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Risk of Nephrolithiasis in Patients With Sleep Apnea: A Population-Based Cohort Study

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Abstract

Study Objectives:

To delineate the relationship between sleep apnea and subsequent risk of nephrolithiasis.

Methods:

We conducted a retrospective cohort analysis of a general population sample from Taiwan National Health Insurance Research Database (NHIRD) from January 1, 2000 to December 31, 2012. Patients with sleep apnea without prior diagnosis of nephrolithiasis (n = 7,831) were identified and subsequent development of nephrolithiasis was compared to an age- and sex-matched control group (n = 31,293) without sleep apnea. The Cox proportional hazard regression models were used to evaluate the association between sleep apnea and subsequent nephrolithiasis development.

Results:

After adjusting for age, sex, and comorbidities, the risk of nephrolithiasis remained significantly increased in the sleep apnea group (hazard ratio [HR] = 1.35; 95% confidence interval [CI] = 1.23–1.48; $P < .001$). Compared to controls, elevated HRs of nephrolithiasis were observed for male patients (HR = 1.22; 95% CI 1.09–1.36; $P < .001$) and those aged 20–39 years (HR = 1.28; 95% CI 1.09–1.49; $P < .01$) and 40–59 years (HR = 1.17, 95% CI 1.03–1.34, $P < .05$) in the sleep apnea cohort. Risk of nephrolithiasis in patients with sleep apnea increased significantly with concomitant metabolic-related comorbidities, gouty arthritis, and urinary tract infection.

Conclusions:

Sleep apnea is associated with an increased subsequent risk of the development of nephrolithiasis. Young male patients with sleep apnea and concomitant comorbidities are at the greatest risk for nephrolithiasis formation.

Citation:

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Keywords: metabolic-related comorbidities, nephrolithiasis, sleep apnea

BRIEF SUMMARY

Current Knowledge/Study Rationale: Although sleep apnea and nephrolithiasis are known to share common risk factors, an association between sleep apnea and stone disease has not been thoroughly investigated. Given the increasing prevalence of both diseases and shared links to metabolic syndrome, identifying nephrolithiasis risk in patients with sleep apnea may provide opportunity for improved counseling and stone prevention.

Study Impact: Sleep apnea is associated with subsequent development of nephrolithiasis. Young male patients with sleep apnea and concomitant comorbidities are at the greatest risk for nephrolithiasis formation.

INTRODUCTION

Nephrolithiasis is a common urologic disease with increasing prevalence globally. The prevalence of nephrolithiasis in the United States population is 10.6% for males and 7.1% for females.[1] Despite improvements in minimally invasive stone removal procedures, stone prevention remains a challenge. Fifty percent of patients with nephrolithiasis will experience stone recurrence within 10 years.[2] Recent epidemiologic studies have shown that nephrolithiasis is associated with coronary artery disease,[3] hypertension,[4] diabetes mellitus,[5] obesity,[6] and dyslipidemia.[7]

Sleep apnea, marked by periodic episodes of nocturnal hypoxia, also is increasing in prevalence globally, especially in middle-aged and elderly subjects. In the general population, it is estimated that 9% of females and 24% of males have sleep apnea.[8] Sleep apnea is often associated with obesity and other components of metabolic syndrome and can lead to pathologic metabolic states of hypoxia and inflammation, with increased risk of severe cardiometabolic dysfunction.[9,10]

Although sleep apnea and nephrolithiasis are known to share common risk factors, an association between sleep apnea and stone disease has not been thoroughly investigated. Given the increasing prevalence of both diseases and shared links to metabolic syndrome, identifying nephrolithiasis risk in patients with sleep apnea may provide opportunity for improved counseling and stone prevention. We sought to better delineate the relationship between sleep apnea and nephrolithiasis by evaluating a large patient cohort within the Taiwan National Health Insurance Research Database (NHIRD).

METHODS

Data Source

Patient data were obtained from the Longitudinal Health Insurance Database (LHID) 2000, a linked longitudinal dataset composed of one million randomly selected patients within the NHIRD. The NHIRD—which provides anonymized comprehensive medical information including ambulatory and inpatient services and prescription details—enrolled 99% of the total population in Taiwan, approximately 23 million people, from 1996 to 2011.[11] Disease and medical procedures were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Procedure Coding System (ICD-9-PCS). The accuracy and wholeness of ICD coding within the NHIRD have been validated.[12] Sex, age, and health care utilization among the LHID 2000 subpopulation had been verified to be statistically representative of the entire Taiwanese population.[13] The study analyzed de-identified secondary data from NHIRD, and no informed consent is required. To ensure patient confidentiality all procedures were performed in accordance with the tenets of the Declaration of Helsinki.

Study Population

Within the LHID 2000, we identified all patients with a new diagnosis of sleep apnea (ICD-9-CM codes 780.51, 780.53, 780.57) between January 1, 2001 and December 31, 2010. The accuracy of ICD coding for sleep apnea within the LHID 2000 has been validated with good positive predictive value.[14,15] Patients with incomplete demographic information, age younger than 20 years, or known diagnosis of nephrolithiasis (ICD-9-CM codes 592.0, 592.1) prior to diagnosis of sleep apnea were excluded from review. A control group was selected from participants without a diagnosis of sleep apnea and nephrolithiasis. Controls were matched 4:1 to the sleep apnea group using propensity score matching for age, sex, insurance coverage area, and income level (**Figure 1**). The date that sleep apnea was initially diagnosed was used as the longitudinal index date for a sleep apnea patient and his/her corresponding controls.

Outcome Assessment and Identification of Confounding Variables

Patients in both groups were evaluated from their respective index date to the date of first diagnosis of nephrolithiasis. Patients were followed through either the end of year 2012 or through the date at which there was documented withdrawal from the national health insurance program. As conditions with known links to urinary stone disease, the following comorbidities were evaluated as potential confounding variables in each cohort: hypertension (ICD-9-CM codes 401.XX–405. XX), coronary artery disease (ICD-9-CM codes 410.XX–414. XX), stroke (ICD-9-CM codes 430.XX–438.XX), diabetes mellitus (ICD-9-CM codes 250.XX), hyperlipidemia (ICD-9-CM codes 272.0–272.2), gouty arthritis (ICD-9-CM codes 274.0), renal failure (ICD-9-CM codes 584.XX–586.XX), and urinary tract infection (ICD-9-CM codes 590.X, 595.0, 599.0). The body mass index (BMI) of participants cannot be extracted from the NHIRD, and we used obesity (ICD-9-CM codes 278.00–278.01) as a confounding variable for multivariate adjustment.

Statistical Analysis

Distribution comparisons of categorical variables (demographic characteristics and comorbidities) were performed via univariate analysis with chi-square testing. The Kaplan-Meier method and the log-rank test were performed to estimate differences of cumulative incidence of nephrolithiasis between groups. Cox proportional hazard regression models adjusting age, sex, and comorbidities, including hypertension, coronary artery disease, stroke, diabetes mellitus, hyperlipidemia, obesity, gouty arthritis, renal failure, and urinary tract infection were developed to assess the risk of nephrolithiasis in the sleep apnea cohort compared to that in the age-matched control cohort. Multiplicative analysis was performed to evaluate the effect of the aforementioned comorbidities on nephrolithiasis development. A two-tailed value of $P < .05$ was deemed significant. The statistical analyses were conducted using SAS software version 9.3 (SAS Institute Inc, Cary, North Carolina, United States).

RESULTS

A diagnosis of sleep apnea was reported in 7,831 patients between January 1, 2001 and December 31, 2010. The control group, matched 4:1 to the sleep apnea group, included 31,293 patients. The mean follow-up was 5.8 ± 2.6 and 5.6 ± 2.6 years in the sleep apnea and control cohorts, respectively. Baseline demographic characteristics for both cohorts are shown in **Table 1**. Compared to controls, patients with sleep apnea demonstrated higher risk of comorbidities including hypertension, coronary artery disease, stroke, diabetes mellitus, morbid obesity, hyperlipidemia, gouty arthritis, renal failure, and urinary tract infection ($P < .001$). The incident rate of nephrolithiasis was significantly higher in the sleep apnea cohort compared to controls (1.59 versus 0.95 per 100 person-years respectively, $P < .001$). Cumulative longitudinal incidence of nephrolithiasis is shown in **Figure 2**, demonstrating significant increased risk of nephrolithiasis in the sleep apnea cohort throughout the study period (for log-rank test, $P < .0001$). Overall, the risk of developing nephrolithiasis in sleep apnea cohort was 1.66-fold higher than that of the control group (**Table 2**).

After adjusting for potential confounding variables (including age, sex, and comorbidities) the increased risk of nephrolithiasis in the sleep apnea cohort remained significant (adjusted hazard ratio [HR] = 1.35; 95% confidence interval [CI] = 1.23– 1.48; $P < .001$). Sex-specific incidence of nephrolithiasis was higher in men than women in both cohorts. In the sleep apnea group, men had a significantly higher risk of nephrolithiasis compared with controls (adjusted HR = 1.22, 95% CI 1.09– 1.36; $P < .001$).

Young patients with sleep apnea (subgroup age 20–39 years) had a 28% increased risk of nephrolithiasis development compared with age-matched controls (adjusted HR = 1.28; 95% CI 1.09–1.49; $P < .001$). However, age-specific risk of sleep apnea related nephrolithiasis diminished in patients older than 60 years (adjusted HR = 1.01; 95% CI 0.78–1.30).

The joint effects of sleep apnea and any single comorbidity on nephrolithiasis risk, as determined by multiplicative analysis, is shown in **Table 3**. A diagnosis of nephrolithiasis was more likely in patients with sleep apnea with any of the following concomitant comorbidities: hypertension, coronary artery disease, stroke, diabetes mellitus, hyperlipidemia, obesity, gouty arthritis, and urinary tract infection ($P < .001$ for all interactions). Urinary tract infection was the comorbidity with the most significant cumulative risk; patients with diagnoses of both sleep apnea and urinary tract infection had a 3.57-fold increased risk of the development of nephrolithiasis compared to participants without sleep apnea and urinary tract infection (adjusted HR = 3.57; 95% CI 3.15–4.04; $P < .001$).

DISCUSSION

At a mean follow up of 5.6 years, the incident rate of nephrolithiasis in patients with sleep apnea was 1.59 per 100 person-years. After adjusting for age, sex, and comorbidities, patients with sleep apnea had a 35% increased risk of nephrolithiasis compared to controls. Overall, in the Taiwanese cohort, the prevalence of nephrolithiasis was 9.6%, compatible with the incidence of stone disease in western countries including the United States.[1,16] In sex-specific analyses, men with sleep apnea had a higher risk of nephrolithiasis compared with men without sleep apnea (adjusted HR = 1.22). In age-specific analyses, young patients (20–39 years) with sleep apnea carried the highest risk of nephrolithiasis compared to those without sleep apnea (adjusted HR = 1.28); the effect of sleep apnea, however, was not observed in the eldest subgroup (older than 60 years, adjusted HR = 1.01). It remains unclear why the specific risk of nephrolithiasis in patients with sleep apnea is attenuated with increasing age.

Not surprisingly, patients with additional cardiometabolic comorbidities (including hypertension, coronary artery disease, stroke, diabetes mellitus, hyperlipidemia, and obesity) had heightened risk for nephrolithiasis compared to patients with an isolated diagnosis of sleep apnea in multiplicative analysis.

These data further support the growing body of literature revealing that nephrolithiasis occurs within a spectrum of systemic pathologic processes related to metabolic disturbances and vascular diseases.[17] In particular, our study identified uri-nary tract infection and gouty arthritis as comorbidities along with sleep apnea that had the greatest effect on the likelihood that nephrolithiasis would develop in a particular patient. Our results support the idea that sleep apnea and cardiometabolic comorbidities may partially share the same mechanisms in stone formation and further synergize with uric acid and infectious stone development.

Sleep apnea was found to be associated with the presence of cardiometabolic dysfunction (**Table 1**). Previous cross-sectional studies have shown high prevalence rates (50% to 87%) of metabolic syndrome in patients with sleep apnea and there appears to be a dose-response relationship that exists between sleep apnea severity and further deterioration related to metabolic syndrome.[9] Sleep apnea is the most prevalent contributor of secondary hypertension and is an independent factor of coronary artery disease.[18,19] Furthermore, patients with severe sleep apnea had a 2.5-fold increased risk of cardiovascular events and a twofold increased risk of stroke when compared to age-matched patients without sleep apnea.[20] Pathophysiologically, sleep apnea-related cardiometabolic dysfunction results from sleep fragmentation, repetitive bouts of apnea, hypoxia, and hypercapnia that trigger systemic sympathetic activation, oxidative stress, endothelial dysfunction, and hypoxia-induced insulin resistance.[10,21] Sleep apnea and nephrolithiasis both have been linked to shared comorbidities within the spectrum of metabolic syndrome.[6,7] In the current analyses, traits of metabolic syndrome (hypertension, diabetes mellitus, hyper-lipidemia and obesity) were all linked to higher rates of nephrolithiasis. We hypothesized that patients with sleep apnea may be at risk for nephrolithiasis due to mechanisms related to metabolic syndrome. However, after adjusting for these potential confounding variable, sleep apnea was associated with an increased risk of subsequent stone development.

Insulin resistance, which is triggered by intermittent hypoxia and subsequent oxidative stress in patients with sleep apnea, is a core feature of metabolic syndrome.[10,22] Insulin resistance impairs ammonium excretion, resulting in two known risk factors for nephrolithiasis: overly acidic urine and decreased urine citrate.[23] Furthermore, oxalate and calcium excretion have been shown to be higher in men with hypertension and obesity.[24,25] Collectively, these changes in urine composition are known to facilitate uric acid and calcium oxalate supersaturation.

Within the renal papilla, turbulent blood flow, relative hypoxia, and hyperosmolar gradients may be associated with microvascular injury/compromise, potentiating biomineralization, Randall plaque formation, and subsequent formation of calcium-based stones.[26] Theoretically, it stands to reason that hypoxia and endothelial dysfunction secondary to sleep apnea may have negative effects on renal papillary physiology that potentiate or worsen mineralization processes associated with Randall plaque.

Sleep apnea also has been linked to subacute and chronic states of systemic inflammation. Elevated circulating inflammatory mediators including C-reactive protein, interleukin 6, interleukin 8, tumor necrosis factor α, and adhesion molecules have been detected in patients with sleep apnea.[27,28] Sleep apnea is associated with increased reactive oxygen species production from leucocytes.[29] In patients with sleep apnea, inflammation and oxidative stress secondary to intermittent hypoxia may mediate components of metabolic syndrome and play a role in the development of nephrolithiasis. Indeed, increased inflammatory proteins have been detected in both the urine and stones of patients with calcium stones.[30] Furthermore, lower quantities of serum antioxidants (α-carotenes, beta carotenes, and β-cryptoxanthin) were detected in stone patients in National Health and Nutrition Examination Survey (NHANES) III database studies.[31] Mechanistically, inflammation facilitating crystal aggregation to the damaged urothelium or denuded Randall plaque increases risk of stone development.[32]

One case-control study disclosed that patients with urinary calculi had a higher prevalence of prior

obstructive sleep apnea.[33] The current analyses further reveal an independent link between sleep apnea and nephrolithiasis using longitudinal population-based data. The analyses are strengthened by the large sample size and extended follow-up, but further work is necessary to confirm these findings.

There are a number of limitations to the current study, especially those inherent to the use of a national administrative health care database. First, the study population was geographically isolated to Taiwan and represents limited diversity in ethnicity (98% of Taiwan's residents were of Han Chinese ethnicity). The results may not be directly representative of other geographic regions or races.[34]

Second, the NHIRD database lacks detailed personal information such as dietary preference, smoking habits, family history, and actual BMI value. The lack of BMI data, an important confounding factor of both sleep apnea and nephrolithiasis, is a major flaw of our study. We used ICD-9-CM codes for obesity as a confounding factor for multivariate analysis. The simplified surrogate of BMI carried bias of underestimating the prevalence of obesity and lacking stratifications to thoroughly investigating impact of obesity on both diseases.[35] Furthermore, relevant image and biochemical profiles such as urinalyses, glomerular filtration rate, and overall stone analysis, which may be potential confounding factors, were unavailable.

Third, although the NHIRD database has been previously validated for standards of accuracy,[11,13,14] the diagnoses and severity of sleep apnea, nephrolithiasis, and comorbidities based on ICD-9-CM coding do not fully encompass the actual incidence of these conditions in the study population.[35,36] Furthermore, surveillance bias, which may increase stone diagnosis in patients with sleep apnea, cannot be fully investigated in the NHIRD database.

Fourth, the effect of treatment on sleep apnea cannot be thoroughly studied. Data from treatments beyond insurance coverage, treatment compliance, and treatment duration were not available in the NHIRD. Finally, the retrospective cohort study design carries potential biases and lowers the statistical quality.

CONCLUSIONS

Sleep apnea was associated with an increased risk of the development of nephrolithiasis. The association between sleep apnea and nephrolithiasis further supports that nephrolithiasis is tightly associated with vascular and metabolic disturbances. Unfortunately, we could not thoroughly adjust the effect of BMI by using the nationwide database. Further well-designed prospective investigations are indicated to elucidate the causal relationship between sleep apnea and nephrolithiasis.

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors report no conflicts of interest.

ABBREVIATIONS

BMI	body mass index
CI	confidence interval
HR	hazard ratio
ICD	International Classification of Diseases
LHID	Longitudinal Health Insurance Database
NHANES	National Health and Nutrition Examination Survey
NHIRD	National Health Insurance Research Database

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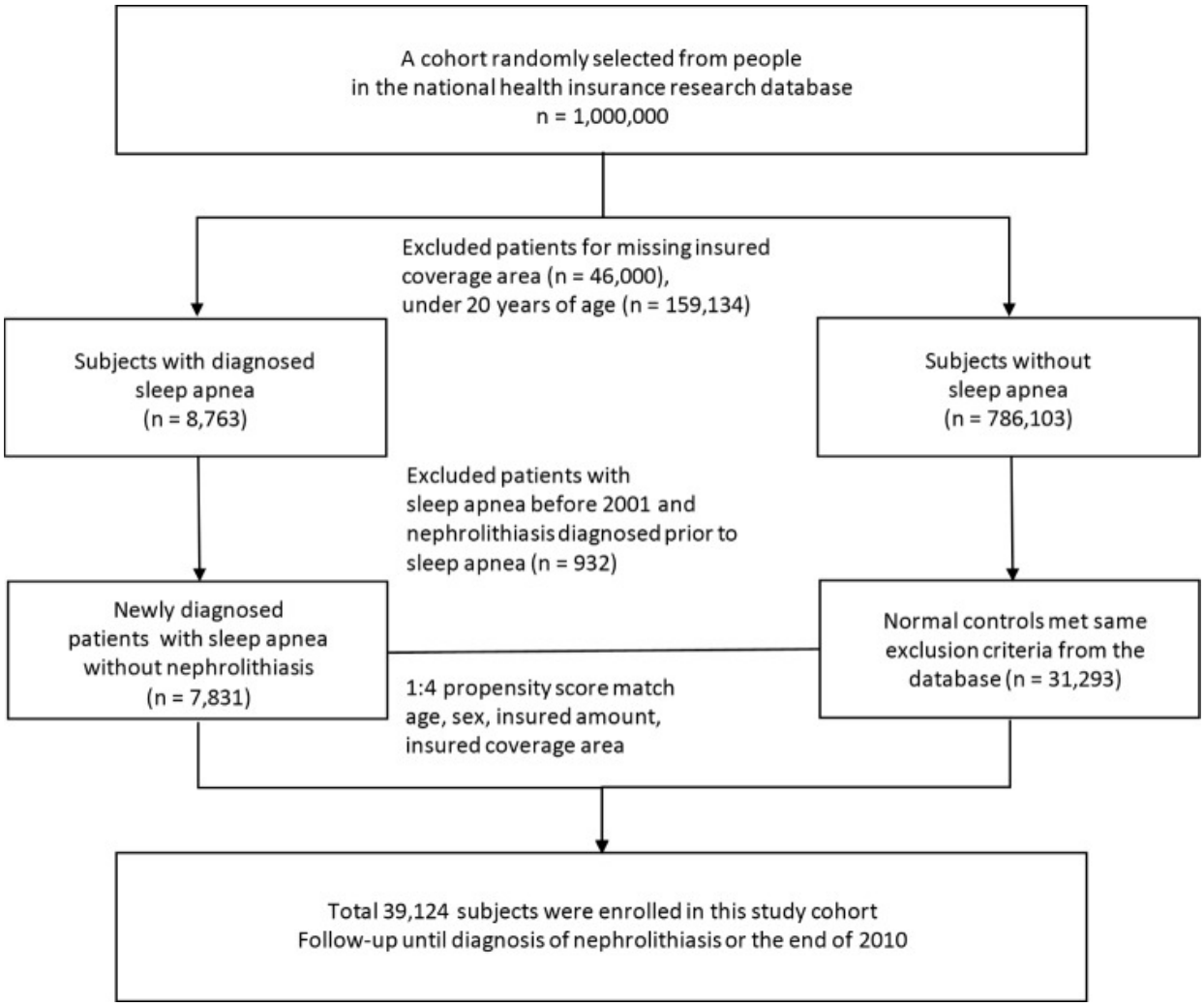
Figures and Tables

Figure 1



Flow chart of selection of the study population.

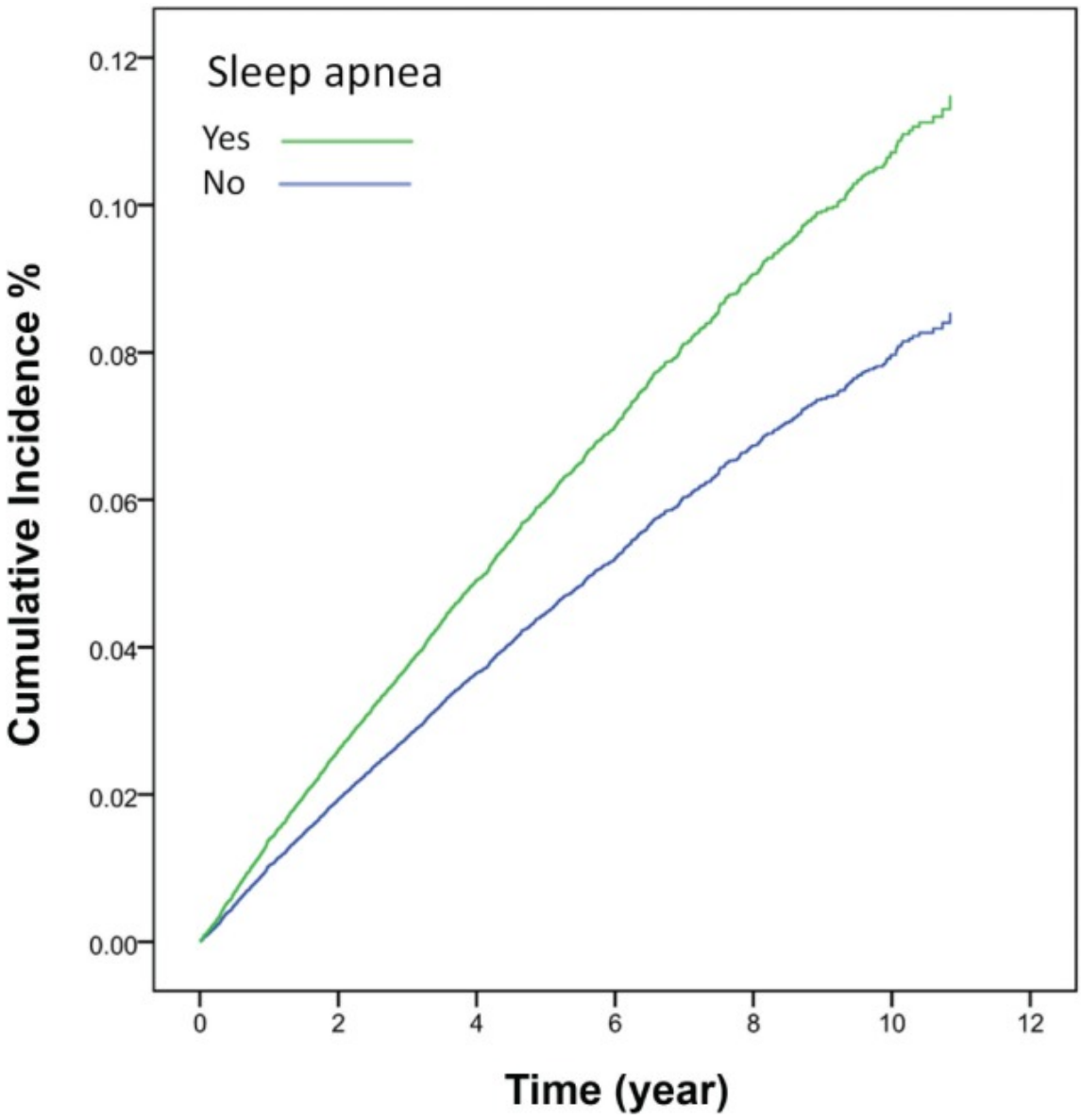
Table 1

Comparisons in demographic characteristics in patients with and without sleep apnea (n = 39,124)

	Without Sleep Apnea (n = 31,293)	With Sleep Apnea (n = 7,831)	*P*
Nephrolithiasis			
No	29,570 (94.5)	7,131 (91.1)	< .001
Yes	1,723 (5.5)	700 (8.9)	
Sex			.96
Male	19,424 (62)	4,863 (62)	
Female	11,869 (38)	2,968 (38)	
Age (years)			> .99
20–39	13,387 (42.8)	3,349 (42.8)	
40–59	13,076 (41.8)	3,274 (41.8)	
≥ 60	4,830 (15.4)	1,208 (15.4)	
Age (years) mean (SD)	43.3 (15.1)		
Follow-up time (years) mean (SD)	5.8 (2.6)	5.6 (2.6)	< .001
Comorbidity			
Hypertension	10,096 (32.3)	3,742 (47.8)	< .001
Coronary artery disease	5,351 (17.1)	2,450 (31.3)	< .001
Stroke	3,425 (10.9)	1,444 (18.4)	< .001
Diabetes mellitus	525 (17.7)	2,107 (26.9)	< .001
Hyperlipidemia	5014 (16.0)	2,251 (28.7)	< .001
Gouty arthritis	3,058 (9.8)	1,184 (15.1)	< .001
Renal failure	1,239 (4.0)	451 (5.8)	< .001
Urinary tract infection	8,416 (26.9)	2,922 (37.3)	< .001
Obesity	426 (1.4)	506 (6.5)	< .001

Values are presented as n (%) unless otherwise indicated. SD = standard deviation.

Figure 2



Cumulative incidence of nephrolithiasis in sleep apnea cohort and controls.

Green line = sleep apnea cohort and blue line = controls. Log-rank test: $P < .001$.

Table 2

Incidence rate and hazard ratio of nephrolithiasis development in patients with sleep apnea and controls by demographic characteristics and comorbidity

	Without Sleep Apnea			With Sleep Apnea				
	Stone Event	Person-Year	Incidence Rate † (95% CI)	Stone Event	Person-Year	Incidence Rate † (95% CI)	Crude HR (95% CI)	Adjusted HR ‡ (95% CI)
All	1,723	180,590	0.95 (0.91–1.00)	700	44,044	1.59 (1.47–1.71)	1.66 (1.52–1.82)***	1.35 (1.23–1.48)***
Sex								
Male	1,258	110,768	1.14 (1.07–1.20)	504	26,947	1.87 (1.71–2.04)	1.64 (1.48–1.82)***	1.22 (1.09–1.36)***
Female	465	69,822	0.66 (0.61–0.73)	196	17,095	1.14 (0.99–1.31)	1.71 (1.45–2.03)***	1.10 (0.92–1.31)
Age (years)								
20–39	564	74,350	0.76 (0.70–0.82)	260	18,120	1.43 (1.27–1.62)	1.89 (1.63–2.19)***	1.28 (1.09–1.49)**
40–59	878	76,203	1.15 (1.08–1.23)	355	18,476	1.92 (1.73–2.13)	1.66 (1.47–1.88)***	1.17 (1.03–1.34)*
> 60	281	30,037	0.94 (0.83–1.04)	85	7,448	1.14 (0.92–1.40)	1.22 (0.96–1.55)	1.01 (0.78–1.30)
Comorbidity §								
No	160	77,097	0.21 (0.18–0.24)	23	10,129	0.23 (0.15–0.33)	1.11 (0.72–1.72)	1.12 (0.73–1.74)
Yes	1,563	103,493	1.51 (1.44–1.59)	677	33,915	2.00 (1.85–2.15)	1.32 (1.20–1.44)***	1.26 (1.15–1.38)***

Asterisks indicate statistical significance: * = $P < .05$; ** = $P < .01$; *** = $P < .001$. Symbols indicate: † = incidence rate per 100 person-years; ‡ = multivariate analysis included age, sex, and comorbidities; § = patients with any one of the comorbidities including hypertension, coronary artery disease, stroke, diabetes, hyperlipidemia, gouty arthritis, renal failure, urinary tract infection, and obesity. CI = confidence interval, HR = hazard ratio.

Table 3

Cox proportional hazard regression analysis for the risk of nephrolithiasis associated with sleep apnea and interaction of the selected comorbidities (n = 39,124)

Variables		n	Event	Adjusted HR (95% CI)	*P*
Sleep apnea	Hypertension				< .001
No	No	21,197	955	1 (referent)	
No	Yes	10,096	768	1.69 (1.52–1.88)***	
Yes	No	4,089	286	1.62 (1.42–1.85)***	
Yes	Yes	3,742	414	2.48 (2.19–2.8)***	
Sleep apnea	Coronary artery disease				< .001
No	No	25,942	1,328	1 (referent)	
No	Yes	5,351	395	1.33 (1.18–1.51)***	
Yes	No	5,381	424	1.59 (1.43–1.78)***	
Yes	Yes	2,450	276	2.12 (1.85–2.42)***	
Sleep apnea	Stroke				< .001
No	No	27,868	1,482	1 (referent)	
No	Yes	3,425	241	1.17 (1.01–1.35)*	
Yes	No	6,387	547	1.67 (1.51–1.84)***	
Yes	Yes	1,444	153	1.80 (1.52–2.14)***	
Sleep apnea	Diabetes mellitus				< .001
No	No	25,768	1,303	1 (referent)	
No	Yes	5,525	420	1.42 (1.27–1.60)**	
Yes	No	5,724	470	1.69 (1.52–1.88)***	
Yes	Yes	2,107	230	2.06 (1.78–2.37)***	
Sleep apnea	Hyperlipidemia				< .001
No	No	26,279	1,289	1 (referent)	
No	Yes	5,014	434	1.72 (1.54–1.92)***	
Yes	No	5,580	440	1.67 (1.49–1.86)***	
Yes	Yes	2,251	260	2.31 (2.02–2.65)***	
Sleep apnea	Obesity				< .001
No	No	30,867	1,693	1 (referent)	
No	Yes	426	30	1.43 (1.00–2.05)	
Yes	No	7,325	636	1.62 (1.48–1.78)***	
Yes	Yes	506	64	2.40 (1.87–3.08)***	
Sleep apnea	Gouty arthritis				< .001
No	No	28,235	1,430	1 (referent)	
No	Yes	3,058	293	1.70 (1.49–1.93)***	
Yes	No	6,647	528	1.62 (1.46–1.79)***	
Yes	Yes	1,184	172	2.64 (2.25–3.09)***	
Sleep apnea	Renal failure				.059
No	No	30,054	1,618	1 (referent)	
No	Yes	1,239	105	1.37 (1.12–1.67)**	
Yes	No	7,380	657	1.70 (1.55–1.86)***	
Yes	Yes	451	43	1.54 (1.14–2.09)**	
Sleep apnea	Urinary tract infection				< .001
No	No	22,877	998	1 (referent)	
No	Yes	8,416	725	2.52 (2.28–2.79)***	
Yes	No	4,909	340	1.60 (1.41–1.81)***	

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