

# Sleep apnea and the subsequent risk of Parkinson's disease: a 3-year nationwide population-based study

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**Purpose:** Sleep apnea (SA)-induced chronic intermittent hypoxia increases oxidative stress and inflammation, which may contribute to the pathophysiology of Parkinson's disease (PD). This study evaluated the risk of PD following SA diagnosis.

**Patients and methods:** This was a 3-year nationwide population-based matched cohort study using claims data from the National Health Insurance Research Database (NHIRD), Taiwan. We analyzed 1,944 patients diagnosed as having SA between 1997 and 2005 and a matched cohort of 9,720 non-SA patients from the NHIRD. Patients with a history of PD were excluded. Each patient was followed up for 3 years to evaluate subsequent PD development.

**Results:** Of the 11,664 patients, 17 (0.9%) and 38 (0.4%) from the SA and matched non-SA cohorts, respectively, were subsequently diagnosed as having PD during follow-up. After adjustments for potential confounders, the SA cohort had a 1.85-fold higher risk of PD than the non-SA cohort (95% confidence interval [CI] =1.02–3.35;  $P=0.042$ ). After age and sex stratification, PD development was independently associated with SA only in men (adjusted hazard ratio [HR], 2.26; 95% CI =1.11–4.63;  $P<0.05$ ) and in patients aged  $\geq 60$  years (adjusted HR, 1.93; 95% CI =1.01–3.71;  $P<0.05$ ).

**Conclusion:** Our study suggests that patients with SA are at an increased longitudinal risk of PD. Furthermore, age and male sex are independently associated with the risk of PD.

**Keywords:** cohort study, intermittent hypoxia, National Health Insurance Research Database, population-based study

## Introduction

Parkinson's disease (PD) is characterized by bradykinesia, tremors, rigidity, and postural instability. A meta-analysis of global data demonstrated an increasing prevalence of PD with age,<sup>1</sup> and a higher prevalence of PD was observed in the Chinese male population.<sup>2</sup> In addition to age and sex, other potential risk factors for PD, including a family history of PD,<sup>3</sup> depression,<sup>4</sup> constipation,<sup>5</sup> and sleep disorders requiring zolpidem,<sup>6</sup> have been reported in epidemiological studies.

The prevalence of sleep disorders in PD is 40%–90%.<sup>7</sup> Sleep disorders negatively affect cognitive functions and quality of life in patients with PD. Insomnia, daytime sleepiness with sleep attacks, restless legs syndrome, and rapid eye movement sleep behavior disorder are the most frequent sleep disorders associated with PD.<sup>8</sup> Furthermore, snoring was observed in up to 70% of patients with PD,<sup>9</sup> and 14.5%–60% of patients with PD were estimated to have an apnea–hypopnea index of  $>15$ .<sup>10</sup> Therefore, a close association between sleep-disordered breathing and PD can be considered.

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Sleep apnea (SA), one of the most common forms of sleep-disordered breathing, is characterized by repeated periods of hypoxia and reoxygenation during sleep. SA may be mild, moderate, or severe, based on the number of apneas and hypopneas occurring per hour.<sup>11</sup> The clinical significance of SA in PD has been discussed but remains controversial.<sup>12,13</sup> SA-induced chronic intermittent hypoxia increases oxidative stress and inflammation,<sup>14</sup> which are involved in PD pathophysiology.<sup>15</sup> Experimental data have demonstrated the role of oxidative stress in  $\alpha$ -synuclein aggregation and dopaminergic cell death.<sup>16</sup> Therefore, SA-induced oxidative stress and inflammation may increase the risk of PD.

The present study investigated the hypothesis that patients with SA are at an increased risk of PD. A nationwide, population-based study was conducted to assess the relationship between SA and subsequent diagnosis of PD within a 3-year follow-up period. In addition, we attempted to determine whether SA is an age- and sex-dependent risk factor for PD.

## Materials and methods

### Data source

This retrospective cohort study was conducted using claims data from the National Health Insurance Research Database (NHIRD), Taiwan. The National Health Insurance (NHI) program, which was implemented on March 1, 1995, has reimbursed the health care costs of 99.9% of Taiwan's population as of 2014. The NHI program provides comprehensive health care information, including demographic data of the insured, clinical visit dates, diagnostic codes, and prescription details. Under the NHI program, the National Health Research Institutes (NHRI) established the NHIRD, subsequently managing and auditing it. Several studies using NHIRD data have been published in peer-reviewed journals.

In the present study, data were obtained from the Longitudinal Health Insurance Database (LHID) 2005, a subset of the NHIRD. The LHID 2005 dataset contains historical ambulatory data and inpatient care data for 1 million randomly sampled beneficiaries who enrolled in the NHI program in 2005. Currently, the LHID 2005 allows researchers to explore the medical service utilization data of these 1 million patients during 1996–2012. The NHRI claims that there are no statistically significant differences in the data on age, sex, geographic region, and health care costs from the LHID 2005 and all claims data.

This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital, Taiwan (KMUHIRB-EXEMPT[II]-20160001). All personal

information was eliminated from the secondary database prior to analyses. Therefore, the review board waived the requirement of obtaining written informed consent from the study patients.

### Participants

We retrospectively examined the SA and matched non-SA cohorts to investigate the relationship between SA and the risk of PD. The SA cohort included patients aged  $\geq 40$  years and diagnosed as having SA (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 780.51, 780.53, 780.57, and 327.23) between January 1, 1997, and December 31, 2005, during inpatient or outpatient care. Patients with a history of SA before January 1, 1997, were excluded from the present study. SA diagnosis was defined according to validated definitions from previous studies.<sup>17,18</sup> The date of initial SA diagnosis for each study patient was considered the index date.

The matched non-SA cohort comprised five non-SA patients who were matched to each patient with SA based on age, sex, and index year, and randomly selected from the remaining population in the same database. Patients who were diagnosed as having SA during follow-up were excluded from the present study. Furthermore, patients with a history of PD (ICD-9-CM 332) before enrollment were excluded from the SA and non-SA cohorts. The study patients were individually followed for 3 years from their index date to evaluate PD development.

We identified several comorbidities before the index date as potential confounding factors for PD, including hypertension (ICD-9-CM 401–405), diabetes mellitus (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), concussion and head trauma (ICD-9-CM 310.2, 852, and 853), COPD (ICD-9-CM 496), and asthma (ICD-9-CM 493).

### Main outcome measures

The outcome of interest was defined as receiving a diagnosis of PD after the index date. PD diagnosis was defined as receiving any outpatient or inpatient care for PD (ICD-9-CM 332). A validation study reported that this definition had favorable diagnostic accuracy.<sup>19</sup> To avoid the misdiagnosis of secondary parkinsonism as idiopathic PD, patients diagnosed as having carbon monoxide intoxication (ICD-9-CM 986), major psychiatric diseases (ICD-9-CM 291, 292, 293.0, 293.1, 293.81, 293.82, and 295–299), and dementia (ICD-9-CM 290.11, 290.12, 290.20, 290.3, 290.41, 290.42, 290.8, 290.9, 294.11, and 294.21) before the index date and during follow-up were excluded from the present study.

## Statistical analyses

A Pearson chi-squared test was performed to evaluate the differences in the categorical variables, including urbanization level, monthly income, geographic region, and comorbidities, of the SA and non-SA cohorts. A Kaplan–Meier survival test was performed to estimate PD-free survival rates in the SA and non-SA cohorts, and a log-rank test was used to analyze the differences between the survival curves. Cox proportional hazards regression analysis was conducted to examine the crude and adjusted hazard ratios (HRs) for PD in the SA cohort, compared to the non-SA cohort during the 3-year follow-up period, after adjustments for sex, age, urbanization level, geographic region, monthly income, hypertension, hyperlipidemia, diabetes mellitus, asthma, COPD, and head injury. Furthermore, an age- and sex-stratified analysis using the Cox proportional hazards regression model was conducted to evaluate the risk of PD in the SA cohort across different age groups and sex. A two-sided  $P < 0.05$  was considered statistically significant.

## Results

A total of 1,944 and 9,720 patients were included in the SA and non-SA cohorts, respectively. Of the 11,664 patients, 42.6%, 30.2%, and 27.1% belonged to the 40–49, 50–59, and  $\geq 60$  years of age groups, respectively; 63.1% of all patients were men. After adjustments for sex, age, and index year, the SA cohort was more likely to reside in urbanized communities and had a higher monthly income than the non-SA cohort. In addition, the SA cohort tended to have more comorbidities, such as hypertension, hyperlipidemia, diabetes mellitus, asthma, COPD, and head injury, than the non-SA cohort. Table 1 presents the demographic data and comorbidities of the SA and non-SA cohorts.

Of the 11,664 patients, 55 (0.5%) patients received a diagnosis of PD during the 3-year follow-up period; 17 (0.9%) and 38 (0.4%) patients in the SA and non-SA cohorts, respectively, developed PD (Table 2). Cox proportional hazards regression analysis demonstrated that the crude HR for PD was 2.25 times higher (95% confidence interval [CI] = 1.27–3.98;  $P < 0.01$ ) in the SA cohort than in the non-SA cohort. The risk of PD remained significant after adjustments for potential confounders, including sex, age, urbanization level, geographic region, monthly income, hypertension, hyperlipidemia, diabetes mellitus, asthma, COPD, and head injury (adjusted HR, 1.85; 95% CI = 1.02–3.35;  $P = 0.042$ ). Kaplan–Meier analysis demonstrated that the SA cohort had a significantly lower 3-year PD-free survival rate than the non-SA cohort (log-rank  $P < 0.01$ ; Figure 1).

**Table 1** Demographic characteristics of the study patients stratified based on the presence or absence of sleep apnea between 1997 and 2005 (n=11,664)

	Patients with sleep apnea (n=1,944)		Patients without sleep apnea (n=9,720)		P-value
	n	(%)	n	(%)	
Gender					
Male	1,226	63.1	6,130	63.1	
Female	718	36.9	3,590	36.9	
Age (years)					
40–49	829	42.6	4,145	42.6	
50–59	588	30.2	2,940	30.2	
$\geq 60$	527	27.1	2,635	27.1	
Hypertension					<0.001
Yes	1,321	68.0	5,104	52.5	
No	623	32.0	4,616	47.5	
Hyperlipidemia					<0.001
Yes	1,205	62.0	4,284	44.1	
No	739	38.0	5,436	55.9	
Diabetes					<0.001
Yes	830	42.7	2,916	30.0	
No	1,114	57.3	6,804	70.0	
Asthma					<0.001
Yes	577	29.7	1,782	18.3	
No	1,367	70.3	7,938	81.7	
COPD					<0.001
Yes	377	19.4	978	10.1	
No	1,567	80.6	8,742	89.9	
Head injury					0.006
Yes	63	3.2	214	2.2	
No	1,881	96.8	9,506	97.8	

**Abbreviation:** COPD, chronic obstructive pulmonary disease.

Table 3 presents the risk for PD between SA and non-SA cohorts after sex stratification. Men with SA had a significantly higher risk of PD than those without SA before (HR, 2.97; 95% CI = 1.50–5.90;  $P < 0.01$ ) and after (adjusted HR, 2.26; 95% CI = 1.11–4.63;  $P < 0.05$ ) adjustments for potential confounders. In contrast, women did not exhibit a significantly increased risk of PD in the SA cohort compared to those in the non-SA cohort during the 3-year follow-up period (adjusted HR, 1.10, 95% CI = 0.36–3.40).

In addition, age stratification demonstrated that only elderly patients (age  $\geq 60$  years) in the SA cohort had a significantly higher risk of PD than those in the non-SA cohort before (HR, 2.29; 95% CI = 1.22–4.30;  $P < 0.05$ ) and after (adjusted HR, 1.93; 95% CI = 1.01–3.71;  $P < 0.05$ ) adjustments for potential confounders (Table 4).

## Discussion

Our study demonstrated an association between SA and the risk of PD using NHIRD data during a 3-year follow-up

**Table 2** Hazard ratios (HRs) for Parkinson's disease (PD) in patients with and without sleep apnea during the 3-year follow-up period

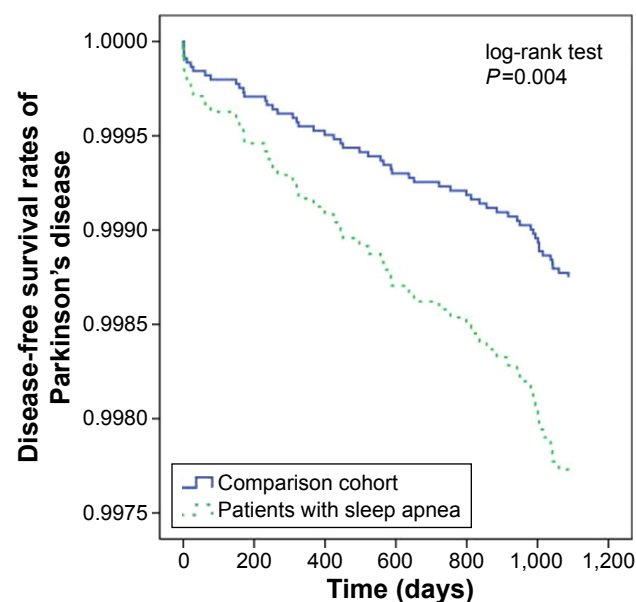
Development of PD	Total		Patients with sleep apnea		Patients without sleep apnea		P-value
	N	(%)	N	(%)	N	(%)	
3-year follow-up period							
Yes	55	0.5	17	0.9	38	0.4	
No	11,609	99.5	1,927	99.1	9,682	99.6	
Crude HR (95% CI)			2.25 (1.27–3.98)**		1		0.006
Adjusted HR (95% CI)			1.85 (1.02–3.35)*		1		0.042

**Notes:** Total sample number = 11,664. Crude and adjusted HRs were calculated by Cox proportional hazards regression analyses. Adjustments were performed for sex, age, urbanization level, geographic region, monthly income, hypertension, hyperlipidemia, diabetes mellitus, asthma, COPD, and head injury; \* $P < 0.05$ ; \*\* $P < 0.01$ .

**Abbreviations:** CI, confidence interval; COPD, chronic obstructive pulmonary disease.

period. The main study finding was that after adjustments for possible confounders, the SA cohort had a 1.85-fold higher risk of PD than the non-SA cohort. Separate analyses revealed that SA is an age- and sex-dependent risk factor for PD. Men and elderly patients (age  $\geq 60$  years) were at a particularly high risk of PD. This finding is in accordance with our hypothesis that patients with SA are at an increased longitudinal risk of PD.

Whether SA is an independent risk factor for PD or merely an early symptom during the prodromal phase of PD remains unclear. The cohort design of this study enabled the identification of a temporal association between SA and PD. To clearly demonstrate the temporal association between SA and PD, patients with a history of PD before the index date were excluded from this study. We observed that the SA cohort had an increased risk of PD, indicating that SA may be an independent risk factor for PD.



**Figure 1** Parkinson's disease-free survival rates of patients with and without sleep apnea between 1997 and 2005.

The pathophysiological mechanisms underlying the association between SA and the risk of PD remain unclear; however, several theories can be discussed. First, SA-induced chronic intermittent hypoxia can activate inflammatory pathways, leading to increased levels of systemic inflammatory markers.<sup>20–22</sup> The brains of patients with PD exhibited signs of neuroinflammatory reactions, contributing to a cascade of events and subsequent neuron death.<sup>23</sup> Furthermore, increased oxidative stress was previously reported in patients with SA.<sup>24</sup> A postmortem study indicated that oxidative stress plays an important role in the pathological processes underlying PD development.<sup>25</sup> Therefore, increased oxidative stress and inflammation due to SA may directly contribute to an increased risk of PD.

In this study, men and elderly patients (age  $\geq 60$  years) with SA were at a significantly increased risk of PD. The prevalence of severe SA is higher in adult men than in adult women.<sup>26</sup> In another study, male sex and age were also independent risk factors for severe SA in the elderly group.<sup>27</sup> Moreover, a strong correlation has been reported between SA severity and biomarkers of systemic inflammation and oxidative stress.<sup>28,29</sup> Therefore, it is reasonable to conclude that men and elderly patients have an increased risk of PD, assuming inflammation and oxidative stress play key roles in PD pathophysiology.

Furthermore, findings from brain imaging studies in patients with SA have demonstrated that SA is associated with the risk of PD. Diffusion tensor imaging studies in patients with SA revealed decreased mean diffusivity in the basal ganglia.<sup>30</sup> Magnetic resonance spectroscopy demonstrated that hypoxia-related metabolites and microstructural changes in the putamen are more pronounced with increasing SA severity.<sup>31</sup> Furthermore, decreased cerebral blood flow was reported in the right red nucleus and right midbrain of patients with SA.<sup>32</sup> These abnormal findings in the basal ganglia and midbrain of patients with SA may indicate an association between SA and the risk of PD.

**Table 3** Hazard ratios (HRs) for Parkinson's disease (PD) in patients with and without sleep apnea after sex stratification during the 3-year follow-up period

Development of PD	Sex			
	Female		Male	
	Sleep apnea	Comparison	Sleep apnea	Comparison
	N (%)	N (%)	N (%)	N (%)
Yes	4 (0.6)	16 (0.4)	13 (1.1)	22 (0.4)
Crude HR (95% CI)	1.25 (0.42–3.75)		2.97 (1.50–5.90)**	
Adjusted HR (95% CI)	1.10 (0.36–3.40)		2.26 (1.11–4.63)*	

**Notes:** Total sample number = 11,664. Crude and adjusted HRs were calculated by Cox proportional hazards regression analyses after sex stratification. Adjustments were performed for sex, age, urbanization level, geographic region, monthly income, hypertension, hyperlipidemia, diabetes mellitus, asthma, COPD, and head injury; \* $P < 0.05$ ; \*\* $P < 0.01$ .

**Abbreviations:** CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Several studies have reported that SA is associated with subsequent PD.<sup>33–35</sup> However, the present study findings were different and had stronger implications than those of previous studies. First, we used validated definitions of SA and PD<sup>17–19</sup> to maximize case ascertainment. Second, we excluded patients with several conditions that may contribute to secondary parkinsonism, such as carbon monoxide intoxication and neuropsychiatric diseases with psychotic features, to appropriately identify patients with idiopathic PD. Third, we identified and adjusted for common confounding comorbidities, including hypertension, hyperlipidemia, diabetes mellitus, asthma, COPD, and head injury, which may affect the subsequent risk of PD, to minimize their influence on PD development.

Nevertheless, the present study had some limitations. First, the diagnoses of SA and PD were completely based on the diagnostic codes recorded by physicians in the database, but information regarding these specialists was unavailable. In addition, we were unable to distinguish between primary and secondary parkinsonism. To maximize case ascertainment, we adopted validated definitions of SA and PD from previous studies.<sup>17–19</sup> Furthermore, we excluded patients who were at a possible risk of secondary parkinsonism, including those who had been diagnosed with carbon monoxide

intoxication, major psychiatric diseases, and dementia, before the index date and during follow-up to improve the diagnostic accuracy. Second, the NHIRD does not record data on the apnea–hypopnea index values, respiratory parameters, and treatment status of patients with SA. Therefore, the duration, severity, and treatment status of SA could not be determined. Third, individual patient information, including family history, environmental factors, toxin exposure, and lifestyle factors, were not available from the NHIRD. Fourth, because of the relatively short follow-up period of 3 years, it was difficult to determine whether SA occurred during the prodromal phase of PD before the onset of motor symptoms. Previous studies with longer follow-up periods have supported our findings, despite using different inclusion and exclusion criteria.<sup>33–35</sup> Fifth, the actual number of patients with SA who developed PD was small, particularly in women and young patients, thus limiting the statistical power in subgroup analysis based on age and sex. Sixth, we did not stratify SA into obstructive or central types. We assumed that most patients had obstructive SA based on the literature about patients with polysomnography-confirmed SA in Taiwan, which states that only 0.8% of patients have pure central SA.<sup>18,36</sup> Further investigation is required to elucidate whether obstructive and central SA differ in the risk of PD.

**Table 4** Hazard ratios (HRs) for Parkinson's disease (PD) in patients with and without sleep apnea after age stratification during the 3-year follow-up period

Development of PD	Age group (years)					
	40–49		50–59		≥60	
	Sleep apnea	Comparison	Sleep apnea	Comparison	Sleep apnea	Comparison
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Yes	2 (0.2)	0 (0)	1 (0.2)	7 (0.2)	14 (2.7)	31 (1.2)
Crude HR (95% CI)			0.72 (0.09–5.81)		2.29 (1.22–4.30)*	
Adjusted HR (95% CI)			0.56 (0.06–4.93)		1.93 (1.01–3.71)*	

**Notes:** Total sample number = 11,664. Crude and adjusted HRs were calculated by Cox proportional hazards regression analyses after age stratification. Adjustments were performed for sex, age, urbanization level, geographic region, monthly income, hypertension, hyperlipidemia, diabetes mellitus, asthma, COPD, and head injury; \* $P < 0.05$ .

**Abbreviations:** CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Finally, despite the temporal relationship between SA and PD, the underlying causal mechanism was not definitively confirmed in this retrospective study. PD may remain asymptomatic for many years, and SA may be regarded as an initial premotor symptom of PD. Therefore, based on our study results, we cannot obviate the possibility that SA may be an early symptom of PD. Moreover, future studies considering these indices must evaluate the association between SA and the risk of PD and investigate the longitudinal effect of treatment on continuous positive airway pressure.

## Conclusion

The present study demonstrated a possible relationship between SA and the risk of PD. The SA cohort had a higher longitudinal risk of PD than the non-SA cohort, particularly elderly people and men. Further prospective studies are warranted to evaluate the causality and underlying mechanisms of the association between SA and the risk of PD.

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## Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest in this work.

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