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Association between obstructive sleep apnea and deep vein thrombosis / pulmonary embolism: A population-based retrospective cohort study

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is a major contributor to cardiovascular disease, and may cause severe morbidity and mortality. Recent studies have indicated that OSA patients exhibited elevated platelet activity, fibrinogen levels, and platelet aggregation.
Objectives: We investigated the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients diagnosed with OSA compared with age- and sex-matched unaffected people.
Patients/Methods: This longitudinal, nationwide, population-based cohort study was conducted using data from Taiwan National Health Insurance Research Database (NHIRD) recorded between January 2000 and December 2011. The study consisted of 3511 patients with OSA and 35110 matched comparison individuals. A Cox proportional hazard regression was used to compute the risk of DVT and PE in patients with OSA compared with those without OSA.
Results: The DVT and PE risks were 3.50- and 3.97-fold higher (95% CI = 1.83–6.69 and 1.85–8.51) respectively, in the OSA cohort than in the reference cohort after we adjusted for age, sex, and comorbidities.
Conclusion: This nationwide population-based cohort study indicates that patients with OSA exhibit a higher risk of subsequent DVT and PE.

Introduction

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing characterized by repetitive episodes of partial or complete upper airway closure with apnea, hypopnea, and intermittent hypoxia. This disorder affects 24% of men and 9% of women in the middle-aged population in the United States [1]. Because of the potentially large economic burden of OSA, OSA comorbidities are focus of numerous researchers. OSA is a major contributor to cardiovascular disease, and may cause severe morbidity and mortality [2,3]. In addition, increasing evidence has indicated that OSA patients exhibit a high risk of other comorbidities, such as depressive disorders, type 2 diabetes mellitus, and motor-vehicle accidents [4–6].

Recent evidence has indicated that OSA patients exhibited elevated platelet activity, fibrinogen levels, plasminogen activator inhibitor-1 levels, erythrocyte adhesiveness, and aggregation [7–9]. All of these conditions may cause OSA patients to develop a hypercoagulopathy status and predispose them to venous thromboembolism (VTE), which consist of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Many previous studies exploring the link between OSA and VTE have been observational or case-controlled [10–14]. However, according to our research, data regarding the longitudinal frequency of PE and DVT development in OSA patients are scant, creating difficulty in generalizing the study results. Thus, we conducted this nationwide population-based study by using data derived from the Taiwan National

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Health Insurance Research Database (NHIRD) to investigate whether OSA increases the subsequent risk of subsequent DVT and PE.

Methods and Materials

Data Source

This retrospective cohort study used data from the Longitudinal Health Insurance Database (LHID), which is a subset of the NHIRD established by the Bureau of National Health Insurance (NHI), The NHIRD covered over 99% of the population of Taiwan (http://www.nhi.gov.tw/). One million insurants were randomly selected from the 2000 registry in the LHID. These data represent all medical claims and insurant information documented from 1996 to 2011. To protect personal information, the identities of insurants were encrypted. This study was approved by the Institutional Review Board of China Medical University Hospital. Diseases were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study Participants

We included 6788 patients with OSA (ICD-9-CM 780.51, 780.53, and 780.57) between 2000 and 2011 in the study, and the date of OSA diagnosis was defined as the index date. Patients with a history of other sleep disorders (ICD-9-CM 307.4 and 780.50, 780.52, 780.54 − 780.56 and 780.58 − 780.59), DVT (ICD-9-CM 453.8), or PE (ICD-9-CM 415.1) were excluded. Comparisons were selected from the population of people with no a history of OSA, DVT, or PE documented in the LHID, The comparison individuals were randomly assigned an index date and were frequency-matched with the OSA patients according to age (5-y stratum) and sex in a 10:1 ratio. All of the participants were followed from the index date to the date of the outcome or the end of 2011.

Baseline Comorbidity

The baseline history of comorbidity for each participants was identified, including hypertension (ICD-9-CM 401-405), atrial fibrillation (AF, ICD-9-CM 427.31), hyperlipidemia (ICD-9-CM 272), diabetes (ICD-9-CM 250), cerebral vascular disease (CVD, ICD-9-CM 430-438), heart failure (ICD-9-CM 428), malignancy (ICD-9-CM 140-208), and lower-leg fracture or surgery (ICD-9-CM 820, 821, and 823 or ICD-9 operation code: 81.51 − 81.54). Malignancy was defined based on the data from the Registry for Catastrophic Illness Patient Database. In Taiwan, patients with malignancies can applied for catastrophic illness certificates, and these malignancies are verified according to histological test results or radiology reports.

Statistical Analysis

All statistical analyses were conducted using SAS Version 9.3 (SAS Institute, Cary, NC), and significance was determined using 2-tailed tests in which the significance level was set at $P < .05$. The chi-square and *t*-tests were used to determine the distributions of categorical and continuous variables. The incidence of PE and DVT (per 10000 person-y) in the 2 cohorts was calculated. The hazard ratios (HRs) and 95% confidence intervals (CIs) of the OSA cohort compared with the comparison cohort were determined using Cox proportional hazard regression. The multivariable model was controlled for age, sex, and comorbidity, and significant differences are shown in Table 1 and the crude Cox proportional HR regression. The risks of DVT and PE were estimated. Based on the number of developed PEs and DVTs, the follow-up duration was stratified into the first 2 years and subsequent 10 years to assess the risks of DVT and PE. Kaplan-Meier analysis was used to plot the cumulative incidence, and a log-rank test was used to determine the differences between the 2 cohorts. The chi-square test, Fisher's exact test, and *t* test were used to identify the characteristics of study subjects with and without VTE.

Results

Baseline Characteristics

We examined 3511 patients with OSA and 35 110 sex- and age-matched comparison individuals in this study. The mean age was 42.4 years (standard deviation = 16.9), and the OSA cohort predominately consisted of men (74.5% vs 25.5%). The OSA patients exhibited a higher prevalence of comorbidity than did the comparison individuals, and the 3 most common comorbidities were hypertension (29.7% vs 16.4%), hyperlipidemia (23.5% vs 11.9%), and diabetes (9.88% vs 6.72%) (Table 1).

Table 1
Demographics between study subjects with and without OSA.

	OSA (N = 3511)		Comparison (N = 35110)		p-value
	n	%	n	%	
Age, years,					0.99
<25	498	14.2	4980	14.2	
25-44	1478	42.1	14780	42.1	
45-64	1204	34.3	12040	34.3	
≥65	331	9.43	3310	9.43	
Mean (SD)†	42.4	(16.9)	42.3	(17.0)	0.66
Sex					0.99
Women	896	25.5	8960	25.5	
Men	2615	74.5	26150	74.5	
Comorbidity					
CVD	108	3.08	611	1.74	<0.0001
AF	34	0.97	132	0.38	<0.0001
Heart failure	108	3.08	380	1.08	<0.0001
Malignancy	84	2.39	476	1.36	<0.0001
Hypertension	1042	29.7	5773	16.4	<0.0001
Hyperlipidemia	824	23.5	4192	11.9	<0.0001
Diabetes	347	9.88	2360	6.72	<0.0001
Lower leg fracture or surgery	72	2.05	530	1.51	0.01

Chi-square test and †t-test.
SD, standard deviation.

Table 2
The risks of DVT and PE in crude and multivariable Cox proportional hazard regression.

	Case no	IR	HR (95% CI) Crude[#]	Adjusted
DVT[1]				
Comparison	30	1.96	1.00 (Ref.)	1.00 (Ref.)
OSA	15	8.62	4.16 (2.23-7.73)***	3.50 (1.83-6.69)***
PE[2]				
Comparison	21	1.37	1.00 (Ref.)	1.00 (Ref.)
OSA	11	6.31	4.60 (2.22-9.56)***	3.97 (1.85-8.51)***

IR, incidence, per 10000 person-years.
* p < 0.05, ** p < 0.01, *** p < 0.001.
[#] Adjusted for age and sex.
[1] Adjusted for age, sex and comorbidity included hypertension, diabetes, hyperlipidemia, heart failure, malignancy, and AF.
[2] Adjusted for age, sex and comorbidity included hypertension, diabetes, hyperlipidemia, heart failure, malignancy, AF, and CVD.

Incidence and Risk of Deep Vein Thrombosis

The incidence of DVT was higher in the OSA cohort than in the comparison cohort (8.62 vs 1.96 per 10000 person-y), and the risk was 3.50 (95% CI = 1.83–6.69) after we controlled for age, sex, hypertension, diabetes, hyperlipidemia, heart failure, malignancy, and AF (Table 2). After a 12-year follow-up, the cumulative incidence in the OSA cohort was approximately 0.8% higher than the comparison cohort (log-rank $P < .0001$) (Fig. 1A). Regardless of the presence or absence of comorbidity, the OSA patients exhibited a higher risk than that did the comparison individuals. In an analysis stratified according to the follow-up duration, the risk was 4.94- and 3.05-fold higher in the OSA cohort than in the comparison cohort during the first 2 years and subsequent 10 years, respectively (95% CI = 1.44–17.0 and 1.42–6.52, respectively) (Table 3).

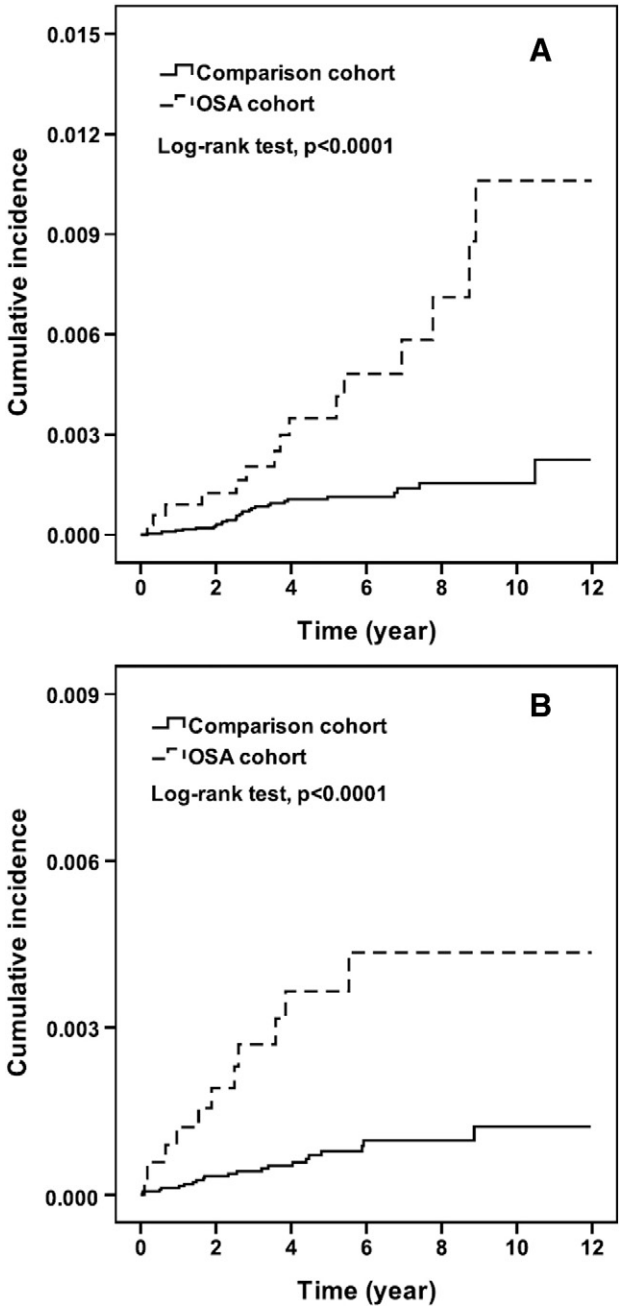

Fig. 1. Cumulative incidences of DVT or PE between the OSA and the comparison cohorts. (A) DVT, (B) PE.

Table 3
The risks of DVT and PE stratified by follow-up years in multivariable Cox proportional hazard regression.

Follow-up years	DVT				HR (95% CI)[1]	PE				HR (95% CI)[2]
	OSA		Comparison			OSA		Comparison		
	Case no	IR	Case no	IR		Case no	IR	Case no	IR	
≤2	4	6.44	8	1.33	4.94 (1.44-17.0)*	6	9.66	10	1.67	4.70 (1.63-13.5)**
>2	11	9.82	22	2.36	3.05 (1.42-6.52)**	5	4.46	11	1.18	3.24 (1.07-9.83)*

IR, incidence, per 10 000 person-years.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
[1] Manual adjusted for age, sex and comorbidity included hypertension, diabetes, hyperlipidemia, heart failure, malignancy, and AF.
[2] Manual adjusted for age, sex and comorbidity included hypertension, diabetes, hyperlipidemia, heart failure, malignancy, AF, and CVD.

Incidence and Risk of Pulmonary Embolism

During the study period, the OSA patients exhibited a higher incidence of PE than the comparisons individuals did (6.31 vs. 1.37 per 10000 person-y) as well as a higher risk (HR = 3.97, 95% CI = 1.85–8.51) after we controlled for age, sex, hypertension, diabetes, hyperlipidemia, heart failure, malignancy, AF, and CVD (Table 2). The cumulative incidence in the OSA cohort was approximately 0.3% higher than that in the comparison cohort after a 12-year follow-up (Fig. 1B). In the analysis stratified according to the follow-up duration, the OSA patients exhibited a significantly higher risk than did the comparison individuals (Table 3).

Characteristics of Study Subjects with and without Venous Thromboembolism

In this study, 70 subjects were diagnosed with VTE and 38 551 subjects did not have VTE. The prevalence of OSA was significantly higher in the subjects with VTE than in the subjects without VTE (30% vs 9.1%). The mean age of the subjects with VTE was significantly higher than that of subjects without VTE (59.9 years vs 42.3 years). The VTE patients exhibited a higher prevalence of comorbidity than the individuals without VTE did, and the 3 most common comorbidities were hypertension (50.0% vs 17.6%), hyperlipidemia (31.4% vs 13.0%), and diabetes (22.9% vs 6.98) (Table 4).

Discussion

In this large follow-up study, we observed that patients with OSA were 3.50-fold and 3.97-fold more likely to develop DVT and PE than the comparison individuals. The risk was slightly higher during the first 2 years, but increased throughout the study period.

Although the patients with OSA in this study exhibited a higher prevalence of comorbidities associated with developing DVT and PE than did the comparison individuals, OSA remained an independent risk factor after we adjusted for covariates. Numerous previous studies exploring the association between OSA and VTE have been cross sectional or case controlled [10–14]. The authors of a retrospective study consisting of 840 participants with PE determined the prevalence of OSA to be 15.5%, which appears to be higher than that of the general population [14]. However, the main limitations of these observational studies were the small sample sizes and lack of prospective control groups. A case-control study examining 164 participants conducted by Arzt et al suggested that the prevalence of sleep-disordered breathing (primarily OSA) was significantly higher among people with DVT or PE than among those without DVT or PE [13]. Alonso-Fernandez et al recently evaluated the relationship between OSA and PE by using a case-control study, determining that the prevalence of OSA was higher in patients with acute PE than in controls, and the odds ratio for PE was 3.7 [12]. However, in a case-control study, obtaining reliable information regarding exposure status over time is difficult. In a previous cohort study, the authors excluded patients younger than 40 years

Table 4
Characteristics of study subjects with and without VTE.

	VTE (N = 70)		Non-VTE (N = 38551)		p-value
	n	%	n	%	
OSA	21	30.0	3490	9.05	<0.0001
Age, years					<0.0001
<25	0	0.00	5478	14.2	
25-44	11	15.7	16247	42.1	
45-64	30	42.9	13214	34.3	
≥65	29	41.4	3612	9.37	
Mean (SD)†	59.9	(14.9)	42.3	(16.9)	<0.0001
Sex					0.050
Women	45	64.3	28720	74.5	
Men	25	35.7	9831	25.5	
Comorbidity					
CVD#	4	5.71	715	1.85	0.04
AF#	2	2.86	164	0.43	0.04
Heart failure	7	10.0	481	1.25	<0.0001
Malignancy	5	7.14	555	1.44	<0.0001
Hypertension	35	50.0	6780	17.6	<0.0001
Hyperlipidemia	22	31.4	4994	13.0	<0.0001
Diabetes	16	22.9	2691	6.98	<0.0001
Lower leg fracture or surgery#	0	0.00	602	1.56	0.63

Chi-square test # Fisher's exact test and †*t*-test.
SD, standard deviation.

because the prevalence of OSA was low in this age group [15]. We examined OSA patients aged less than 25 years and those aged 25 to 44 years, and observed that the risk of VTE is increased in OSA patients (HR = 3.50, 95% CI = 1.83–6.69 for DVT and HR = 3.97, 95% CI = 1.85–8.51 for PE). The differences in incidence may be explained by the finding of a previous study that indicated that the prevalence of OSA tends to increases with age, whereas the severity of apnea decreases with age [16]. Therefore, the association between OSA and DVT and PE in the younger populations might be stronger than that in older populations.

The specific underlying mechanisms explaining the association between OSA and VTE remain unclear. The pathogenesis of VTE is associated with 3 mechanisms, namely vascular endothelial injury, stagnant blood flow, and a hypercoagulable blood state (Virchow's triad). We speculate that OSA leads to the development of VTE through all 3 mechanisms. Similar to VTE, OSA is associated with a sedentary lifestyle and physical inactivity, which can result in venous stasis and thrombosis [17,18]. Recurrent episodes of hypoxia and reoxygenation in OSA can increase the production of reactive oxygen species or inflammatory mediators, thus reducing nitric oxide availability and impairing vascular endothelial function [19–22]. Although data are inconsistent, various endothelial injury markers, such as P-selectin, the intercellular adhesion molecule, C-reactive protein, and the vascular cell-adhesion molecule-1, are associated with impaired endothelial function in OSA [21,23]. Furthermore, previous studies have reported that OSA patients exhibit elevated platelet activity, fibrinogen levels, plasminogen activator inhibitor-1 levels, erythrocyte adhesiveness, and aggregation, but reduced fibrinolytic capacity [7–9,24]. All of these factors may contribute to the hypercoagulable state of OSA patients.

In this study, we determined the incidence of DVT and PE in the comparison groups to be 1.96 and 1.37 per 10 000 person-years, respectively; these values are similar to those reported by a previous study that examined the Taiwanese population [25]. These values are also consistent with a study indicating that the incidence of VTE is lower among Asians than among Europeans [26]. In addition, our data suggest that both old age and comorbidities were associated with VTE, and this finding is consistent with those of previous studies [25,27].

The strength of this study is that it was a nationwide population-based longitudinal cohort study on the subsequent risk of DVT and PE in Asian people with OSA. However, it has several limitations that should be considered. First, because the definitions of each disease were based on ICD-9-CM codes, we could not determine the location of DVT. Second, data on the severity of OSA are not provided in the NHIRD; therefore, we could not determine whether the severity of OSA is positively associated with the risks of VTE. Third, the NHI program does not cover continuous positive airway pressure (CPAP), which is the primary treatment for OSA; therefore, this information is unavailable in the NHIRD. Studies have indicated that CPAP treatment may reduce platelet activation, the risk of thrombosis, oxidative stress, and endothelial function in OSA patients [22,28–30]. Finally, detailed information on the daily lives of the patients, such as data on cigarette smoking, alcohol consumption, family history, and body mass index, is not available in the NHIRD. Although some studies have reported that obesity is strongly associated with both OSA and VTE, other studies have indicated that most Asian patients with OSA are not obese [31–33]. Moreover, for the same degree of OSA severity, Caucasians are more obese than Asians, whereas Asians exhibit more craniofacial bone restriction [34,35]. Therefore, we speculate that the influence of obesity on both OSA and VTE in our population might not be as strong as it is in Caucasian populations. Despite these limitations, the data regarding the relationship between OSA and DVT and PE is highly reliable because of the validity of the database, large sample size, and long follow-up period.

In summary, this nationwide study revealed that OSA patients have 3.50-fold and 3.97-fold increased risks of developing DVT and PE, respectively, compared with the general population. Future studies can include the OSA severity index, health-risk behaviors, and OSA treatment in analyses to clarify the association between OSA and DVT and PE.

These authors' individual contributions are identified as follows.

Conception and design: Y. H. Peng, W. C. Liao, C. H. Kao

Administrative support: C. H. Muo, C. H. Kao

Collection and assembly of data: All authors

Data analysis and interpretation: Y. H. Peng, W. C. Liao, C. H. Muo, C. H. Kao

Manuscript writing: All authors

Final approval of manuscript: All authors

Critical writing or revising the intellectual content: C. H. Kao

Conflict of Interest Statement

The authors have no actual or potential conflicts of interest concerning the publication of this paper.

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