Original Article

Sleep disorders increase risk of subsequent erectile dysfunction in individuals without sleep apnea: a nationwide population-base cohort study

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ABSTRACT

Background: Sleep disorders (SD) and erectile dysfunction (ED) both play crucial roles in quality of life and have received increasing attention in the general population and among physicians.
Methods: This study investigated the risk of ED in people diagnosed with SD compared with that in age- and sex-matched unaffected people. This longitudinal, nationwide, population-based cohort study was conducted using data in the Taiwan National Health Insurance Research Database (NHIRD) from January 1998 to December 2011. The sample consisted of 603 people with sleep apnea, 17,182 people with non-apnea SD, and 35,570 matched comparisons as controls. A Cox proportional hazard regression was used to compute the risk of ED in people with SD relative to that in people without SD.
Results: The ED incidences were 9.44-fold higher (95% CI 6.49–13.7) in the sleep apnea cohort and 3.72-fold higher (95% CI 3.13–4.41) in the non-apnea SD cohort than in the control cohort, respectively, after age, sex, and comorbidities were adjusted for. The incidence of ED was higher in younger adults (adjusted hazard ratio (HR), 10.4 (95% CI 5.93–18.4) in the sleep apnea cohort and adjusted HR, 4.20 (95% CI 3.07–5.76) in non-apnea SD cohort) and those using benzodiazepine (adjusted HR, 9.69 (95% CI 5.48–10.6) in the sleep apnea cohort and adjusted HR, 3.83 (95% CI 3.20–4.59) in the non-apnea SD cohort).
Conclusion: This nationwide population-based cohort study provides evidence that people with SD, particularly those with sleep apnea, exhibit an increased risk of subsequent ED.

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1. Introduction

Erectile dysfunction (ED) is the inability to achieve or maintain a sufficient penile erection during sexual activity. The prevalence of erectile dysfunction (ED) in the general population has increased [1]. This may be because: people with ED have the courage to seek medical help; people, in general, have a longer life span; of the advancement in diagnostic tools and treatments; or there is an increased prevalence of possible etiologies. Several risk factors are associated with ED, including: hypertension, diabetes mellitus, obesity, dyslipidemia, cardiovascular disease, smoking, medication use, sleep disorders, and emotional problems [2–5]. According to the International Classification of Sleep Disorders (ICSD-3) (American Academy of Sleep Medicine [AASM], 2014), sleep disorders (SDs) are divided into seven broad categories, namely: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep disorders, parasomnias, sleep-related movement disorders, and other sleep disorders; insomnia is the most common. Increasingly more diseases have been found to correlate with SD, including: cardiovascular disease, stroke, hypertension, cognitive impairment, headache, and ED [6–12].

Sleep disorders and ED both play crucial roles in quality of life and have received increasing attention in the general population and among physicians. Therefore, a longitudinal nationwide population-based cohort study was conducted to investigate whether SDs increase the subsequent risk of ED.

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2. Methods

2.1. Data source

The data were accessed from the Taiwan National Health Insurance Research Database (NHIRD). The National Health Insurance (NHI) program, which was initiated in 1995, covers approximately 99% of the 23.74 million residents in Taiwan, and 97% of Taiwan clinics are enrolled in the NHI system [13,14]. The Bureau of NHI possesses registration and claims data on one million insurants systematically selected from all residents in Taiwan. The NHIRD comprises many registration records, including details on inpatient, outpatient, ambulatory and inpatient care, and contains registration files that have been published in previous studies [15,16]. Diagnoses were coded by physician specialists according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The accuracy and high validity of diagnoses in the NHIRD have been demonstrated [17,18]. To protect the privacy of all persons registered in the program, the NHRI encrypts and converts the identification numbers of all NHIRD records before releasing them for researchers. Thus, the institutional research ethics committee fully reviewed and approved the present study (CMU-REC-101-012).

2.2. Participants

People who were diagnosed with SD between 1998 and 2001 and >20 years of age were distributed into two case cohorts: a sleep apnea cohort (ICD-9-CM codes 780.51, 780.53, and 780.57) and a non-apnea SD cohort (ICD-9-CM codes 307.4 and 780.5, excluding 780.51, 780.53, and 780.57). Non-apnea SD was divided into insomnia (ICD-9-CM code 780.52), sleep disturbance (ICD-9-CM codes 780.5, excluding 780.51, 780.53, and 780.57), and others (ICD-9-CM codes 307.4, 780.50, 780.54–780.56, and 780.58–780.59). The date of the first visit, during which a person was diagnosed with an SD, was defined as the index date. People with a history of SD before the index date, or for whom age or sex information was incomplete, were excluded. A control cohort of people without SD was randomly selected from the NHI beneficiaries and frequency matched with the SD cohort at a 2:1 ratio according to age (in 5-year increments), sex, and year of SD diagnosis. All three cohorts were followed until: an initial diagnosis of ED (ICD-9-CM code 607.84); loss to follow-up; death; withdrawal from the NHI; or December 31, 2011. The following diagnoses were recorded to establish the baseline comorbidity history for each participant: hypertension (ICD-9-CM codes 401–405); diabetes (ICD-9-CM code 250); hyperlipidemia (ICD-9-CM code 272); chronic kidney disease (CKD) (ICD-9-CM codes 580–589); coronary artery disease (CAD) (ICD-9-CM codes 410–414); stroke (ICD-9-CM codes 430–438); chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 490–496); cancer (ICD-9-CM codes 140–208); depression (ICD-9-CM codes 296.2, 296.3, 300.4, and 311); and anxiety (ICD-9-CM code 300.00). A medical history of benzodiazepine and zolpidem use was included in the analysis.

2.3. Statistical analysis

The demographic characteristics and clinical characteristics of the SD (sleep apnea and non-apnea SD) and comparison cohorts, including age (20–39 years, 40–64 years, and ≥65 years), comorbidities, and medical treatments, were compared using the Chi-squared test. For continuous variables, the *t* test was used to compare the SD and comparison cohorts. The incidence rate (per 1000 person-years) of follow-up for each cohort was also computed. A Poisson regression model was applied to measure the incidence rate ratios (IRRs) with 95% CIs for ED of the sleep apnea and non-apnea SD cohorts compared with that of the control cohort.

Hazard ratios (HRs) and 95% CIs were estimated using multivariable Cox proportional hazard models. The multivariable models were simultaneously adjusted for demographic characteristics, comorbidities, and a medical history of benzodiazepine and zolpidem use. The cumulative incidence of ED was calculated using the Kaplan–Meier method. Statistical significance was evaluated using the log-rank test. All analyses were conducted using SAS statistical software (Version 9.2 for Windows; SAS Institute, Inc., Cary, NC, USA), with statistical significance set at $p < 0.05$ for a two-tailed test.

3. Results

Between 1998 and 2001, a total of 17,785 people were newly diagnosed with SD (603 in the sleep apnea cohort, and 17,182 in the non-apnea cohort) (Table 1). The mean age of the SD cohort was 53.9 years and the control cohort was 53.8 years; nearly 75% of the participants were aged <65 years. The participants with sleep apnea were six years younger than those with non-apnea SD (54.1 years vs 48.2 years). The participants in the SD cohort were more likely to have hypertension, diabetes, hyperlipidemia, CKD, CAD, stroke, COPD, cancer, depression, anxiety, and a medical history of benzodiazepine and zolpidem use than those in the control cohort ($p < 0.001$). The participants with non-apnea SD were more likely to have comorbidities (excluding hyperlipidemia and COPD) and use benzodiazepine and zolpidem than those with sleep apnea.

The overall incidence density of ED was significantly higher in the sleep apnea cohort than in the control cohort (73.6 vs 10.1 per 1000 person-years) (Table 2). The overall incidence rate of ED was 7.45-fold higher in the sleep apnea cohort than in the control cohort, with an adjusted HR of 9.44 (95% CI 6.49–13.7). The incidence of ED was 3.05-fold higher in the non-apnea SD cohort than in the control cohort (30.6 vs 10.1 per 1000 person-years), with an adjusted HR of 3.72 (95% CI 3.13–4.41). An age-specific analysis revealed a 4.2-fold significantly higher risk of developing ED in the participants in the non-apnea SD cohort aged <40 years compared with those in the control cohort (95% CI 25.6–5.52). A higher risk of ED was observed in the participants in the sleep apnea cohort aged <40 years than in those in the control cohort (adjusted HR 10.4, 95% CI 5.93–18.4). Participants with SD and comorbidities demonstrated a higher risk of developing ED than those in the control cohort without comorbidities (adjusted HR in the sleep apnea cohort 13.1, 95% CI 7.31–23.3; adjusted HR in the non-apnea SD cohort 3.61, 95% CI 2.78–4.67). The participants with SD who used benzodiazepine and zolpidem exhibited a significantly higher risk of developing ED than those in the control cohort (sleep apnea cohort: adjusted HR of those using benzodiazepine 9.69, 95% CI 6.56–14.3, adjusted HR of those using zolpidem 12.1, 95% CI 5.17–28.5; non-apnea SD cohort: adjusted HR of those using benzodiazepine 3.83, 95% CI 3.20–4.59, adjusted HR of those using zolpidem 5.08, 95% CI 2.74–9.39).

Compared with the control participants, those with sleep apnea exhibited a significantly higher risk of developing ED (adjusted HR 7.86, 95% CI 5.66–10.9) (Table 3). In the non-apnea SD cohort, participants with non-apnea SD exhibited the highest risk of developing ED (adjusted HR 3.69, 95% CI 2.83–4.82), followed by those with sleep disturbance (adjusted HR 3.51, 95% CI 2.90–4.25). Fig. 1 shows that the cumulative incidence of ED was higher in the sleep apnea cohort than in the other two cohorts (log rank, $p < 0.001$) by the end of follow-up.

4. Discussion

In this longitudinal population-based cohort study, it was observed that participants with SD had an increased risk of developing ED during a 13-year follow-up period. Those with sleep apnea and those with non-apnea SD had 9.44-fold and 3.72-fold increased risks

Table 1
Comparison of demographics and comorbidity between people with SD and controls.

	Sleep disorder						Control (N = 35,570)		p
	Sleep apnea (N = 603)		Non-apnea sleep disorder (N = 43,844)		Total (N = 17,785)				
	n	%	n	%	n	%	n	%	
Age, years									0.99
≤39	363	60.2	7420	43.2	7783	43.8	15,566	43.8	
40–64	143	23.7	4325	25.2	4468	25.1	5534	31.1	
>64	97	16.1	5437	31.6	5534	31.1	11,068	31.1	
Mean (SD)[#]	48.2	14.4	54.1	16.6	53.9	16.5	53.8	16.6	0.21
Comorbidity									
Diabetes	41	6.80	1392	8.10	1433	8.06	1725	4.85	<0.001
Hypertension	239	39.6	7336	42.7	7575	42.6	8633	24.3	<0.001
Hyperlipidemia	158	26.2	3362	19.6	3520	19.8	3298	9.27	<0.001
CKD	52	8.62	1825	10.6	1877	10.6	1754	4.93	<0.001
CAD	138	22.9	4003	23.3	4141	23.3	3576	10.1	<0.001
Stroke	20	3.32	913	5.31	933	5.25	1163	3.27	<0.001
COPD	244	40.5	6859	39.9	7103	39.9	7554	21.2	<0.001
Cancer	8	1.33	441	2.57	449	2.52	588	1.65	<0.001
Anxiety	25	4.15	825	4.80	850	4.78	162	0.46	<0.001
Depression	39	6.47	1130	6.58	1169	6.57	148	0.42	<0.001
Treatment									
Benzodiazepine	556	92.2	16,745	97.5	17,301	97.3	23,911	67.2	<0.001
Zolpidem	326	54.1	10,858	63.2	11,184	62.9	3400	9.56	<0.001

Chi-squared test compared to total SD; [#]t-test.
Diseases in this study were identified using codes from the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). They were: sleep apnea disorder (780.51, 780.53 and 780.57); erectile dysfunction (ICD-9-CM 607.84); non-apnea sleep disorder (non-apnea SD) including patients with unspecified insomnia (ICD-9-CM codes 780.52), sleep disturbance (ICD-9-CM codes 780.5), and others (ICD-9-CM codes 307.4, 780.50, 780.54–780.56, 780.58–780.59); diabetes (ICD-9-CM 250); hypertension (ICD-9-CM 401–405); hyperlipidemia (ICD-9-CM 272); chronic kidney disease (CKD) (ICD-9-CM 585); coronary artery disease (CAD) (ICD-9-CM 410–414); stroke (ICD-9-CM 430–438); chronic obstructive pulmonary disease (COPD) (ICD-9-CM 490–496); cancer (ICD-9-CM 140–208); anxiety (ICD-9-CM 300.00); and depression (ICD-9-CM 296.2–296.3, 300.4).

of developing ED, respectively, compared with the general population after adjustment for age, sex, and comorbidities. Some previous studies have explored the association between SD and ED, particularly apnea SD [4,5]. Younger adults (≤39 years) and people with SD and COPD using benzodiazepine also appeared to be at higher risk. The highest incidence of ED was associated with sleep apnea, followed by non-apnea SD. Therefore, it is suggested that sleep apnea and non-apnea SD increase the risk of developing ED.

In 2002, Seftel et al. observed that the urology patients reported a variety of sleep problems, but neither persistent snoring nor suspected obstructive sleep apnea syndrome was uniquely correlated to ED [4]. Four years later, Teloken et al. demonstrated that men presenting with symptoms consistent with sleep apnea had a significant risk of ED, and that the correlation between the severity of sleep apnea and the severity of ED was strong [19]. Furthermore, Budweiser et al. confirmed by polysomnography that

Table 2
Comparisons of incidence densities and hazard ratio of erectile dysfunction in study cohorts.

	Control		Sleep apnea		Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)	Non-apnea sleep disorder		Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)
	Case	Rate[a]	Case	Rate[a]			Case	Rate[a]		
All	324	10.1	43	73.6	7.45 (5.42, 10.2)***	9.44 (6.49, 13.7)***	480	30.6	3.05 (2.65, 3.51)***	3.72 (3.13, 4.41)***
Age										
≤39	85	5.52	22	60.8	11.5 (7.20, 18.4)***	10.4 (5.93, 18.4)***	189	25.6	4.69 (3.63, 6.06)***	4.20 (3.07, 5.76)***
40–64	139	16.3	16	116.3	7.35 (4.38, 12.3)***	7.77 (4.13, 14.6)***	183	45.3	2.81 (2.25, 3.50)***	3.67 (2.80, 4.81)***
>64	100	12.3	5	58.8	5.02 (2.04, 12.3)***	9.33 (3.45, 25.2)***	108	25.3	2.07 (1.58, 2.72)***	3.49 (2.51, 4.85)***
Comorbidity[d]										
No	133	6.65	13	68.6	10.5 (5.96, 18.6)***	13.1 (7.31, 23.3)***	105	21.3	3.23 (2.50, 4.17)***	3.61 (2.78, 4.67)***
Yes	191	15.9	30	76.0	4.94 (3.36, 7.26)***	4.97 (3.34, 7.38)***	375	34.9	2.22 (1.87, 2.64)***	2.18 (1.83, 2.60)***
Treatment										
Benzodiazepine										
No	100	9.30	1	21.1	2.34 (0.33, 16.7)	2.79 (0.38, 20.3)	8	18.4	2.00 (0.97, 4.10)	2.35 (1.13, 4.88)*
Yes	324	10.5	42	78.2	7.62 (5.48, 10.6)***	9.69 (6.56, 14.3)***	472	30.9	2.97 (2.53, 3.48)***	3.83 (3.20, 4.59)***
Zolpidem										
No	313	10.7	24	91.2	8.74 (5.77, 13.3)***	8.67 (5.61, 13.4)***	249	44.9	4.18 (3.54, 4.94)***	3.47 (2.89, 4.17)***
Yes	11	3.84	19	59.1	15.0 (7.12, 31.5)***	12.1 (5.17, 28.5)***	231	22.8	5.87 (3.21, 10.7)***	5.08 (2.74, 9.39)***

[a] Rate, incidence rate per 1000 person-years.
[b] Crude HR, relative hazard ratio per 10,000 person-years.
[c] Adjusted HR, multivariable analysis including age, sex, co-morbidities of diabetes, hypertension, hyperlipidemia, CKD, CAD, stroke, COPD, cancer, anxiety and depression and medication of benzodiazepine and zolpidem.
[d] Comorbidity: classified as the comorbidity group if has one comorbidity or more (including diabetes, hypertension, hyperlipidemia, CKD, CAD, stroke, COPD, cancer, anxiety and depression).
* p < 0.05.
*** p < 0.001.

Table 3
Comparisons of incidence, and hazard ratios of erectile dysfunction by subtypes of sleep disorders.

Variables	N	Event	Rate[a]	Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)
No sleep disorder	35,570	324	10.1	1 (Reference)	1 (Reference)
Sleep apnea	603	43	73.6	7.42 (5.40, 10.2)***	7.86 (5.66, 10.9)***
Non-apnea sleep disorder					
Insomnia	7032	186	29.8	3.00 (2.51, 3.59)***	3.46 (2.82, 4.25)***
Sleep disturbance	7439	217	30.8	3.03 (2.55, 3.59)***	3.51 (2.90, 4.25)***
Others	2711	77	32.0	3.22 (2.51, 4.13)***	3.69 (2.83, 4.82)***

ICD-9-CM: sleep apnea: 780.51, 780.53 and 780.57; insomnia: 780.52; sleep disturbance: 780.5 (excluded 780.51, 780.53 and 780.57); others: 307.4, 780.50, 780.54–780.56, 780.58–780.59.

[a] Rate, incidence rate per 1000 person-years.
[b] Crude HR, relative hazard ratio.
[c] Adjusted HR, multivariable analysis including age, sex, comorbidities of diabetes, hypertension, hyperlipidemia, CKD, CAD, stroke, COPD, cancer, anxiety and depression and medication of benzodiazepine and zolpidem.
*** $p < 0.001$.

obstructive sleep apnea is an independent risk factor of ED [20]. Treatment with continuous positive airway pressure may improve or preserve sexual function [21]. The present results indicate that the incidence of ED was higher in the sleep apnea cohort than in the control cohort after age and comorbidities were controlled for; these results are consistent with those of previous studies.

It is believed that, to date, few studies have examined the correlation between non-apnea SD and ED. Most studies that have discussed the correlation between SD and ED have not excluded sleep apnea and obstructive sleep apnea groups. The proposed mechanisms include: decreased levels of luteinizing hormone and testosterone; increased sympathetic activity; peripheral nerve dysfunction, which is related to nocturnal hypoxia; decreased NO levels; and increased production of endothelin [22]. In the present study, it was observed that the non-apnea SD cohort had a 3.05-fold increased risk of developing ED compared with the control cohort after age and comorbidities were controlled for. The age-specific analysis revealed a 4.2-fold higher risk of developing ED in people <40 years of age in the non-apnea SD cohort compared with those in the control cohort. These results suggest that non-apnea SD is a considerable factor in diagnosing or treating ED, particularly in young people.

The possible mechanisms through which non-apnea SD increases the risk of ED are unclear. Involuntary sleep-related erections occur naturally during REM sleep. This may be a clue. The hypothalamus is an import area for controlling sleep cycles and the primary regulatory center for the autonomic nervous system. The parasympathetic nervous system is active during REM sleep and releases both Ach and NO, which are considered to play an essential role in cavernosal vasodilatation. Sleep deprivation may induce sympathetic overactivity, which possibly affects the antagonistic functions of the sympathetic and parasympathetic nervous systems [23]. Another finding is that benzodiazepine use, which reduces REM sleep, increases the risk of ED. Testosterone cannot be ignored as a possible mechanism. The normal diurnal rhythm of testosterone may be disturbed by fragmented sleep, and the testosterone level peaks near the transition from NREM to REM sleep [24–26]. The parvocellular neurons of the hypothalamus secrete hypophysiotropic hormones, which control the release of corresponding pituitary hormones through the portal vascular network. The hypothalamus is the common pathway of the neural and endocrine systems. These proposed mechanisms require evidence from further study.

In conclusion, both sleep apnea and non-apnea SDs increase the risk of ED, independent of age and comorbidities, and may share certain aspects of common mechanisms such as the autonomic system and testosterone.

The strength of this study was its use of population-based data, which are highly representative of the general population. However, the study also had limitations. First, the NHIRD does not contain detailed information on smoking habits, body mass index, dietary preference, occupational exposure, reproductive history, and socioeconomic status, all of which are potential risk factors for ED. Second, evidence derived from a retrospective cohort study is generally of lower statistical quality than that from randomized trials because of potential biases related to adjustment for confounding variables. Although this study design was meticulous and included control for confounding factors, bias resulting from unknown confounders could have affected the results. Third, all data in the NHIRD are anonymous; therefore, relevant clinical variables such as serum laboratory data, polysomnography, and imaging and pathology results were unavailable.

Taiwan launched the NHI program in 1995, and a single payer – the government – operates this program. Medical reimbursement specialists and peer reviewers scrutinize all insurance claims. The diagnoses of SD and ED were based on ICD-9-CM codes and were determined by relevant specialists and physicians, according to
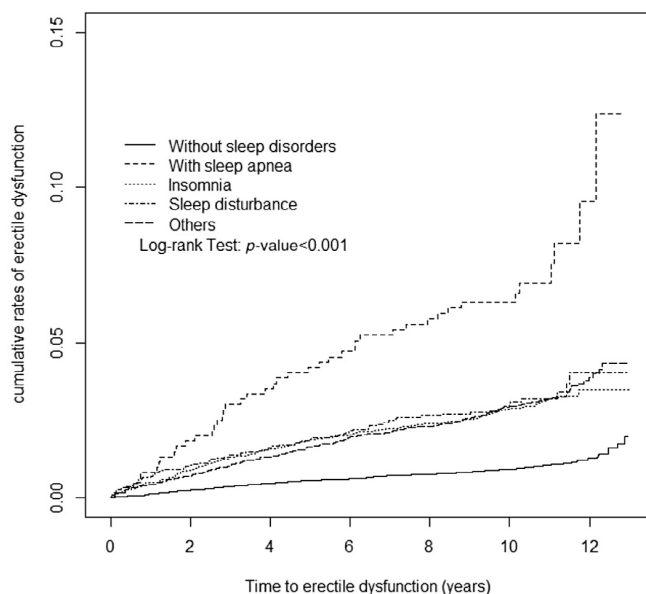

Fig. 1. Kaplan–Meier method determined cumulative incidence of erectile dysfunction compared between sleep disorder cohorts and controls without sleep disorders.

standard clinical criteria. The data on the diagnoses of SD and ED can thus be considered reliable.

Authorship contributions

The authors' individual contributions were as follows: conception and design – all authors; administrative support – Chia-Hung Kao; collection and assembly of data – all authors; data analysis and interpretation – all authors; manuscript writing – all authors; final approval of manuscript – all authors.

Conflict of interest

This paper is associated with no actual or potential conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.05.018.

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