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Original Article

Sleep apnea and risk of aortic dissection: A nonrandomized, pair-matched cohort study

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Abstract

Background: Sleep apnea (SA) was associated with increased prevalence of aortic dissection (AD) in studies that were criticized for either their small sample size or lack of prospective observation. Using a considerably larger nationwide, population-based database and a long-term prospective cohort design, our study strived to explore the relationship between SA and the subsequent development of AD.
Methods: From 2000 to 2007, we gathered a study cohort consisting of 15,848 newly diagnosed cases of SA from Taiwan's National Health Insurance Research Database. For the control group, another 39,826 individuals without SA were matched for age, sex, and comorbidity. The two cohorts were followed-up to observe the occurrence of AD.
Results: During an average 3.59 ± 2.41 years of follow-up, we observed 33 cases of new AD occurrence [non-SA (22, 0.1%) vs. SA (11, 0.1%), $p = 0.669$], and the incidence of AD was similar for both groups. After adjusting for age, sex, and comorbidity, only age [hazard ratio (HR) 1.03; 95% confidence interval (CI), 1.01−1.06; $p = 0.006$], male gender (HR 2.49; 95% CI, 1.07−5.79; $p = 0.034$), and hypertension (HR 6.28; 95% CI, 2.36−16.67; $p < 0.001$) were independently associated with AD diagnosis.
Conclusion: SA was not associated with an increased risk of AD using a large nationwide cohort database. Nonetheless, larger prospective studies or meta-analyses are recommended to confirm our findings.

Keywords: aortic dissection; sleep apnea

1. Introduction

Sleep apnea (SA) is a common disorder characterized by cessation of breath during sleep, resulting from repetitive upper airway collapse [namely, obstructive SA (OSA)].[1] OSA affects ~24% of men and ~9% of women in the middle-aged population of the US[2] and is associated with a variety of

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cardiovascular diseases, such as hypertension, coronary artery disease, stroke, and aortic aneurysm.[3−6] Aortic dissection (AD), a catastrophic illness often presenting as acute hemodynamic compromise, shares some common risk factors with SA. Based on their study showing a high prevalence (13/19, 68%) of SA in patients with AD, Sampol and colleagues[7] recently reported SA as a possible risk factor for AD, in addition to the well-known risk factors of hypertension, male sex, and increasing age. Also, a growing body of evidence supports a tendency toward increased aortic size and aortic dissection events among patients with SA.[7−10] Although taken as indicating a possible link between OSA and AD, these studies have also been criticized for their limited sample size and lack of information from a prospective cohort.

Hypothesizing that SA may contribute independently to the development of AD, we used a nationwide database to conduct a nonrandomized, pair-matched cohort study to investigate the relationship between SA and subsequent development of AD.

2. Methods

2.1. Database

Taiwan's National Health Insurance (NHI) program, in operation since 1995, has enrolled nearly all the inhabitants of Taiwan (21,869,478 beneficiaries out of 22,520,776 inhabitants at the end of 2002).[11] The National Health Insurance Research Database (NHIRD) at the National Health Research Institutes (NHRI; http://w3.nhri.org.tw/nhird/en/index.htm) in Miaoli, Taiwan is in charge of the entire NHI claims database and publishes numerous extracted datasets for researchers. The NHRI released a cohort dataset comprised of 1,000,000 randomly sampled people who had been insured from the start of NHI to 2000, collecting all records of these individuals from 1995 onwards. The database has been confirmed by NHRI to be representative of Taiwan's population.[12] It is also one of the largest nationwide population-based databases in the world, with > 280 published scientific articles using its data.[13] In this cohort dataset, each patient's original identification number has been encrypted to protect privacy. The encrypting procedure is consistent so claims belonging to the same patient can be linked within the NHIRD datasets.

2. 2. Study sample and controls

We identified patients who were newly diagnosed with SA [International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 780.51, 780.53, and 780.57] from a 1,000,000 sampled cohort dataset going back to January 1, 2000. An age-, sex-, and comorbidity-matched control group was selected from the patients without SA throughout the study period. Patients diagnosed with AD (ICD-9-CM code 441.0) before enrollment were excluded from this study.

Comorbidity matched in the two groups included pre-existing (upon enrollment) hypertension (ICD-9-CM codes 401.xx−405.xx), diabetes mellitus (ICD-9-CM code 250.xx), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 494, 492, and 496), coronary artery disease (ICD-9-CM codes 411.xx, 413.xx, and 414.xx), ischemic stroke (ICD-9-CM codes 433.xx, 434.xx, 436, and 437.1), intracerebral hemorrhage [ICD-9-CM codes 430.xx−432.9x], chronic renal disease [ICD-9-CM codes 580.xx−587.xx], and peripheral arterial occlusive disease [ICD-9-CM code 443.9]. Both the SA cohort and the control cohort were followed-up from enrollment to the date of AD diagnosis, death, withdrawal from insurance, or until December 3, 2007; the end of the follow-up period (Fig. 1).

2.3. Main outcome

The end point of the study was defined as diagnosis with AD (ICD-9-CM code 441.0). In this database, the ICD codes for SA and AD did not change throughout the follow-up period (2001−2007), assuring the consistency of the disease registry.

2.4. Statistical analysis

A Microsoft SQL Server 2005 (Microsoft Corporation, Redmond, WA, USA) was used for data management and computing. Statistical analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). All data are expressed as mean ± standard deviation or percentage. Comparisons between the two groups were determined by independent Student t test for continuous variables, or Pearson's χ^2 test, Yates' correction for continuity/Fisher's exact test for categorical variables. We used Cox proportional hazard models to test the association between SA and AD. Survival analysis was assessed using the Kaplan−Meier method, with significance based on the log-rank test. Statistical significance was inferred as a two-sided p value < 0.05.

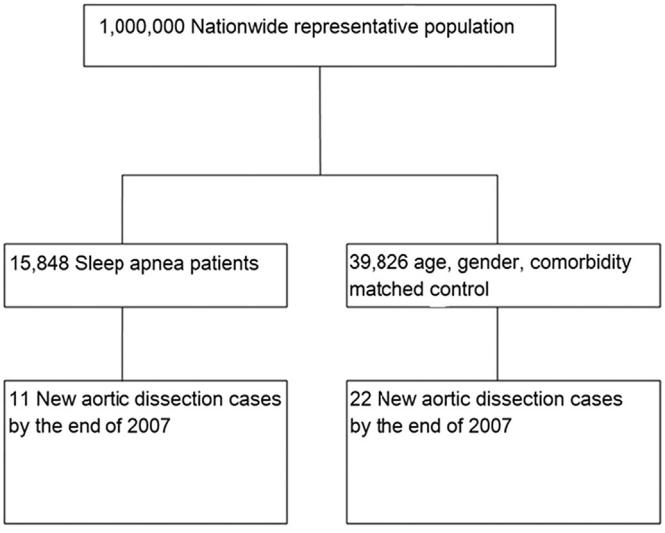

Fig. 1. Flowchart illustrating the follow-up of sleep apnea patients and matched controls.

3. Results

A total of 15,848 newly diagnosed SA patients (mean age, 44.92 ± 17.34 years) were identified from the 1,000,000 sampled cohort dataset between January 2000 and December 2007. Another 39,826 patients without SA (mean age, 44.73 ± 17.46 years) were matched for age, sex, and comorbidity to serve as the control group. The demographic parameters of the study participants are listed in Table 1.

During an average follow-up period of 3.59 ± 2.41 years, there was no significant difference in the incidence of AD among SA patients compared with the control group [11 (6.9 per 100,000 person−years) vs. 22 (5.5 per 100,000 person−-years), $p = 0.669$]. Figure 2 outlines the results of a Kaplan−Meier analysis and the log-rank test, which showed that patients with SA had no significant difference in AD incidence compared to patients without SA ($p = 0.654$). Comparison between patients with and without AD is shown in Table 2. Patients with AD were older, more likely to be male, and more likely to have hypertension, diabetes mellitus, coronary artery disease, or ischemic stroke. A Cox proportional hazard regression model was used to determine the factors independently associated with the development of AD. After adjusting for age, sex, and the above comorbidity, only age [hazard ratio (HR) 1.03; 95% confidence interval (CI), 1.01−1.06; $p = 0.006$], male sex (HR 2.49; 95% CI, 1.07−5.79; $p = 0.034$), and hypertension (HR 6.28; 95% CI, 2.36−16.67; $p < 0.001$) were independently associated with AD development. After adjusting for age, sex, and comorbidity, SA was not associated with occurrence of AD (Table 3). Analysis was performed to demonstrate the role of SA as a factor determining the risk of AD in subgroups, and SA remained insignificant (Fig. 3).

Table 1
Baseline characteristics of the study population.

	Sleep apnea		p
	No ($n = 39,826$)	Yes ($n = 15,848$)	
Age (y)	44.73 ± 17.46	44.92 ± 17.34	0.267
Male	25,407 (63.8)	10,087 (63.6)	0.753
Hypertension	11,820 (29.7)	4,660 (29.4)	0.528
Diabetes	4,536 (11.4)	1,753 (11.1)	0.276
COPD	8,587 (21.6)	3,372 (21.3)	0.468
Coronary artery disease	5,787 (14.5)	2,263 (14.3)	0.455
Ischemic stroke	1,589 (4.0)	644 (4.1)	0.707
Intracerebral hemorrhage	381 (1.0)	176 (1.1)	0.110
Chronic renal disease	1,820 (4.6)	722 (4.6)	0.961
PAOD	893 (2.2)	363 (2.3)	0.753
Antihypertensive medication			
ACEI	3,146 (7.9)	1,381 (8.7)	0.002
ARB	2,924 (7.3)	1,611 (10.2)	0.261
α Blocker	6551 (16.4)	3545 (22.4)	< 0.0001
β Blocker	6390 (16.0)	3415 (21.5)	< 0.0001
CCB	6882 (17.3)	3207 (20.2)	< 0.0001
Aortic dissection	22 (0.1)	11 (0.1)	0.669

Data are presented as n (%) or mean ± standard deviation. Student t test and χ^2 tests were used for continuous variables and categorical variables, respectively. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; PAOD = Peripheral arterial obstructive disease.

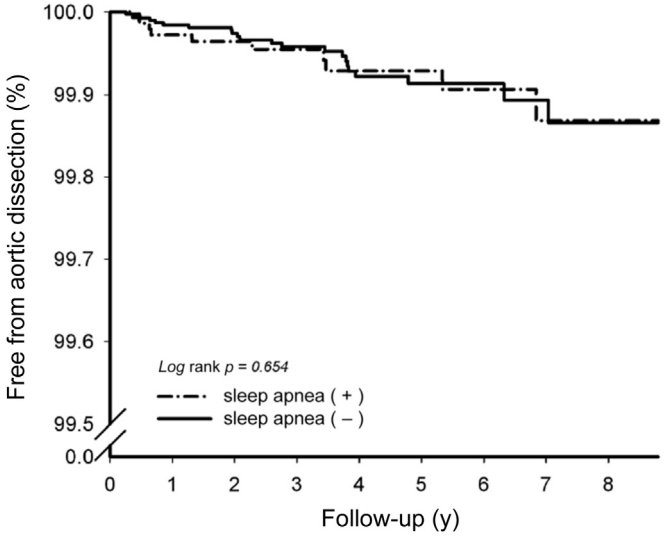

Fig. 2. Kaplan−Meier estimates of survival free aortic dissection events in patients categorized with sleep apnea. The event-free survival rates were insignificant in the two groups ($p = 0.654$).

Table 2
Baseline characteristics of the study population.

	Aortic dissection		p
	No ($n = 55,641$)	Yes ($n = 33$)	
Age (y)	44.77 ± 17.43	58.48 ± 13.19	< 0.001
Male	35,468 (63.7)	26 (78.8)	0.106
Hypertension	16456 (29.6)	24 (72.7)	< 0.001
Diabetes	6285 (11.3)	4 (12.1)	1.000
COPD	11,948 (21.5)	11 (33.3)	0.148
Coronary artery disease	8041 (14.5)	9 (27.3)	0.065
Ischemic stroke	2230 (4.0)	3 (9.1)	0.296
Intracerebral hemorrhage	556 (1.0)	1 (3.0)	0.766
Chronic renal disease	2541 (4.6)	1 (3.0)	0.996
PAOD	1255 (2.3)	1 (3.0)	1.000
Antihypertensive medication			
ACEI	4524 (8.1)	3 (9.1)	1.000
ARB	4532 (8.1)	3 (9.1)	1.000
α Blocker	9796 (17.6)	9 (27.3)	0.219
β Blocker	10,087 (18.1)	9 (27.3)	0.256
CCB	10,075 (18.1)	14 (42.4)	0.001
Sleep apnea	15,837 (28.5)	11 (33.3)	0.669

Data are presented as n (%) or mean ± standard deviation. Student t test and χ^2 tests were used for continuous variables and categorical variables, respectively. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; PAOD = Peripheral arterial obstructive disease.

4. Discussion

Using a large nationwide database, we found that SA was not associated with future risk of AD. Furthermore, our study confirmed increasing age, hypertension, and male gender as independent predictors for AD events, consistent with the results of previous studies.[14−16] In particular, the risk of AD associated with hypertension and being male was upwards of 6.28 (95% CI, 2.36−16.67; $p = 0.002$) and 2.49 (95% CI, 1.07−5.79; $p = 0.039$), respectively. All these results strengthened the reliability of our findings.

Table 3
Independent predictors of AD identified by Cox regression analysis.

AD occurrence	Hazard ratio (95% CI)	*p*
Age (y)	1.03 (1.01–1.06)	0.010
Male	2.49 (1.07–5.79)	0.039
Hypertension	6.28 (2.36–16.67)	0.002
COPD	1.06 (0.49–2.31)	0.911
Coronary artery disease	0.86 (0.36–2.06)	0.391
Antihypertensive medication		
CCB	1.20 (0.53–2.70)	0.884
Sleep apnea	1.28 (0.62–2.65)	0.644

AD = aortic dissection; CCB = calcium channel blocker; CI = confidence interval; COPD = chronic obstructive pulmonary disease.

lack of prospective design. Our study is the first to use a nationwide insurance cohort database to investigate whether SA is independently associated with higher risk of developing AD. Our results show that the incidence of AD was similar between the SA group and the age-, gender-, and comorbidity-matched controls. Only increasing age, hypertension, and male gender, but not SA, were significantly associated with increased risk of developing AD.

Our findings correlate with the results of previous studies. Baguet et al[10] showed that greater aortic root size was associated with severity of OSA in univariate analysis, but after using a multivariate stepwise regression model to analyze

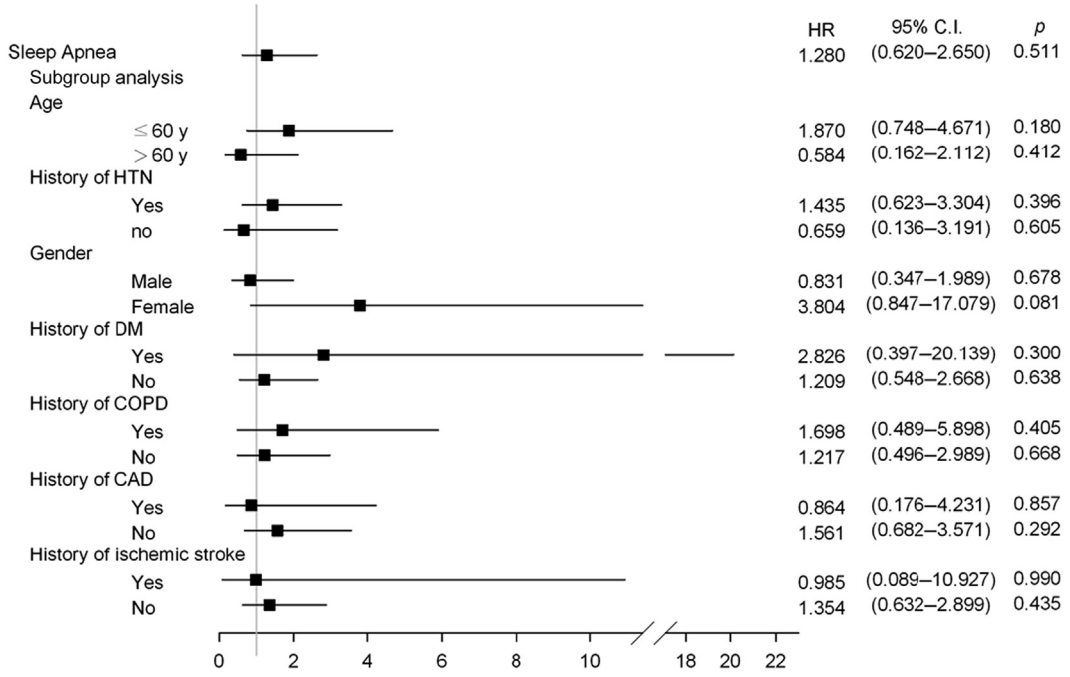

Fig. 3. Hazard ratios, with 95% confidence intervals, for aortic dissection events, according to prespecified sleep apnea subgroups. CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HTN = hypertension.

An association between SA and AD has been reported in clinical observations. Cistulli et al[14] reported two cases of Marfan syndrome in which treatment of SA by continuous positive airway pressure was associated with marked attenuation in aortic dilatation. Furthermore, Sampol et al[7] found that 19 patients with thoracic AD also had a high prevalence (13/19, 68%) of previously undiagnosed and frequently severe OSA, suggesting that SA was associated with the development of AD. Although detailed mechanisms for such an association remain undetermined, several possibilities, such as induced oxygen free-radical production,[16,17] activated inflammatory pathways impairing endothelial function of vessels,[18–20] increased sympathetic activity, and precipitating surges in blood pressure[21] have been associated with cardiovascular system damage, and are suspected of contributing to the development of AD. However, most of these studies were based on patients with Marfan syndrome or small, cross-sectional observations, and have been criticized for their aortic root size among patients with SA syndrome, diastolic blood pressure (BP) was the only significant factor for aortic root size ($p = 0.0003$). Kohler et al[15] reported that an association between SA and AD was no longer significant when other covariates were forced into multivariate analysis of patients with Marfan syndrome, suggesting SA is not an independent factor, but that multiple associated covariates may combine to contribute to AD.

Using a nationwide cohort design, our study confirmed that increasing age, hypertension, and male gender are important risk factors for developing AD, as previously reported.[14–16] Patients with acute D were mostly men aged 60–80 years.[22–24] Larson et al[22] reported on 161 necropsy patients with AD, and found that their mean age was 40–63 years, AD was more common in men, and 52% of these patients had a history of hypertension. Spittell et al[23] reported on 236 patients with AD, observing that hypertension was the most common predisposing factor (78% of patients overall). In a

review of 464 patients from the International Registry of Acute Aortic Dissection (IRAD), the mean age was 63 years and 65% were men. In the IRAD registry data, 72% had a history of hypertension.[24] Taken together, our study results combined with other observations demonstrate that the most important predisposing factor for acute AD is systemic hypertension.[22−24]

Increased aorta size is known to be related to aging, male gender, hypertension, atherosclerosis and Marfan syndrome,[25] and several studies have shown compatible results. Dapunt et al[9] reported that a history of hypertension correlated with a greater aortic diameter upon diagnosis. Increased thoracic aorta size is possibly caused by hypertension, but not by SA. Baguet et al[10] concluded that in patients with OSA, nocturnal hypoxemia decreased baroreflex sensitivity and increased diastolic BP, the main factor influencing aortic root size. Although univariate analysis revealed greater aortic root size was associated with more severe OSA, after using a multivariate stepwise regression model, diastolic BP was the only significant factor for aortic root size ($p = 0.0003$),[10] indicating that higher BP is still the strongest risk factor for AD. Even so, it is well established that SA is associated with multiple comorbidity. Further larger prospective studies or meta-analyses are recommended to investigate a possible causal role of SA in determining AD.

The main strength of our study was its nationwide population-based database, which can be used to trace nearly all cases of SA and AD in Taiwan over the study period, because all cardiologists' and sleep specialists' practices are covered in our insurance system. Additionally, the large sample size and cohort study design with controls affords considerable statistical power for detecting real differences between the two cohorts, even subtle ones.

There were some limitations of this study worth noting. Importantly, diagnoses of SA and AD that rely on administrative claims data registered by physicians or hospitals may be less accurate than diagnoses made according to standardized criteria. However, AD is always a serious condition and is usually diagnosed at a hospital with imaging studies, so these diagnoses should be correct. In addition, because AD was identified through ICD codes in an insurance claims database, it is possible that the incidence of AD may have been underestimated. However, the incidence of AD (6.9 per 100,000 person−years in the SA group, and 5.5 per 100,000 person−years in the non-SA group) found in our study is consistent with previously reported cases,[26] indicating our identification of AD was reliable. Additionally, some personal information was not available in the administrative data used, including crack cocaine use and high-intensity weight lifting or other strenuous resistance training, preventing accurate assessment of the contributory and confounding effect of these factors. Crack cocaine accounted for 37% of dissections in a report of a largely African−American, inner city population.[27] High-intensity weight lifting or other strenuous resistance training may also cause acute ascending AD, possibly mediated by transient marked elevation in BP.[28] Obesity is also an association factor for SA. However, body mass index was not available in our database because of the lack of body weight and height data. Therefore, the evaluation of obesity was not possible in our study. There were no significant differences between underlying diseases, including coronary artery disease, stroke, chronic obstructive pulmonary disease, hypertension, and diabetes mellitus, but significant differences between drug therapy, including angiotensin-converting enzyme inhibitors, β blockers, and calcium channel blockers. Moreover, the SA group might be associated with more cardiovascular system damage and high severity and therefore needs more types of medication. However, we calculated the incidence of AD in both groups. No significantly higher incidence of AD was noted in the SA group compared to the control group (6.9 per 100,000 person−years vs. 5.5 per 100,000 person−years, $p = 0.669$). Finally, we did not further divide SA into OSA or central type SA, as the 2001 version of the ICD-9 coding system adopted by our insurance system has not done so either. Nonetheless, >90% of patients with SA presenting for polysomnography have OSA.[8] OSA has also been the focus of reports about cardiovascular events associated with SA. Whether OSA or central type SA differ in their contribution to AD deserves further exploration. The severity of OSA, which was categorized by Apnoea−Hypopnoea Index, may contribute to AD in different degrees. However, the Index was not available in our NHIRD because of the lack of polysomnography results. Therefore, the severity of OSA was difficult to evaluate in our study.

In conclusion, we have shown that SA is not associated with a greater risk of AD, using a large nationwide database. Furthermore, our study confirmed that increasing age, hypertension, and male gender are independent predictors for AD, consistent with the results of previous studies. Larger prospective studies or meta-analyses are recommended to confirm our findings.

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