0.438, 1.487)	0.500	1.323 (0.743, 2.356)	0.353	1.607 (0.879, 2.935)	0.139	
BMI								0.964
BMI<25	Ref	1.055 (0.493, 2.260)	0.884	1.245 (0.666, 2.330)	0.472	2.018 (0.959, 4.246)	0.062	
25≤BMI<30	Ref	0.851 (0.493, 1.468)	0.568	1.065 (0.591, 1.921)	0.836	1.419 (0.854, 2.356)	0.191	
BMI≥30	Ref	0.757 (0.453, 1.267)	0.271	1.258 (0.784, 2.020)	0.322	**1.649 (1.102, 2.468)**	**0.017**	
Hypertension								0.932
Yes	Ref	0.907 (0.519, 1.584)	0.716	1.283 (0.763, 2.158)	0.326	1.742 (0.999, 3.038)	0.050	
No	Ref	0.826 (0.535, 1.278)	0.402	1.177 (0.767, 1.807)	0.464	**1.678 (1.128, 2.498)**	**0.019**	
Diabetes								0.189
Yes	Ref	0.960 (0.484, 1.903)	0.908	0.854 (0.468, 1.557)	0.611	1.288 (0.660, 2.514)	0.467	
No	Ref	0.814 (0.570, 1.162)	0.271	1.302 (0.882, 1.923)	0.200	**1.757 (1.260, 2.452)**	**0.004**	
Smoking								0.909
Never smoker	Ref	0.847 (0.547, 1.311)	0.464	1.076 (0.673, 1.723)	0.762	1.508 (0.988, 2.300)	0.071	
Former smoker	Ref	0.743 (0.370, 1.492)	0.383	1.268 (0.651, 2.470)	0.466	1.730 (0.903, 3.315)	0.093	
Current smoker	Ref	1.015 (0.510, 2.019)	0.964	1.277 (0.609, 2.678)	0.497	1.926 (0.968, 3.830)	0.060	

Notes: Adjusted for sex, age, race, education status, marital status, PIR, BMI, smoking status, hypertension, diabetes, serum calcium, creatine and uric acid. Significant results were presented in BOLD type.

Abbreviations: PIR, poverty-to-income ratio; BMI, body mass index.

also affect kidney stone formation via oxalate transporter modulation and GPR43-dependent immune regulation.[24,25] Alteration of microbiota may reduce the abundance of oxalate-degrading bacteria and the levels of short-chain fatty acids, thereby leading to the development of kidney stones.[26] Additionally, systematic inflammation, which also increases the risk of kidney stones, is widely observed in patients with sleep disorders.[21,27] Patients with OSA were characterized as intermittent hypoxia, which then promote production of oxidative stress and sympathetic activation.[28] Another study suggested that immune and inflammatory responses may contribute to the pathogenesis of insomnia.[29] As for how systematic inflammation contributes to kidney stones, current evidence suggests that kidney crystal deposition may be associated with inflammasome activation, increased reactive oxygen species, and elevated expression of inflammation-related molecules.[30] However, more in-depth investigations were still needed for specific mechanisms. Moreover, circadian rhythm disruption has also been reported in patients with sleep disorders.[31] Elevated expressions of circadian

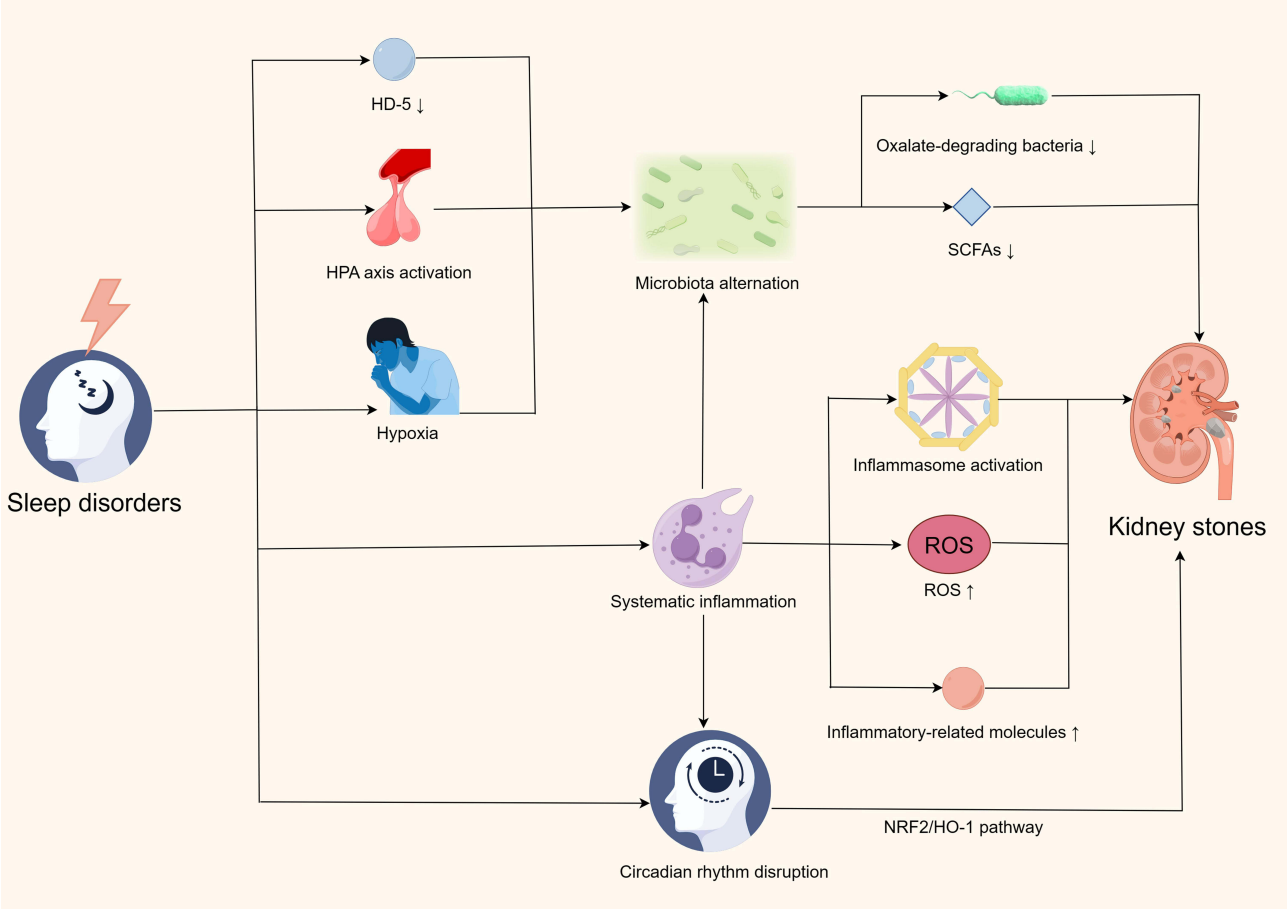

Figure 2 Potential mechanisms over how sleep disorders affect the pathogenesis of kidney stones, created by Figdraw.
Abbreviations: HD-5, human defensin 5; HPA axis, hypothalamus-pituitary-adrenal axis; SCFAs, short-chain fatty acids; ROS, reactive oxygen species; NRF2/HO-1, nuclear factor erythroid 2-related factor/heme oxygenase-1.

clock genes were observed in patients with OSA in the morning, which may be associated with their comorbid affective disorders.[32] Wang et al reported that the expression of brain and muscle Arnt-like protein 1 (BMAL1) may regulate the nuclear factor erythroid 2-related factor/heme oxygenase-1 (NRF2/HO-1) pathway, thereby reducing urinary stone formation, suggesting that circadian rhythm may also participate in the pathogenesis of kidney stones.[33] Compared with the effects of sleep disorders over kidney stones, limited evidence has been reported on how kidney stones contribute to the pathogenesis of sleep disorders. Although it was well-acknowledged that the acute onset of kidney stones may directly disrupt the sleeping process via worsening pain, further research was still needed to understand the intricate pathological process.

The results of interaction tests revealed that marital status and smoking significantly interacted with the relationship between snorting/stopping breathing and kidney stones (both $p < 0.05$). Previous studies have shown that smoke exposure is strongly associated with impaired health, including an increased risk of kidney stones. Huang et al analyzed data from 2007 to 2018 in the NHANES and reported that current smoking may be associated with an increased risk of kidney stones.[34] Another study reported that secondhand smoke is an important risk factor for developing kidney stone disease and that the impact of secondhand smoke is not inferior to that of smoking.[35] The mechanism by which smoke exposure causes kidney stones is complex, and harmful substances in tobacco smoke such as cadmium and lead may increase the risk of kidney stones. Additionally, smoking may increase vasopressin levels, which leads to a decrease in urine output and promotes stone formation. Smoking can also release reactive oxygen species, causing kidney damage and accelerating the development of chronic kidney disease, eventually leading to the development of kidney stones.[34–37] Therefore, tobacco control is important for the management of kidney stone disease. However, few studies have explored

the interactive role of marital status in this relationship, which warrants further investigation. Of course, there are many risk factors for kidney stone disease, and interpretation of the current findings should be combined with other clinical information of the patients.

This study had several limitations. (1) The study had a cross-sectional design, so we could not determine the causal relationship between OSA-related symptoms and kidney stones. Further longitudinal studies with large sample size are needed to verify these findings. (2) Although we adjusted for possible covariates, there were unadjusted confounding factors that may affect our results. For example, as diet plays a crucial role in the pathogenesis of kidney stones, inadequate adjustments of diet-related covariates may induce potential bias, thereby affecting the reliability of these results. Future researches may consider collecting dietary and hydration data from patients in their own centers via more detailed clinical consultation and laboratory tests to control these variables better. (3) The diagnoses of OSA-related symptoms and kidney stones were obtained via a questionnaire, and recall bias was inevitable, which may have affected our results. Moreover, participants with OSA-related symptoms or asymptomatic kidney stone formation may be unaware of their conditions, making it harder for questionnaire screening to reach accurate diagnoses.[38] (4) Results of this study were achieved based on a single, cross-sectional dataset, which was associated with insufficient generalizability. (5) Data over subtypes of kidney stones were unavailable in this study, making it hard to determine the detailed relationship between self-reported symptoms of OSA and different types of kidney stones. Moreover, although circadian rhythm has been shown to affect the formation of calcium oxalate stones,[33] whether different sleep disorders may interact differently with different types of kidney stones was still unclear. Further studies may record stone composition for patients with kidney stones and conduct clinical and mechanical investigations to address this intricate connection.

Conclusion

Taken together, based on data from NHANES, self-reported obvious snorting/stopping breathing and sleepiness may be associated with increased risk of kidney stones. However, considering the nature of cross-sectional design, potential risk of bias and insufficient generalizability of the results, future prospective, multi-center studies with large sample size are needed to verify our findings.

Data Sharing Statement

All data used in this cross-sectional study are available on the NHANES website (NHANES - National Health and Nutrition Examination Survey Homepage (cdc.gov)).

Ethnic Approval

Due to the approval of Ethics Review Board of National Center for Health Statistics (Protocol #2018-01 and Protocol #2011-17) and the well-obtained written informed consent from all participants in NHANES, the IRB of West China hospital of Sichuan University waived the ethical approval and written informed consent of this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declared no competing interest for this work.

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