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Original Article

Sleep disorders in individuals without sleep apnea increase the risk of peripheral arterial disorder: a nationwide population-based retrospective cohort study

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ABSTRACT

Study objectives: Previous literature lacks the analysis of non-apnea sleep disorder (NASD) and peripheral arterial disease (PAD). The aim of this study was to evaluate the association between NASD and risk of developing PAD using retrospective data from a national database in Taiwan.
Design, setting, and participants: We identified 46,064 patients with NASD using the catastrophic illness registry of the Taiwan National Health Insurance Research Database (NHIRD) from 1996 to 2010. We also selected a comparison cohort of 92,128 subjects who were randomly frequency-matched by age, sex, and entry year of the NASD cohort from the same database.
Interventions: non-apnea sleep disorders.
Main outcome and measurements: The study followed up all subjects from their entry date to the occurrence of PAD. We evaluated the risks of PAD using Cox proportional hazards regression models. The survival function for PAD was assessed using the Kaplan–Meier method.
Results: The risk of PAD was 1.49-fold in patients with NASD compared with patients without NASD after adjusting for age, sex, and comorbidities. Patients with NASD and diabetes or with NASD and hyperlipidemia had an increased risk of PAD compared to those without NASD and diabetes or hyperlipidemia.
Conclusions: We demonstrated the significantly increased risk of PAD in NASD patients through a nationwide population-based retrospective cohort study.

1. Introduction

Peripheral arterial disorder (PAD) is an arterial disease that leads to blood flow obstruction, arterial lumen narrowing, or stenosis [1]. The prevalence of PAD is 1.8–25% in the general population. Related risk factors include age, sex, diabetes mellitus, hypertension, hyperlipidemia, metabolic syndrome, and smoking [2,3]. PAD is usually underdiagnosed and undertreated as most patients with PAD are symptom free [4]. It is also related to some biomarkers, including C-reactive protein (CRP), beta 2-macroglobulin, cystatin C, lipoprotein, and homocysteine [1,3–7]. Patients with renal disease and diabetes mellitus are more likely to have PAD [5]. In addition, patients with symptomatic extremity PAD develop intermittentclaudication, chronic limb ischemia, or acute limb

Abbreviations: NASD, Non-apnea sleep disorder; PAD, Peripheral arterial disease; NHIRD, National Health Insurance Research Database; NHI, National Health Insurance; NHRI, National Health Research Institute.

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ischemia, and these patients often need revascularization, surgical bypass, or amputation during the later stages [6]. PAD not only influences the quality of life of the patient but is also associated with increasing mortality and morbidities of developing coronary arterial disease (CAD) and cerebrovascular disease [3–6].

We spend >30% of our life sleeping. Sleep problems are a common complaint in the general population. Insomnia is a sleep disorder defined as having a difficulty falling asleep, staying asleep, waking early in the morning, or experiencing non-restorative sleep [8]. Insomnia is the most noted in Western countries with a prevalence of 27–37% [9–11], 22.8% in Korea [12], and 25% in Taiwan [13]. Our study investigates the influence of sleep disorders upon and the pathogenesis of cardiovascular diseases and the progression of heart and vessel diseases.

In a recent cross-sectional study, Utriainen et al. indicated that the prevalence of obstructive sleep apnea (OSA) is common in patients with PAD [14]. Nachtmann et al. showed that OSA may contribute to the development of PAD [15]. However, the discussion about sleep disorders and PAD is scarce. Taiwan established its National Health Insurance (NHI) program in 1995, which, using the data available from this program, offers a unique opportunity for research. In the present study, we used a 13-year nationwide population-based dataset to determine the association between NASD and PAD.

2. Methods and materials

2.1. Data source

Our retrospective cohort study used the reimbursement data acquired for the period from 1996 to 2010 from the NHI system in Taiwan. The NHI program includes the complete medical information of >23.74 million Taiwanese residents, with a coverage rate of >99% [16]. For the purpose of research, the Taiwan National Health Research Institute (NHRI) manages and releases the National Health Insurance Research Database (NHIRD) on an annual basis. The identification numbers of patients have been scrambled to protect the privacy of insured residents before releasing the data. The data used in this study are from a sub-dataset of the NHIRD. The data comprise one million randomly sampled beneficiaries enrolled in the NHI program, which collected all records on these individuals from 1996 to 2010. Disease diagnoses were identified and coded using the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM). This study was exempted from ethical review (institutional review board (IRB) permit number: China Medical University (CMU)-REC-101-012).

2.2. Sampled participants

Based on the NHI database, subjects with sleep disorders other than sleep apnea (SA) (ICD-9-CM codes 307.4 and 780.5) newly diagnosed between January 1998 and December 2001 were included in the non-apnea sleep disorder (NASD) cohort. The first date of NASD diagnosis was defined as the entry date. We excluded patients who had SA syndrome (ICD-9-CM codes 780.51, 780.53, and 780.57) and patients with a history of PAD (ICD-9-CM codes 440.2, 443.81, 443.9, 444.2, and 444.89) before the entry date. The sample size of the comparison cohort was twice the size of the NASD cohort with similar age and gender frequency. We selected insured residents without a history of sleep disorders, SA, and PAD for the comparison cohort.

2.3. Outcome and relevant variables

Both the NASD and the comparison cohort were followed up until the end of 2010 to estimate the incident cases with the diagnosis of PAD. The diagnosis of PAD began with physical examination, and then it was confirmed by image study that included ultrasound, computed tomographic angiography, or angiography. To compare the effects of different types of NASD on PAD incidence, we further classified NASD into insomnia (ICD-9-CM: 780.52), sleep disturbance (ICD-9-CM: 780.5, 780.50, 780.54–780.56, 780.58–780.59), and other sleep disorders (ICD-9-CM: 307.4) according to the standardized classification of International Classification of Sleep Disorders, version 2, published in 2005 and the varied nature and diagnostic steps of these disorders [17]. In addition, variables also relevant to PAD were age, gender, and comorbidities, such as hypertension (ICD 401–405), diabetes (ICD-9-CM codes 250), hyperlipidemia (ICD-9-CM codes 272), CAD (ICD-9-CM code 410–414), stroke (ICD-9-CM codes 430–438), heart failure (ICD-9 code 428), anxiety (ICD-9 code 300.00), and depression (ICD-9 code 296.2, 296.3, 300.4, 311). All comorbidities were confirmed and validated with at least three medical visits.

2.4. Statistical analysis

The chi-squared test and *t*-test were used to, respectively, evaluate the distributions of discrete and continuous variables between the NASD cohort and the comparison cohort. The incidence densities of PAD were calculated by sex, age, and comorbidity for each cohort. Our study used univariable and multivariable Cox proportional hazard regression models to assess the risk of PAD in the NASD cohort compared to comparison cohort. We included baseline characteristic variables such as age, gender, and comorbidities in the multivariate model for adjustment. We estimated the hazard ratio (HR) and 95% confidence interval (CI) in the Cox model. We used multiplicative analysis to evaluate the interaction effect of NASD and comorbidities on PAD risk. To assess the difference in the PAD-free rates between the two cohorts, we applied the Kaplan–Meier analysis and the log-rank test. We performed all statistical analyses using Statistical Analysis System (SAS) 9.2 (SAS Institute Inc., Cary, NC, USA), with $P < 0.05$ in two-tailed tests considered to be significant.

3. Results

Females represented the majority of the study cohorts (63.6%); half of subjects were >50 years old (Table 1). Compared to the comparison cohort, the NASD cohort had a higher prevalence of common comorbidities, including hypertension, diabetes, hyperlipidemia, CAD,

Table 1
Comparisons in demographic characteristics and comorbidities in patients with and without non-apnea sleep disorders (NASDs).

	Sleep disorders		*p*-value
	No	Yes	
	(*N* = 92128)	(*N* = 46064)	
Gender			
Women	58,608 (63.6)	29,304 (63.6)	0.99
Men	33,520 (36.4)	16,760 (36.4)	
Age, mean ± SD[a]	52.0 ± 16.4	52.2 ± 16.3	
≤49	43,704 (47.4)	21,852 (47.4)	0.99
50–64	24,762 (26.9)	12,381 (26.9)	
65 +	23,662 (25.7)	11,831 (25.7)	
Comorbidity			
Hypertension	22,685 (24.6)	17,970 (39.0)	<0.0001
Diabetes	5223 (5.67)	3946 (8.57)	<0.0001
Hyperlipidemia	10,040 (10.9)	9354 (20.3)	<0.0001
CAD	9504 (10.3)	9836 (21.4)	<0.0001
Stroke	2384 (2.59)	1723 (3.74)	<0.0001
Heart failure	1315 (1.43)	1111 (2.41)	<0.0001
Anxiety	706 (0.77)	2550 (5.54)	<0.0001
Depression	730 (0.79)	3102 (6.73)	<0.0001

Chi-squared test, [a]*t*-test.